Health Information and Quality Authority
An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Health Technology Assessment of Metabolic Surgery for the Treatment of Comorbid Type 2 Diabetes and Obesity

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About the Health Information and Quality Authority

The Health Information and Quality Authority (HIQA) is an independent statutory authority established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.

HIQA's mandate to date extends across a wide range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children, Equality, Disability, Integration and Youth, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.
- **Regulating social care services** — The Chief Inspector within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.
- **Regulating health services —** Regulating medical exposure to ionising radiation.
- **Monitoring services** — Monitoring the safety and quality of health services and children's social services, and investigating as necessary serious concerns about the health and welfare of people who use these services.
- **Health technology assessment** — Evaluating the clinical and cost-effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.
- **Health information** — Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information on the delivery and performance of Ireland's health and social care services.
- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health services, in conjunction with the Department of Health and the HSE.

Foreword

Type 2 diabetes (T2D) is a metabolic disorder characterised by high blood sugar levels caused by insulin resistance and varying degrees of abnormal insulin production. Overweight and obesity are associated with an increased risk of developingT2D. It is estimated that approximately 130,000 people in Ireland have medically-treated T2D. Of these, approximately half are living with comorbid obesity. T2D is associated with a greater risk of a range of health problems including cardiovascular disease, blindness, amputation and kidney disease. Such complications negatively impact quality of life for patients and create a burden on the healthcare system.

Weight loss is an important component of T2D management. International diabetes associations have recommended the use of metabolic surgery as a tool to produce weight loss and improvements in glycaemic control in patients with comorbid T2D and obesity. Despite these recommendations, metabolic surgery has not yet been included in T2D treatment algorithms in Ireland.

Work on the health technology assessment (HTA) was undertaken by an Evaluation Team from the HTA Directorate in HIQA. A multidisciplinary Expert Advisory Group was convened to advise the Evaluation Team during the course of the HTA. HIQA would like to thank its Evaluation Team, the members of the Expert Advisory Group and all who contributed to the preparation of this report.

Dr Máirín Ryan

Deputy Chief Executive and Director of Health Technology Assessment

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Expert advisory group membership

The membership of the EAG was as follows:

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Conflicts of interest

Professor Carel le Roux declared receiving funding from the Health Research Board, Irish Research Council, Science Foundation Ireland, European Federation for Study of Diabetes, European Union Innovative Medicine Initiative for research related to metabolic surgery. Professor le Roux also has served on Global Advisory Boards for a number of pharmaceutical companies focussed on obesity management.

There were no reported potential conflicts of interest for other members of the Expert Advisory Group or Evaluation Team.

Advice to the Minister for Health and the Health Service Executive

Metabolic surgery refers to the use of bariatric surgery procedures with the aim of improving T2D control in patients with comorbid T2D and obesity. At present, metabolic surgery is not part of the T2D clinical care pathway in Ireland. Following a formal request from the Clinical Lead of the National Clinical Programme for Diabetes in the Health Service Executive (HSE), with support from the National Clinical Programme for Obesity, a health technology assessment of a metabolic surgery programme for patients with comorbid T2D and obesity was prioritised for inclusion in the HIQA HTA work plan.

The key findings of this HTA, which informed HIQA's advice, were:

- Comorbid T2D and obesity is associated with considerable morbidity and mortality. Obesity increases the risk of developing insulin resistance, which over time may progress to T2D. Together these diseases are characterised by a clustering of metabolic and cardiovascular risk factors including hypertension and dyslipidaemia. Diabetes-related morbidity, such as renal disease, diabetic foot, and retinopathy, has important implications for the burden of T2D on the healthcare system.

- For many patients, treatment targets for T2D are not met despite best medical care, resulting in an increased risk of developing T2D-related complications. It is estimated that 32% of patients with comorbid T2D and obesity enrolled in the Diabetes Cycle of Care programme in 2017 had a HbA1c >58 mmol/mol (7.5%), that is, did not meet what is considered a reasonable target for most adults with T2D.

- Standard care for patients with comorbid T2D and obesity includes patient education programmes, multicomponent behavioural interventions (such as, dietary changes, physical activity and smoking cessation advice) and cardiovascular risk factor reduction with or without anti-hyperglycaemic medication(s). Weight loss is an important part of T2D management and can result in improved cardio-metabolic risk factors and an associated decreased risk of T2D-related complications.

- Bariatric surgery alters the anatomy and physiology of the gastrointestinal tract resulting in weight loss. It has traditionally been used as a weight-loss intervention in patients with obesity based on BMI-centric eligibility criteria. In patients with T2D pre-operatively, bariatric surgery has been shown to have

additional metabolic effects, leading to the coining of the term "metabolic surgery" to refer to the use of bariatric surgery procedures with the aim of improving T2D control in patients with comorbid T2D and obesity. Numerous diabetes and obesity organisations recommend that metabolic surgery should be an accepted treatment option for people with comorbid T2D and obesity.

- In Ireland, based on national datasets, approximately 50,000 people may be eligible for metabolic surgery with consideration to their T2D status and obesity only. In practice, not all of these patients would be considered surgical candidates, or would wish to undergo metabolic surgery. Based on existing demand for bariatric surgery among patients with T2D, there would be demand for at least 200 metabolic surgery procedures per year. Estimates of the size of the population with T2D are subject to considerable uncertainty due to the absence of a national diabetes register.

- A systematic review was undertaken to assess the clinical effectiveness and safety of metabolic surgery for the treatment of comorbid T2D and obesity compared with best medical care or another metabolic surgery.

    - Twenty-four randomised controlled trials (RCTs) were included. Trials generally included short- to medium-term follow-up data, with one trial reporting up to ten years' follow-up data.

    - Metabolic surgery was found to be more effective than best medical care at all time points, producing clinically significant reductions in HbA1c, body mass index and medication use, irrespective of the type of procedure.

    - There was no evidence of clinically significant differences in effectiveness between laparoscopic Roux-en-Y gastric bypass (LRYGB) and laparoscopic sleeve gastrectomy (LSG), the two most commonly performed procedures in Ireland and globally. Limited evidence was available for other head-to-head comparisons of surgeries including laparoscopic one-anastomosis gastric bypass (LOAGB), biliopancreatic diversion (BPD), laparoscopic silastic ring RYGB (LSR-RYGB), metabolic RYGB (mRYGB), and greater curvature plication (GCP).

    - There was no evidence of serious adverse events associated with surgery. No surgery-related mortality was reported. RCTs were not powered to detect differences in the rate of surgery-related adverse events; however, large registry-based studies report a low rate of complications.

- Evidence of effectiveness is predominantly based on body mass index and HbA1c, as a surrogate marker of T2D-related complications. Evidence of reductions in morbidity and mortality is constrained by the small trial sizes and relatively short term follow-up in included RCTs. However, observational evidence consistently demonstrates clinically significant reductions in T2D-related cardiovascular complications.

- Treatment options and guidelines for the management of T2D are continuously evolving, with substantial ongoing innovation in this area. A notable limitation of these trials is that they pre-date the widespread use of a number of new, effective medication classes which may alter our understanding of the relative benefit of surgery.

- A systematic review of published economic evaluations was undertaken and found, across 30 studies, consistent evidence that metabolic surgery was considered cost-effective or cost-saving compared with best medical care. The applicability of identified economic evaluations to the Irish healthcare setting is limited due to changes in the underlying evidence base over time and differences in healthcare systems.

- An Irish-specific economic model was developed to estimate the cost-effectiveness and budget impact of introducing a metabolic surgery programme compared with best medical care. Metabolic surgery was found to be cost-effective at a willingness-to-pay threshold of €20,000 per quality-adjusted life year (QALY) gained (€4,079 per QALY, 95% CI: 946 to 7,418). The incremental cost effectiveness ratio (ICER) was robust in sensitivity and scenario analyses.

- Compared with best medical care, the incremental budget impact of a metabolic surgery programme was estimated at €7.39 million (95% CI: €5.41 to €9.54) over a five-year time horizon, assuming an annual cohort size of 200 patients. Demand was estimated based on the number of patients with T2D currently waiting for bariatric surgery. The majority of expenditure over a five year time horizon directly relates to provision of surgery and the associated multidisciplinary support. The cost of the programme would be partially offset by reductions in anti-hyperglycaemic medication use.

- This assessment considered metabolic surgery in the context of a programme delivering end-to-end care, from referral to long-term post-operative follow-up. The organisational structure adopted by a metabolic surgery programme will likely influence its acceptability to patients and clinicians.

  - In order to ensure that metabolic and bariatric surgery services do not compete for resources, consideration should be given to the establishment of metabolic surgery services in hospitals not currently conducting bariatric surgery, and ideally in a way that would provide an equitable geographic distribution of services.

  - Provision of a metabolic surgery programme would be associated with additional costs in the short-term predominantly driven by the upfront cost of providing surgery and multidisciplinary (MDT) support. As such, additional staff would be required to avoid existing surgical care being displaced and to allow for timely pre-operative MDT assessment and follow-up. The number and type of staff required at a hospital or hospital group level will depend on the volume of procedures and the available skills mix.

  - Operational efficiencies could be achieved by integrating the metabolic surgery programme with standard T2D management delivered as part of the HSE's Chronic Disease Management Programme in primary care. Key enablers will include clear eligibility criteria, referral and escalation pathways, and support from community services. Of note, financial and logistical barriers to care may be experienced by patients who are not eligible for the Chronic Disease Management Programme, as this is currently limited to those with a GP visit card or medical card.

- Patient and provider education regarding the benefits and risks of metabolic surgery for the cohort of patients with comorbid T2D and obesity would be necessary to support diffusion of changes to treatment guidelines into clinical practice.

- The incremental budget impact was estimated at €7.4 million to provide 1,000 surgeries and follow-up care over five years. An annual cohort of 200 undergoing surgery was assumed based on the number of patients with T2D currently waiting for bariatric surgery. However, it is noted that the budget impact would be directly proportional to the number of patients treated. A number of factors may influence demand for surgery such as the accessibility of services for acute and chronic care, waiting times for surgery, visibility of metabolic surgery within T2D treatment pathways and provision of educational interventions.

- Appropriate quality assurance mechanisms would be necessary to facilitate monitoring of effectiveness and safety outcomes and healthcare service quality. Data on metabolic surgery outcomes could be recorded as part of a dedicated

metabolic surgery registry and or as part of an existing system such as the HSE's Chronic Disease Management Programme.

HIQA's advice to the Minister for Health and the HSE is as follows:

- In patients with comorbid type 2 diabetes and obesity, the current evidence suggests that metabolic surgery is safe, and is more effective than best medical care in producing weight loss and improvements in glycaemic control. Metabolic surgery would likely result in a reduced risk of T2D-related complications and a reduction in associated health service utilisation over the longer term.
- Even based on conservative assumptions, a metabolic surgery programme provided as part of the T2D clinical care pathway would be an efficient and highly cost-effective use of healthcare resources relative to best medical care.
- The incremental budget impact was estimated at €7.4 million to provide 1,000 surgeries and follow-up care over five years. While an annual cohort of 200 patients was assumed, the budget impact would be directly proportional to the number of patients undergoing surgery.
- In the event that metabolic surgery is provided, it should be in the context of a programme including end-to-end care, from referral, pre-operative assessment, the acute surgical care episode through to long-term follow-up. Additional staff would be required to avoid existing surgical care being displaced.
- The success of a metabolic surgery programme would be dependent on the integration of patient management between primary and secondary care. Development of care pathways that include linkage to hospital and community services would be necessary to support GPs in providing long-term follow-up to these patients.
- The epidemiology of comorbid T2D and obesity in Ireland is not known with certainty due to the absence of up-to-date, nationally-representative data. Consideration should be given to the establishment of a national diabetes registry to support healthcare service planning in response to epidemiological trends.

Executive summary

A health technology assessment (HTA) is intended to support evidence-based decision-making in regard to the optimum use of resources in healthcare services. Measured investment and disinvestment decisions are essential to ensure that overall population health gain is maximised, particularly given finite healthcare budgets and increasing demands for services provided. The aim of the HTA was to establish the clinical effectiveness, cost-effectiveness and budget impact of establishing a metabolic surgery programme for the treatment of patients with comorbid T2D and obesity. This HTA considered the following domains:

- description of technology
- epidemiology
- clinical effectiveness and safety
- systematic review of the cost-effectiveness literature
- economic evaluation
- organisational issues
- ethical issues.

1 Background

The Health Information and Quality Authority (HIQA) agreed to undertake a health technology assessment (HTA) in relation to providing access to metabolic surgery as part of the type 2 diabetes (T2D) clinical care pathway. Following a formal request from the Clinical Lead of the National Clinical Programme for Diabetes in the Health Service Executive (HSE), with support from the National Clinical Programme for Obesity, this topic was prioritised for inclusion in the HIQA HTA work plan.

2 Description of the technology

Diabetes is a chronic, metabolic disease characterised by hyperglycaemia (elevated levels of blood glucose) in the absence of treatment and is caused by defects in insulin secretion, insulin action or both. Excess weight is a risk factor for the development of type 2 diabetes mellitus (T2D) and other metabolic and cardiovascular complications. Diagnosis of T2D and ongoing measurement of glycaemic control is carried out using validated plasma glucose criteria and or HbA1c concentrations.

The long-term vascular complications of diabetes can be divided into microvascular and macrovascular complications which affect small and large blood vessels, respectively. Intensive glycaemic control can reduce the risk or slow the progression of diabetes-related complications.

Standard care for patients with comorbid T2D and obesity includes patient education programmes, multicomponent behavioural interventions (such as, dietary changes, physical activity and smoking cessation advice) and cardiovascular risk factor reduction with or without anti-hyperglycaemic medication(s). Metabolic surgery is not currently included within the T2D clinical care pathway in Ireland.

Bariatric surgery alters the anatomy and physiology of the gastrointestinal tract. Metabolic surgery refers to the use of bariatric surgical procedures with the intention of achieving improvements in T2D control in patients with comorbid T2D and obesity. There is no internationally accepted and routinely implemented definition of T2D remission. The ultimate goal of treatment is to reduce the risk of micro- and macrovascular complications through the control of glycaemia and cardiovascular risk factors.

Metabolic surgery is now recommended for inclusion within the T2D treatment algorithm by the American Diabetes Association (ADA), the International Diabetes Federation (IDF) and the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO). Established bariatric procedures in current use for the treatment of obesity and obesity-related comorbidities include adjustable gastric banding (AGB), sleeve gastrectomy, Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion with duodenal switch (BPD-DS). Other newer or alternative procedures are in development, but are not widely available in Ireland or other European countries.

Indications for metabolic surgery vary internationally. Traditionally, metabolic surgery is indicated for patients with obesity and a BMI ≥40 kg/m^2, or BMI 35-39.9 kg/m^2 and obesity-related comorbidities. In some countries, it is considered as a treatment option for patients with a BMI 30 to 34.9 kg/m^2 with T2D above treatment targets. Lower BMI thresholds are used for some ethnic groups.

3 Epidemiology

Diagnoses of Type 2 diabetes (T2D) are primarily driven by rising levels of overweight and obesity and by the ageing population. T2D is more prevalent in males and those with lower socioeconomic status. Onset of illness typically occurs in middle-aged and older adults, with the highest prevalence found in those >75 years of age. Estimates of the size of the population with T2D are subject to considerable uncertainty due to the absence of national data sources such as a national diabetes register, centralised database of electronic medical records or a population-based survey of T2D.

Estimates from the first wave (2009 to 2011) of The Irish Longitudinal Study on Ageing (TILDA) indicate that 4.52% (95% CI: 4.00 to 5.12) of adults ≥50 years in Ireland have comorbid T2D and obesity (BMI ≥30 kg/m^2), while the estimated prevalence in the population aged 18 to 49 years is less than 1% according to 2019 Healthy Ireland Survey data. While the estimated prevalence of diabetes in Ireland is lower than that reported for other European countries, this may be related to the lack of up-to-date national estimates on the prevalence of T2D in Ireland.

There is no internationally accepted definition for T2D control that is above treatment targets despite best medical care. At a population-level, blood glucose levels can be used as a simplified means of approximating the risk of T2D-related complications. Among patients with T2D and obesity enrolled in the HSE's Diabetes Cycle of Care programme, 32% had glycaemic control above target despite best medical care.

T2D and obesity are typically characterised by a clustering of metabolic and cardiovascular risk factors including hypertension and dyslipidaemia. As a result, T2D is associated with considerable morbidity. T2D is associated with a two-fold increase in the risk of cardiovascular disease (CVD) compared with the general population. It is estimated that 90% of patients with T2D in Ireland have at least one additional chronic disease. General reductions in cardiovascular risk factors have led to reduced CVD-mortality over time. Although improved life expectancy could contribute to relative increases in diabetes-related morbidity, this may be moderated by cardiovascular risk factor reduction (for example, smoking cessation) which may result in improved patient outomes.

People with T2D and obesity have reduced quality of life relative to the general population, particularly for patients with intensive treatment regimes, higher HbA1c levels and or T2D-related complications. T2D is also associated with a considerable medication burden for patients and increased health service utilisation relative to those without T2D, particularly for patients with T2D-related complications or multimorbidity.

According to the most recent International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) global registry report, patients with comorbid T2D and obesity are under-represented among bariatric surgery candidates within existing bariatric surgery services. Patients with T2D currently represent approximately 24% of patients undergoing bariatric surgery in Ireland.

4 Clinical effectiveness and safety

A systematic review was undertaken to assess the clinical effectiveness and safety of metabolic surgery for the treatment of comorbid type 2 diabetes (T2D) and obesity.

Twenty-four randomised controlled trials (RCTs) enrolling 1,712 participants were included that compared metabolic surgery with best medical care or another metabolic surgery. Trials generally included short- to medium-term follow-up data (18 RCTs with ≤3 years' follow-up). Six RCTs followed participants for a least five years, with one trial reporting at ten years' follow-up. Mean age ranged from 37 to 56 years.

Evidence was retrieved for 11 metabolic surgery procedures including:

- three in routine clinical use for the treatment of obesity (Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG) and one anastomosis gastric bypass (OAGB))
- two that are not widely used (biliopancreatic diversion (BPD) and laparoscopic adjustable gastric banding (LAGB))
- four variations of RYGB (laparoscopic silastic ring-RYGB (LSR-RYGB), metabolic RYGB (mRYGB), small pouch RYGB and large pouch RYGB
- two newer procedures that are not widely adopted (greater curvature plication (GCP) and sleeve gastrectomy with transit bipartition (SG-TB)).

There was considerable variability in remission rates between RCTs. Remission rates were highly dependent on the definition used and the length of follow-up. In general, metabolic surgery was associated with significantly increased probability of T2D remission (defined as HbA1c <6.5% (48 mmol/mol) without pharmacological management) relative to best medical care up to five years' follow-up. An additional 25 participants per 100 followed in the RYGB group were in T2D remission relative to best medical care at five years (95% CI: 12 to 38, four RCTs GRADE=low). SG increased T2D remissions by an additional 23 participants per 100 followed at five years (RR=18.69, 95% CI: 1.14 to 307.22; RD= 0.23, 95% CI: 0.11 to 0.36, one RCT, GRADE=low) compared with best medical care. While surgery was associated with a statistically significant increase in the number of patients in T2D remission, the effect reduced over time indicating that a proportion of those in T2D remission relapsed. However, glycaemic control as measured with HbA1c remained significantly improved relative to best medical care irrespective of the procedure.

The effect of metabolic surgery on T2D is mainly mediated through reductions in HbA1c and BMI. Metabolic surgery resulted in improvements in some, but not all cardiovascular risk factors relative to best medical care, although not all participants had dyslipidaemia or hypertension at baseline. Where pharmacological management of cardiovascular risk factors was indicated, metabolic surgery was associated with a reduction in medication use relative to best medical care.

For the majority of metabolic outcomes there was no evidence of significant differences between surgeries, although the evidence base was limited for most comparisons other than RYGB versus SG. RYGB was associated with a greater reduction in BMI relative to SG and LAGB at medium term follow-up. At short-term follow-up, RYGB may be associated with small or non-significant improvements in cardiovascular outcomes relative to SG.

Based on limited evidence, metabolic surgery may be associated with an improvement in nephropathy in participants with albuminuria at baseline compared with best medical care. There was no significant difference in the incidence or progression of retinopathy or neuropathy. Investigation of the impact of metabolic surgery on macrovascular disease was not possible due to the small sample sizes and relatively short duration of follow-up of included RCTs.

Metabolic surgery may be associated with improvements in quality of life (QoL) relative to best medical care as measured using validated instruments. The effect, which was observed in some studies, was largely due to improvements in physical rather than mental health domains. In general, for head-to-head comparisons of surgeries, there were no differences in improvement in QoL from baseline. No surgery-related mortality was reported in the trials. RCTs were not powered to detect differences in the rate of technical complications; however, where reported, they were generally not associated with long-term morbidity.

Metabolic surgery may be associated with medium- to long-term adverse events including gastroesophageal reflux, dumping syndrome and gallstones. A limited number of RCTs reported nutritional deficiencies during the post-operative period. However, data were generally not reported in the context of clinical manifestations or adherence to prescribed micronutrient supplementation making interpretation challenging.

Lack of blinding was a limitation of RCTs comparing metabolic surgery with best medical care, particularly in relation to subjective outcomes such as QoL. Attrition is also a considerable challenge in RCTs comparing surgery with best medical care, with higher loss to follow-up typical in the best medical care arm. The evidence base is constrained by the small sample sizes of included RCTs (range n=20 to 169) and the limited head-to-head evidence between surgical procedures.

5 Systematic review of cost-effectiveness

A systematic review was undertaken to assess the available international evidence on the cost-effectiveness of metabolic surgery compared with usual care in patients with comorbid T2D and obesity. Thirty studies were identified, of which, 16 were

conducted specifically in a T2D population. Patients with T2D represented a subgroup of the population of interest in 14 studies.

Twenty-eight studies were model-based economic evaluations. Two evaluations were based on a single trial or observational study without extrapolation beyond the study period. Of model-based economic evaluations, 20 studies used a Markov model to estimate the costs and benefits of surgery compared with usual care. Three studies used a hybrid decision-tree and Markov model and two evaluations used a microsimulation model. The model structure was unclear in three studies.

Of studies carried out specifically in a population with T2D, metabolic surgery was reported to be cost-effective in 10 studies, with incremental cost-effectiveness ratios (ICERs) ranging from €360 to €17,029/QALY. Surgery was reported to be cost-saving in eight analyses (from six studies). Of studies in which patients with T2D were considered in subgroup analysis, metabolic surgery was cost-saving in 10 studies. Metabolic surgery was cost-effective in three studies, with ICERs ranging from €2,462 to €10,651/QALY. In one study the outcome varied depending on the procedure and BMI category.

The quality of included studies was variable, mainly due to insufficient reporting of input parameters and structural shortcomings. Studies were categorised as high (n =15), moderate (n = 5) or low (n = 10) quality using the Consensus Health Economics Criteria (CHEC)-list quality appraisal instrument. However, where undertaken, the results remained robust during sensitivity and scenario analyses within the plausible ranges.

None of the studies were considered directly applicable to the Irish context. Seventeen studies were said to be partially applicable. The transferability of identified economic evaluations was limited by the health states and time horizon considered, the sources and applicability of clinical effectiveness estimates and differences in health systems.

6 Economic evaluation

An economic model was developed to estimate the cost-effectiveness and budget impact of metabolic surgery with or without pharmacological management compared with pharmacological management only (that is, current best medical care) in patients with comorbid T2D and obesity in Ireland. A Markov model was used to estimate the costs and outcomes associated with changes in pharmacological management of T2D and the risk of cardiovascular events for patients with both T2D and obesity following metabolic surgery compared with best medical care. A time horizon of ten years was used in the base case analysis. It was assumed that a

metabolic surgery programme in Ireland would comprise a mix of Roux-en-Y gastric bypass and sleeve gastrectomy.

The cost of a metabolic surgery programme included pre-surgical assessment, the acute surgical care episode and long-term follow-up. The estimated treatment effects were obtained from the systematic review of clinical effectiveness and safety and the published literature. Metabolic surgery was assumed to have diminishing benefits over time in terms of HbA1c and BMI based on extrapolation of RCT evidence.

Based on a conservative approach over a ten year time horizon, compared with best medical care, the incremental cost-effectiveness ratio (ICER) for a metabolic surgery programme was estimated at €4,079 (95% CI: 946 to €7,418) per quality-adjusted life year (QALY) gained. In the probabilistic sensitivity analysis, metabolic surgery was considered cost-effective at a willingness to pay (WTP) threshold of €20,000 per QALY gained in all simulations. Extension of the time horizon yielded more favourable ICERs.

One-way sensitivity analysis demonstrated that the model was most sensitive to treatment-related costs and transition probabilities between health states. The results of the base case analysis were stable in multiple sensitivity and scenario analyses.

The incremental budget impact over five years was estimated at €7.39 million (95% CI: €5.41 to €9.54), assuming an annual cohort size of 200 patients. The five-year budget impact was most sensitive to the cost of metabolic surgery. The additional costs associated with the provision of metabolic surgery are offset by savings associated with reductions in anti-hyperglycaemic medication use. The estimated incremental budget impact did not include capital investment costs or specialist training. Any requirements for additional theatre space or training of existing staff would be associated with additional costs.

7 Organisational issues

The delivery of a metabolic surgery programme for patients with comorbid T2D and obesity would depend on several critical enablers:

- clear eligibility criteria
- pathways for referral and escalation of care
- scaling up of hospital capacity
- support from community services

- patient and provider education
- the availability of specialist staff.

It is estimated that treating a cohort of 200 patients per year would be associated with an estimated 230 multidisciplinary team (MDT) pre-operative assessments (including expertise in surgery, dietetics, psychology and endocrinology), 85 theatre days and 400 hospital beds days for the index admission. During the first year post-operatively, a minimum of 800 specialist MDT follow-up visits would be required.

It would be important that the healthcare system is adequately resourced to undertake lifelong follow-up of these patients. Resource requirements for long-term follow-up would depend on organisational structures. Capacity for annual review would need to be factored into the staffing of specialist centres until discharge to primary care is considered appropriate. To achieve operational efficiency, long-term follow-up care for uncomplicated cases discharged to primary care may be incorporated into existing reviews for T2D management.

The success of a shared model of care between primary care, community and hospital services will depend on training tailored to the information needs of providers at different levels of care, adequate resourcing of community services, strong communication networks supported by IT infrastructure, protocols outlining provider roles and responsibilities, and clear criteria for referral, discharge and escalation of care. However, from a patient's perspective not everyone with comorbid T2D and obesity is eligible for the HSE's Chronic Disease Management Programme, which may result in financial and logistical barriers to accessing metabolic surgery for these patients.

Without investment in community resources to support discharge of appropriately risk-stratified patients from acute hospital services, an imbalance would be created between an increasing number of patients requiring follow-up, and the availability of resources in metabolic surgery units. This would present a risk to the sustainability of the programme. Ongoing investment would be required as the size of the patient cohort increases.

Development of key performance indicators (KPIs) would help support the delivery of a metabolic surgery programme through the collection of robust data to monitor outcomes and identify organisational challenges. Revisions to the care pathway should be driven by a review of the programme's KPIs, of the identified needs within the Irish healthcare system, and of changes in best practice guidelines.

Should a decision be made to implement a national metabolic surgery programme, consideration should be given to the development of national disease registries for

diabetes and bariatric/metabolic surgery to support quality assurance processes, healthcare service planning in response to epidemiological trends and monitoring of patient outcomes. Consideration should be given to the variables recorded in other international registries to facilitate international collaboration and benchmarking.

8 Ethical issues

In terms of the benefit-harm balance, the proposed metabolic surgical programme will result in a higher proportion of patients achieving treatment targets and a reduced risk of developing complications of T2D. The harms of surgery relate primarily to the significant dietary changes required post-surgery and the generally irreversible nature of the intervention.

Patients may have unrealistic expectations regarding the outcome of the procedure and the impact it may have on their lifestyle. The pre-operative assessment process will have to ensure that patients have a clear understanding of the purpose and impact of the intervention.

The perception of T2D and obesity as issues of lifestyle could lead to stigma about the intervention that may create a reluctance to seek treatment. There is a risk of a perception that individuals have failed treatment.

A metabolic surgery programme will have similar resource requirements to bariatric surgery in terms of staff and facilities. There is a risk that the introduction of a metabolic surgery programme may reduce capacity for bariatric surgery, thereby creating inequities for candidates for bariatric surgery and potentially for other procedures requiring similar surgical expertise.

The primary outcomes reported in clinical trials were intermediate outcomes of diabetes remission and reductions in HbA1c, rather than improved quality of life or long-term reduction in complications or mortality. However, despite the limited data available, the intervention is considered a cost-effective use of resources.

9 Conclusions

The prevalence of comorbid T2D and obesity in Ireland will likely increase in Ireland in the coming years based on current trends. There is a substantial burden of disease associated with T2D for both patients and the health service. Implementing more effective treatment strategies to reduce both the clinical and economic burden of comorbid T2D and obesity is of increasing importance in the context of ageing populations and the increasing burden of chronic disease. Metabolic surgery has been shown in RCTs to be effective in reducing HbA1c and BMI, to reduce the

necessary intensity of pharmacological treatment, and to lead to remission of T2D in some patients.

Metabolic surgery should not be considered a one-time intervention. Patients require lifelong follow-up care to ensure optimal outcomes. To this end, the cost-effectiveness, budget impact and organisational implications associated with metabolic surgery were considered in the context of a programme that reflects all aspects of care from the pre-operative phase to long-term follow-up. Based on an economic evaluation of a metabolic surgery programme in Ireland, it is considered a cost-effective intervention. However, delivery of a safe and effective metabolic surgery programme would require considerable reorganisation of health service delivery and buy-in from healthcare professionals across all levels of the healthcare system to ensure continuity of care for patients. Metabolic surgery brings with it a need for significant lifestyle changes. Patients require long-term follow-up to maximise clinical outcomes, including reductions in HbA1c and BMI and to monitor for post-surgical complications including micronutrient deficiencies. Management of these patients would require a shared model of care between primary care, community and hospital services. The success of that model will depend on a range of factors, including training, resourcing, communication, and clear criteria for referral, discharge and escalation of care.

Demand for metabolic surgery will depend on patient and provider education as well as the effectiveness of alternative non-surgical interventions. Given the estimated large number of patients who may be eligible for surgery, if the acceptability of metabolic surgery is high in the population with comorbid T2D and obesity, then demand will likely greatly exceed available capacity. Where demand exceeds capacity, it will be important to ensure that there is a coherent approach to referral and assessment. If a decision is made to introduce a metabolic surgery programme, the potential impact on existing bariatric surgery services must be considered. It is important that organisational workflows are properly designed and adequately resourced to support both pathways.

Plain language summary

Type 2 diabetes occurs as a result of the body's inability to produce or respond to insulin, causing blood sugar levels to become higher than normal. Insulin is a hormone that causes blood sugar to be taken up by the body's cells. High blood sugar levels can result in many health problems and a shorter life expectancy. Medical care for type 2 diabetes and obesity involves a variety of treatments including diabetes medication with or without other treatments to promote behaviour change and well-being such as diet, exercise or psychological counselling.

While the available treatments are effective for many patients, more effective options are needed for other patients. Weight loss is an important part of type 2 diabetes management and can help to reduce blood sugar levels and the risk of complications related to type 2 diabetes. "Bariatric surgery" involves changing how the stomach and small intestine process food, resulting in weight loss and improvements in obesity-related health complications. Traditionally, it is used as a weight-loss intervention in patients with obesity. However, studies have shown that bariatric surgery is particularly beneficial in patients with both type 2 diabetes and obesity. "Metabolic surgery" refers to the use of bariatric surgery procedures for type 2 diabetes treatment. A number of different metabolic surgeries are available, which work in different ways. This assessment considered the available evidence to inform a decision to invest in a metabolic surgery programme for the treatment of people with both type 2 diabetes and obesity in Ireland. We considered the potential health benefits, value for money and the impact on the wider healthcare system.

Overall, metabolic surgery was found to be more effective than best medical care for blood sugar control and weight loss. Many patients enter type 2 diabetes remission after surgery, meaning that they no longer need diabetes medication to maintain normal blood sugar levels. Body weight and blood sugar may start to increase slowly over time after surgery, but still remain lower than they were before surgery in the long-term. This period of improved type 2 diabetes control may result in a lower risk of type 2 diabetes-related complications, such as heart attack or stroke. Metabolic surgery is considered safe. Some patients will experience surgery-related complications, such as bleeding or intestinal obstructions, but these do not usually result in long-term consequences for patients. Some complications can occur later after surgery, such as low levels of essential vitamins and minerals, but these can be managed through dietary changes, supplements and regular blood tests.

We assessed whether metabolic surgery was good value for money compared with the current standard of care. Based on our analysis, introducing a metabolic surgery programme would be a good use of healthcare resources. Metabolic surgery will lead

to improved quality of life for patients at a reasonable additional cost to the healthcare system. It was estimated that a metabolic surgery programme would cost €7.4 million over five years. It was recommended that a metabolic surgery programme should be integrated with standard type 2 diabetes care in the long-term. However, not all patients with both type 2 diabetes and obesity are eligible for the HSE Chronic Disease Management Programme. Some patients would have to pay out-of-pocket for follow-up care in the community, which could be a barrier to accessing care and could lessen the benefit of surgery.

A key challenge in setting up a metabolic surgery programme would be making sure there are enough staff in hospitals to support the programme. Another challenge is avoiding competition with the bariatric surgery service. This could be avoided by providing metabolic surgery procedures in hospitals not currently carrying out bariatric surgery.

Demand for metabolic surgery is difficult to predict as not all patients who are considered eligible for surgery may wish to access it. A number of issues would need to be tackled to ensure metabolic surgery becomes an accepted treatment option for patients with comorbid type 2 diabetes and obesity. These issues include shorter waiting lists, improved access to services across regions, and education of patients and healthcare providers. Stigma around obesity might make patients reluctant to seek surgery.

Conclusions

Metabolic surgery is a safe, clinically-effective and cost-effective treatment for patients with both type 2 diabetes and obesity. Over a patient's lifetime, metabolic surgery will likely reduce the number of complications relating to type 2 diabetes that a patient experiences. As a result, patients may visit their doctor or attend hospitals less often. This would result in improved quality-of-life for patients and lower healthcare costs in the future. It would be important that patient care is linked between the hospital and GP so that there are no gaps.

List of abbreviations

ADA	American Diabetes Association
BIA	budget impact analysis
BMC	best medical care
BMI	body mass index
BOMSS	British Obesity and Metabolic Surgery Society
BPD	biliopancreatic diversion
CEA	cost-effectiveness analysis
CUA	cost utility analysis
DPP-4	dipeptidyl-peptidase 4
EAC-BS	European Accreditation Council for Bariatric Surgery
EQ-5D	EuroQol five-dimension
GERD	gastro-eosophageal reflux disease
GLP-1 RA	glucagon-like peptide-1 receptor agonists
GP	general practitioner
GRADE	grading of recommendations, assessment, development and evaluations
HbA1c	glycated haemoglobin
HDL-C	high-density lipoprotein cholesterol
HIPE	Hospital In-Patient Enquiry
HSE	Health Service Executive
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
IFSO	International Federation for the Surgery of Obesity and Metabolic Disorders
IU	international unit
LAGB	laparoscopic adjustable gastric banding
LDL-C	low-density lipoprotein cholesterol
LGBP	laparoscopic gastric bypass
LOAGB	laparoscopic one anastomosis gastric bypass
LOS	length of stay
(L)RYGB	(laparoscopic) Roux-en-Y gastric bypass
LSAGB	laparoscopic single anastomosis gastric bypass
(L)SG	(laparoscopic) sleeve gastrectomy
LSG+TB	laparoscopic sleeve gastrectomy with transit bipartition

LSR-RYGB	laparoscopic silastic ring Roux-en-Y gastric bypass
LTI	long-term illness
MD	mean difference
MDT	Multidisciplinary team
MGB	mini gastric bypass
mRYGB	metabolic Roux-en-Y gastric bypass
NBSR	National Bariatric Surgery Register
OPD	outpatient department
PCRS	Primary Care Reimbursement Service
PICO	population, intervention, comparator(s), outcome(s)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
QALY	quality-adjusted life year
QoL	quality of life
RCT	randomized controlled trial
RD	risk difference
RoB	risk of bias
RR	risk ratio
SF-36	short form 36
SGLT2	sodium-glucose co-transporter-2
SMD	standardised mean difference
SOReg	Scandinavian Obesity Surgery Registry
T2D	type 2 diabetes
WTP	willingness-to-pay

1 Introduction

1.1 Background to the request

The Health Information and Quality Authority (HIQA) agreed to undertake a health technology assessment (HTA) in relation to providing access to metabolic surgery as part of the type 2 diabetes (T2D) clinical care pathway. Following a formal request from the Clinical Lead of the National Clinical Programme for Diabetes in the Health Service Executive (HSE), with support from the National Clinical Programme for Obesity, this topic was prioritised for inclusion in the HIQA HTA work plan. The aim of the HTA was to establish the clinical and economic impact of establishing a metabolic surgery programme for the treatment of patients with comorbid T2D and obesity.

During the World Health Assembly in 2013 member states of the World Health Organization agreed to work towards global health targets.[(1)] The targets included a 25% reduction in mortality from several leading non-communicable diseases, including diabetes, by 2025, and no increase in the prevalence of adult obesity and diabetes between 2010 and 2025.[(1)] In 2020, a report from the World Obesity Federation estimated that over 90% of countries globally, including Ireland, are not on track to meet these targets.[(2)] In March 2022, the International Diabetes Federation and World Obesity Federation published a policy brief recommending a renewed policy focus to reduce the burden of T2D and obesity, two pandemics linked in terms of pathophysiology and treatment.[(3)]

In Ireland, the demand for bariatric surgery exceeds supply, and is likely to continue to do so based on current epidemiological trends.[(4-6)] Implementation of a strategy to optimise the selection of candidates for surgery is a considerable challenge. In recent years there has been a shift in the focus of bariatric surgery from primarily a weight-loss intervention towards consideration of metabolic and cardiovascular outcomes. Evidence from randomised controlled trials (RCTs) (reviewed in chapter 4) indicate that bariatric surgery can achieve improvements in glycaemic control and a reduction in or discontinuation of anti-hyperglycaemic medications in patients with comorbid T2D and obesity. The benefits of bariatric surgery in this population have led to the coining of the term “metabolic surgery” to describe the use of bariatric surgical procedures with the intention of achieving improvements in glycaemic control in patients with comorbid T2D and obesity.

In 2016, a joint statement by international diabetes federations was published recommending the use of metabolic surgery to treat T2D in patients with class III obesity (BMI ≥40 kg/m^2) and class II obesity (BMI 35.0–39.9 kg/m^2), and potentially in those with class I obesity (BMI 30.0–34.9 kg/m^2), when hyperglycaemia is

inadequately controlled by lifestyle interventions and optimal medical management.[7] Since then, numerous national and international guidelines have been updated to include metabolic surgery in the treatment algorithm for T2D including guidance from the European Association for Endoscopic Surgery (EAES),[8] the American Diabetes Association (ADA),[9] the National Institute for Health and Care Excellence (NICE) in England,[10, 11] the Belgian Health Care Knowledge Centre (KCE),[12] the German Society for General and Visceral Surgery (DGAV),[13] and Obesity Canada.[14] Access to metabolic surgery is not currently provided within the diabetes clinical care pathway in Ireland.

It has been estimated that approximately 2% of the Irish population ≥50 years have T2D and a BMI of ≥35kg/m^2,[4] corresponding to an estimated 33,564 individuals based on census population projections for 2021. Of these, almost 50% have evidence of T2D-related complications including retinopathy, peripheral vascular disease or a previous myocardial infarction.[4] These existing estimates are in accordance with traditional BMI-based eligibility criteria, however the burden of comorbid T2D and obesity would be greater if the entire population of adults and those with class I obesity (BMI ≥30 kg/m^2) are considered, in line with current guidance from the ADA.[15] While not all patients with comorbid T2D and obesity will need or want metabolic surgery, a substantial proportion of patients are at an elevated risk of T2D- and obesity-related complications and may benefit from access to metabolic surgery. HIPE data indicate that in the public hospital system on average approximately 24% of patients accessing bariatric surgery between 2009 and 2019 had comorbid T2D and obesity; with an average of only 74 procedures undertaken each year, this would suggest that bariatric surgery is an underutilised resource for patients with T2D and obesity.[16] It was not possible to determine the level of activity in the Irish private healthcare system.

The clinical criteria, resource and infrastructural requirements for metabolic surgery services are distinct from bariatric surgery. The provision of metabolic surgery with the primary aim of treating T2D may have implications for clinical practice including the need for specific outcome measures (T2D remission), participation of appropriate multidisciplinary teams and support systems, as well as patient expectations.[17] This HTA will inform a decision regarding the introduction of a metabolic surgery programme as part of the T2D clinical care pathway in addition to the existing bariatric surgery services, and is not intended to inform re-prioritisation of access to bariatric surgery within the obesity treatment pathway. The aim of this assessment is to examine the clinical and cost-effectiveness of providing metabolic surgery services compared with best medical care (that is, behavioural intervention and optimal medical management) as part of the diabetes clinical care pathway in Ireland.

1.2 Terms of reference

The HTA will be submitted as advice to the HSE to inform a decision as to whether metabolic surgery services should be included as part of the diabetes clinical care pathway. In consultation with the HSE, HIQA's Evaluation Team developed a set of objectives with consideration to the evidence needs of the decision-makers.

The terms of reference of the HTA, agreed with the National Clinical Programme for Obesity and the National Clinical Programme for Diabetes are to:

- describe the treatment options for the management of T2D in adults with obesity in Ireland
- describe the burden of disease and outcomes associated with T2D in adults with obesity in Ireland
- review the current evidence of clinical effectiveness and safety of metabolic surgery in adults with T2D and obesity with a clinical indication for surgery
- review the current evidence of cost-effectiveness of metabolic surgery in adults with T2D and obesity with a clinical indication for surgery
- assess the clinical outcomes, cost-effectiveness and budget impact of providing metabolic surgery services, specifically for the treatment of obesity and T2D in the context of the Irish public healthcare system
- consider any potential organisational and resource implications of providing metabolic surgery services in Ireland
- consider any ethical and social implications that the provision of metabolic surgery services may have for patients, the general public or the healthcare system in Ireland
- based on the evidence in this assessment, provide advice to the decision maker on whether and for whom metabolic surgery should be provided for the treatment of T2D as part of the diabetes clinical care pathway.

1.3 Overall approach

Following initial scoping of the available evidence, the terms of reference of this assessment were agreed between HIQA and the HSE. HIQA appointed an Evaluation Team comprising staff from the HTA Directorate to carry out the assessment.

HIQA convened an Expert Advisory Group comprising representation from key stakeholders including the Health Service Executive, clinicians with specialist

expertise in the management of patients with comorbid T2D and obesity, methodological experts and patient representation. The role of the Expert Advisory Group is to inform and guide the process, provide expert advice and information, and to provide access to data where appropriate. A full list of the membership of the Expert Advisory Group will be made available in the acknowledgements section of this report.

The Terms of Reference of the Expert Advisory Group are to:

- contribute to the provision of high quality and considered advice by the Authority to the Health Service Executive
- contribute fully to the work, debate and decision making processes of the group by providing expert guidance, as appropriate
- be prepared to provide expert advice on relevant issues outside of group meetings, as requested
- provide advice to the Authority regarding the scope of the analysis
- support the Evaluation Team led by the Authority during the assessment process by providing expert opinion and access to pertinent data, as appropriate
- review the project plan outline and advise on priorities, as required
- review the draft report from the Evaluation Team and recommend amendments, as appropriate
- contribute to the Authority's development of its approach to HTA by participating in an evaluation of the process on the conclusion of the assessment.

The Terms of Reference of the HTA were reviewed by the Expert Advisory Group at its first meeting. Draft chapters will be circulated to the Expert Advisory Group for review and discussed at three formal meetings of the group, with amendments made, where appropriate. The final version will be submitted to the Board of HIQA for approval. The completed assessment will be submitted to the Minister for Health and the HSE as advice, and published on the HIQA website.

HIQA is a national representative body for the European Network for Health Technology Assessment (EUnetHTA), which is funded by a grant from the European Commission. Its mission is to support collaboration between European HTA organisations and bring added value to healthcare systems at the European, national

and regional levels. It is intended that work undertaken by, and output from, EUnetHTA will be applicable at local, regional and national levels across Europe and will therefore limit unnecessary duplication of research and improve efficiency in the assessment of new medical technologies. In 2019, HIQA agreed to act as co-author for a relative effectiveness assessment of surgical methods for treating people with morbid obesity as part of its commitment to EUnetHTA. Work completed as part of this collaborative assessment was considered in the findings of this HTA. The assessment, led by The Norwegian Institute of Public Health (NIPH), was published by EUnetHTA in August 2021.[18]

2 Description of the Technology

Key points

- Diabetes is a chronic, metabolic disease characterised by hyperglycaemia (elevated levels of blood glucose) in the absence of treatment and is caused by defects in insulin secretion, insulin action or both. Excess weight is a risk factor for the development of type 2 diabetes mellitus (T2D) and other metabolic and cardiovascular complications.
- Diagnosis of T2D and ongoing measurement of glycaemic control is carried out using validated plasma glucose criteria and, or HbA1c concentrations.
- The long-term vascular complications of diabetes can be divided into microvascular and macrovascular complications which affect small and large blood vessels, respectively. Intensive glycaemic control can reduce the risk or slow the progression of diabetes-related complications.
- Standard care for patients with comorbid T2D and obesity includes diabetes self-management education and support (that is, nutrition therapy, physical activity, smoking cessation and diabetes self-management support) with or without anti-hyperglycaemic medication(s). Metabolic surgery is not currently included within the T2D clinical care pathway in Ireland.
- Bariatric surgery alters the anatomy and physiology of the gastrointestinal tract. Metabolic surgery refers to the use of bariatric surgical procedures with the intention of achieving improvements in T2D control in patients with comorbid T2D and obesity.
- The ultimate goal of treatment is to reduce the risk of micro- and macrovascular complications through the control of glycaemia and cardiovascular risk factors.
- There is no internationally accepted and routinely implemented definition of T2D remission.
- Metabolic surgery is now recommended for inclusion within the T2D treatment algorithm by the American Diabetes Association (ADA), the International Diabetes Federation (IDF) and the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO). Established bariatric procedures in current use for the treatment of obesity and obesity-related comorbidities include adjustable gastric banding (AGB), sleeve gastrectomy, Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion with duodenal switch (BPD-

DS). Other newer or alternative procedures are in development, but are not widely available in Ireland or other European countries.

- Indications for metabolic surgery vary internationally. Traditionally, metabolic surgery is indicated for patients with obesity and a BMI ≥40 kg/m^2, or BMI 35-39.9 kg/m^2 and obesity-related comorbidities. In some countries, it is considered as a treatment option for patients with a BMI 30-34.9 kg/m^2 with T2D above treatment targets. Lower BMI thresholds are used for some ethnic groups.

2.1 Introduction

The purpose of this chapter is to describe the use of metabolic surgery for the treatment of comorbid type 2 diabetes (T2D) and obesity. To facilitate understanding, a brief description of the disease, the methods and criteria for diagnosing T2D and a brief description of current approaches to disease management are provided. The various types of metabolic procedures are described in detail.

2.2 Relationship between obesity and T2D

Obesity is a chronic, complex, progressive disease characterised by excessive adipose tissue mass that can result in multiple organ-specific consequences resulting in adverse metabolic, biomechanical and psychosocial consequences.[19-22]

Obesity places physiological demands on almost every organ system including the cardiovascular, respiratory and musculoskeletal systems. Many of the complications of obesity are driven by adipose tissue dysfunction which usually occurs due to pathological expansion of fat mass (hypertrophic adipose tissue cells) and or unhealthy body fat distribution (central and visceral adiposity) resulting in inflammatory and cardio-metabolic derangements.[23] The adverse cardiovascular, metabolic and inflammatory profile observed in obesity increases the risk of developing insulin resistance, which over time may progress to T2D and the development of diabetes-related complications. Improvements in glycaemic control in those with comorbid T2D and obesity are usually accompanied by significant and sustained weight loss. The underlying mechanism of action is believed to be a reduction in intra-organ fat content, including the liver and pancreas, facilitating recovery of the insulin-producing pancreatic β cells.[24-26]

Body mass index (BMI) is the most widely used proxy to estimate excess adiposity at a population level, and is easily calculated using a person's weight and height.[22]

BMI is interpreted using standardised weight categories, regardless of sex or age, although cut-offs can vary based on ethnicity.[27, 28] The World Health Organization (WHO) definitions of overweight and obesity sets BMI cut-off points of 25-29.9 kg/m^2 and greater or equal to 30 kg/m^2, respectively (based on Europeans with a Western lifestyle) (Table 2.1).[22] In general, as BMI increases so does the risk of complications related to excess adiposity, such as T2D.[27] It is increasingly recognised that the relationship between obesity and the development of obesity-related complications, such as T2D, is not straightforward. Body fat mass as measured with BMI does not always adequately correlate with the risk of obesity-related complications,[7, 23, 29] although at a population level it can be used as an indicator of risk.

Table 2.1. Weight-related risk of obesity-associated comorbidities based on WHO BMI ranges[27]

WHO Classification (Europeans)	BMI (kg/m^2)	Risk of obesity-related complications
Underweight	<18.5	Low†
Normal range	18.5 - 24.9	Average
Overweight	25.0 - 29.9	Increased
Obese	≥30	
Obese class I (mild)	30.0 – 34.9	Moderate
Obese class II (severe)	35.0 – 39.9	High
Obese class III*(morbid)	≥40.0	Very high

Key: BMI – Body Mass Index; WHO – World Health Organization.
*Commonly referred to as morbid or extreme obesity.
†The comorbidities associated with underweight are distinct from those associated with increased adiposity. At a BMI <18.5, the risk of other clinical problems is increased.
Source: World Health Organization 2000.[27]

2.3 Diabetes

Insulin is a hormone produced by the endocrine pancreas that regulates the body's blood sugar levels. Deficient action of insulin on target tissues due to inadequate insulin secretion and/or diminished tissue responses to insulin causes blood glucose levels to become elevated above the normal range, a condition known as hyperglycaemia.[30] Diabetes is a chronic, metabolic disease characterised by

hyperglycaemia in the absence of treatment and is attributable to defects in insulin secretion, insulin action or both leading to disturbed glucose metabolism.[31, 32] Over time hyperglycaemia can lead to clinically significant damage to the heart, blood vessels, eyes, kidneys, and nerves in addition to other complications.[32]

The underlying cause of diabetes varies by type. The most common types of diabetes are type 1, type 2 and gestational diabetes.[32] There are also other rare types of diabetes.[31] T2D accounts for the vast majority of diagnosed diabetes cases.[33] This assessment is specifically concerned with the management of T2D. Although diabetes-related complications are similar for type 1 and type 2 diabetes, the frequency and time of onset can vary.

2.3.1 Type 2 diabetes

Individuals with T2D (formerly called adult-onset or non-insulin-dependent diabetes) usually have insulin resistance accompanied by relative (rather than absolute) insulin deficiency.[34] The degree of pancreatic β-cell secretory dysfunction and insulin resistance varies between individuals.[31] In patients with pre-diabetes (that is, blood sugar levels are elevated above normal, but are not high enough to be considered diagnostic of T2D) or T2D, the body's cells do not respond fully to insulin (known as insulin resistance), resulting in elevated blood sugar levels.[35] This leads to a compensatory increase in insulin secretion by pancreatic β-cells to maintain normoglycaemia.[35] When the compensatory process is adequate, normal blood glucose levels can be maintained.[35] However, over time, failure of β-cell compensation, against a background of increasing insulin resistance results in increased blood glucose levels, ultimately leading to either impaired glucose tolerance or the development of T2D.[35] T2D is commonly associated with overweight and obesity, which contribute to the development of insulin resistance, and typically occurs in the setting of the metabolic syndrome, characterised by abdominal obesity, hypertension, dyslipidaemia and hyperglycaemia.[31, 36]

T2D frequently goes undiagnosed for years because insulin resistance and the associated hyperglycaemia typically develop gradually over time and are often not severe enough in the early stages of the disease process for affected individuals to notice any of the classic symptoms of diabetes.[34] As a result, there is often a long pre-diagnostic period and the exact time of disease onset cannot be determined.[35]

Patients with T2D are at risk of developing macrovascular and microvascular complications associated with elevated blood sugar levels and other metabolic and cardiovascular complications.[34] In some individuals with T2D, adequate glycaemic control can be achieved with weight reduction, exercise and oral glucose-lowering agents.[34] Others who have minimal residual insulin secretion require exogenous

insulin for adequate glycaemic control. For individuals with extensive pancreatic β-cell destruction, and therefore no residual insulin secretion, exogenous insulin is necessary for survival.[34] The severity of hyperglycaemia can progress, regress, or stay the same over time, but is seldom restored to normal with pharmacological treatment and non-surgical weight-loss interventions.[34]

2.3.2 T2D-related complications

The long-term vascular complications of diabetes are divided into microvascular (involving small blood vessels such as capillaries) and macrovascular complications (involving large blood vessels such as arteries and veins).[37, 38]

Microvascular and macrovascular complications often occur concomitantly, and share similar risk factors and underlying pathological processes (Table 2.2). Chronic hyperglycaemia activates multiple biochemical pathways leading to endothelial dysfunction, resulting in anatomic, structural, and functional changes to the vasculature, potentially progressing to multi-organ dysfunction in the absence of appropriate treatment.[37] Interventions aimed at achieving glycaemic control reduce the risk that tissues in the body will become damaged in response to chronically raised blood glucose, and reduce the morbidity and mortality associated with these complications. The risk of developing vascular complications is proportional to both the magnitude and duration of hyperglycaemia, although genetic and environmental risk factors (for example, behavioural factors or access to care) affect an individual's risk of developing such complications.[36]

Table 2.2. T2D-related complications

T2D-related complication	Long-term clinical manifestations	Clinical risk factors*
Microvascular complications		
Retinopathy	Non-proliferative retinopathy, proliferative retinopathy; macular oedema; cataracts; glaucoma; visual impairment; blindness	▪ Metabolic syndrome ▪ Hypertension ▪ Dyslipidaemia ▪ Hyperglycaemia (duration and severity) ▪ Insulin resistance ▪ Overweight and obesity (particularly increased abdominal adiposity)
Nephropathy	Proteinuria; end-stage renal disease; kidney failure	
Neuropathy - autonomic (internal organs) - peripheral (extremities)	Ulceration; infection; sensory impairment (neuropathic pain and numbness); "Diabetic foot"; gangrene; non-traumatic lower extremity amputations	
Macrovascular complications		
Cerebrovascular disease	Stroke or TIA	▪ Hypertension ▪ Dyslipidaemia ▪ Hyperglycaemia (duration and severity) ▪ Insulin resistance ▪ Overweight and obesity (particularly increased abdominal adiposity)
Cardiovascular disease	Cardiovascular events e.g. coronary heart disease, angina, myocardial infarction, heart failure	
Peripheral vascular disease	"Diabetic foot"; intermittent claudication; non-traumatic lower extremity amputations	

Key: TIA - Transient ischemic attack.
*Not an exhaustive list.

Microvascular complications

Diabetic retinopathy refers to damage to the retina (that is, the light-sensitive layer of tissue at the back of the eye) leading to vascular abnormalities and can be divided into two phases: non-proliferative diabetic retinopathy (NPDR), potentially progressing to proliferative diabetic retinopathy (PDR).[38] During the non-proliferative phase, the earliest clinical manifestation of diabetic retinopathy is microaneurysm formation as a result of capillary occlusion, endothelial changes, increased capillary permeability and

increased intraluminal pressure.[38, 39] Non-proliferative retinopathy can progress from mild to severe as more capillaries become occluded resulting in more significant bleeding. As the disease progresses, ischemia (that is, restriction of blood supply and thus oxygen to body tissues), which occurs as a result of vascular occlusion, results in the activation of biochemical pathways leading to excessive overcompensatory growth of blood vessels that are often fragile and prone to leakage, characteristic of proliferative retinopathy.[39] Proliferative retinopathy can lead to blurring or loss of vision in advanced disease.[38, 40]

Diabetic nephropathy refers to the deterioration of kidney function.[41] Filtering of blood occurs in the kidney nephrons. Damage to capillaries in the kidney as a result of hyperglycaemia and hypertension means that the filtering function of the kidneys becomes compromised, leading to increased capillary permeability to macromolecules such as albumin (which are too big to pass through capillary walls under normal conditions). These proteins are then excreted in the urine (proteinuria).[38, 41] The first manifestation of diabetic nephropathy is typically microalbuminuria (that is, increased levels of a protein called albumin in the urine) which progresses to macroalbuminuria, indicating more severe renal dysfunction, which can eventually progress to end-stage renal disease and renal failure.[38, 41] However, disease progression is not a linear process for all patients. Albuminuria can be a dynamic, fluctuating condition.[42] Intensive glycaemic control may lead to improvements in or delay the progression of diabetic nephropathy.[41]

The pathophysiology of neuropathy in T2D is complex.[38] Diabetic neuropathy is recognised by the American Diabetes Association (ADA) as “the presence of symptoms and or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes.”[43] Diabetes is associated with dyslipidaemia, hyperglycaemia, and cell signalling abnormalities, leading to attachment of blood glucose to blood vessels and nerves (glycation) causing impairment of normal cellular and tissue functions.[38] Diabetic neuropathies are heterogeneous, affecting different parts of the nervous system that present with diverse clinical symptoms depending on the site of nerve damage, ranging from pain or numbness in the limbs (particularly the legs and feet) to impaired functioning of internal organs such as the heart and bladder.[43, 44]

Regular screening, particularly for those with poorly controlled diabetes including measurement of proteinuria, a comprehensive eye examination and assessment of signs and symptoms of diabetic neuropathy (for example, pain, numbness, or ulceration) is necessary to monitor for the onset or progression of nephropathy, retinopathy and neuropathy, respectively.[36, 38, 43]

Macrovascular complications

The underlying pathological process in macrovascular disease is atherosclerosis, characterised by the accumulation of atherosclerotic plaque in the coronary arteries, peripheral arteries, and cerebrovasculature, which leads to narrowing of the artery.(38) Over time the build-up of atherosclerotic plaque can lead to partial or complete obstruction of blood vessels. The resulting impairment of blood flow can increase the risk of macrovascular complications affecting the cardiovascular system (for example, angina and myocardial infarction), the cerebrovascular system (for example, stroke) and the peripheral blood supply to the lower limbs (for example, intermittent claudication and peripheral tissue damage).(38)

The precise mechanisms by which diabetes enhances the atherogenic process are not fully understood, but are known to be multifactorial, including complex interactions between metabolic, genetic and environmental risk factors. Although diabetes alone has been shown to be independently associated with an increased risk of cardiovascular disease,(45) people with T2D frequently have many traditional risk factors for cardiovascular disease including those of the 'metabolic syndrome' characterised by abdominal obesity, hypertension, and dyslipidaemia (that is, increased serum triglyceride, low density lipoprotein (LDL) and free fatty acid levels and decreased high-density lipoprotein (HDL) levels) in addition to hyperglycaemia.(38) The combination of hyperglycaemia, insulin resistance, dyslipidaemia, hypertension, and chronic inflammation frequently observed in those with comorbid T2D and obesity can cause pathological changes in the vascular endothelium over time leading to macrovascular complications.(38) The prevention of diabetic macrovascular complications, therefore, requires reduction of multiple other risk factors, in addition to achieving and maintaining good glycaemic control.

2.4 Methods and criteria for diagnosis

During the natural history of all types of diabetes, the condition progresses through a stage of altered glucose metabolism. During this time, measured blood glucose levels do not meet the criteria for diabetes; however, they are too high to be considered normal.(34) Above the normal range, the risk of developing T2D increases progressively with increasing blood glucose levels.(34) "Prediabetes" includes impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), measured using the two hour post-prandial glucose test and the fasting blood glucose test, respectively. IGT and IFG are said to be the intermediate hyperglycaemic states between normal glucose levels and those typically associated with diabetes.(32) While intermediate hyperglycaemic states are thought to be the precursors of T2D, progression is not inevitable.(32, 34)

There is no single assay that can be considered the gold standard for the diagnosis of diabetes.[46] Four diagnostic tests are currently recommended by the International Diabetes Federation (IDF),[33] the World Health Organization (WHO)[31] and the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD)[47] namely, measurement of fasting plasma glucose, 2-hour post-prandial plasma glucose after a 75g oral glucose tolerance test (OGTT), glycated haemoglobin (HbA1c) or a random blood glucose in the presence of signs and symptoms of diabetes. Any one of these tests can be used to diagnose diabetes. ESC/EASG Guidelines recommend glucose testing with HbA1c and/or fasting plasma glucose initially, followed by an oral glucose tolerance test in the case of inconclusive results.[47] Repeat testing on a subsequent day is usually required to confirm the diagnosis, particularly in asymptomatic individuals.[47, 48]

Table 2.3. Diagnostic criteria for T2D

Test	Increased risk of diabetes	Diabetes
Fasting plasma glucose (FPG)	5.6 to 6.9 mmol/L (100-125 mg/dL)† *or* 6.1 and 6.9 mmol/L (110-125 mg/dL)‡	≥7.0 mmol/L (≥126 mg/dL)
2-hour glucose following ingestion of 75g glucose load (OGTT)	≥7.8 to <11.0 mmol/L (≥140–199 mg/dL)	≥11.1 mmol/L (≥200 mg/dL)
HbA1c*	42-47 mmol/mol (5.7% to 6.4%)	48 mmol/mol (≥6.5%)
Random plasma glucose in a symptomatic patient		11.1 mmol/L (≥200 mg/dL)

Key: HbA1c - glycated haemoglobin.
Source: WHO 2019;[31] IDF 2017;[33] ESC/EASD 2019.[47]
* Standardised results of the HbA1c test can be reported in accordance with two reference measurement systems: the Diabetes Control and Complications Trial (DCCT), given as a percentage, or the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), expressed as mmol/mol.[49] Since 2010, laboratories in Ireland have reported HbA1c in accordance with the IFCC reference measurement system.[49]
† ADA 2020.[34]
‡ WHO 2011.[48]

The diagnostic thresholds for diabetes, outlined in Table 2.3, are based on the correlation of these values with the risk of developing microvascular complications,[47] although blood glucose levels begin to have an impact on morbidity and mortality even below the diagnostic threshold.[32, 46] The relationship between chronic hyperglycaemia and the risk of long-term complications of T2D may be better expressed as a disease continuum (that is, extending below the lower limit

of the range and becoming disproportionately greater at the upper end of the range)[34], rather than as a strictly dichotomous relationship, particularly in relation to interventions to reduce the risk of long-term complications.

The available diagnostic testing methods reflect different physiological measures of glucose metabolism, thus the tests are not completely concordant.[50, 51] Direct blood glucose tests (fasting plasma glucose, oral glucose tolerance test, and random plasma glucose) measure blood glucose levels at a single point in time. Limitations of these tests include the requirement for fasting, and day-to-day variance in fasting blood glucose levels.[48] HbA1c (also called, A1c, haemoglobin A1c, glycated haemoglobin) is a form of haemoglobin that is chemically linked to glucose. As red blood cells have a life of approximately three months, measurement of HbA1c levels can be used as an indirect measure of average glucose levels during that period.[52]

2.5 Management of T2D

Appropriate disease management including key interventions and regular follow-up can potentially prevent complications and premature mortality associated with T2D. A range of treatment options are available, with significant advances made in recent years. Components of the T2D management pathway can include:[7, 32, 53]

- glucose monitoring
- behavioural change including:
  - increased physical activity
  - nutrition therapy
  - smoking cessation, as appropriate
- diabetes self-management education and support (DSMES) to facilitate self-care
- pharmacological interventions to:
  - improve glycaemic control
  - manage cardiovascular risk (such as, statins, anti-hypertensive treatments)
  - improve both glycaemic control and cardiovascular risk factors using newer anti-hyperglycaemic agents (for example, sodium-glucose co-transporter-2 (SGL2T2) inhibitors)
  - manage diabetes-related complications (such as, fibrates for retinopathy; atypical analgesics for painful neuropathy)
- regular screening for early detection and treatment of complications (for example, retinopathy screening)
- metabolic surgery (in appropriately risk-stratified patients).[53]

T2D is heterogeneous in its clinical presentation, the frequency and severity of complications, and the response to treatment.[53] Therefore, optimal disease management is challenging and requires consideration at an individual level.[53] Guidance from the ADA and EASD guidelines recommend the use of tailored treatment approaches with consideration of a person's clinical status, environmental and other contextual factors to better predict clinical outcomes from available disease management strategies.[53]

Shared decision-making is important in discussions regarding changes to T2D management.[54] A patient-centred treatment approach that uses inclusive and non-judgmental language, elicits patient preferences and beliefs, and assesses potential barriers to care has been recommended in order to optimise clinical outcomes and health-related quality of life.[9] Healthcare professionals working with people living with comorbid T2D and obesity should aim to enable patients to make informed decisions regarding the best course of action to manage their disease and the associated complications.[55]

For some patients diabetes control may be above treatment targets despite best medical care. For these patients, timely recommendations regarding changes to the treatment approach such as access to self-management support services, intensification of pharmacological treatment, or referral to specialist services including metabolic surgery, should be made through discussion to facilitate informed consent.[54]

2.5.1 Treatment targets

It is suggested that an HbA1c of 53 to 58 mmol/mol (<7 to 7.5%) is a reasonable target for most adults with T2D in order to achieve a reduction in the risk of microvascular complications.[33, 47, 56, 57] Although the absolute risk reduction becomes smaller with decrements below this value, the risk of complications associated with T2D decreases with progressively lower values of HbA1c down to the normal range (that is, <38 mmol/mol (<5.6%)).[30] Glycaemic targets should be set on an individual basis with consideration of the clinical status and age of the patient.[47, 58] More stringent HbA1c targets (for example, <48 mmol/mol (<6.5%)) may be appropriate for selected patients (such as, younger patients, those with a recently diagnosed diabetes, absence of severe additional comorbidities) if they can be achieved without significant hypoglycaemia or other adverse effects of treatment.[33, 47, 56, 59] Less stringent goals (for example, HbA1c ≤ 58 mmol/mol (≤8%)) may be appropriate for patients with a history of severe treatment-related hypoglycaemia, limited life expectancy, advanced microvascular or macrovascular complications, multimorbidity

or where social circumstance preclude tight glucose control.[47] HbA1c values above 64 mmol/mol (8%) are generally considered unacceptable for most patients.[33]

T2D remission

There is no internationally agreed definition of T2D remission.[33, 60, 61] The term remission is used as opposed to cure due to the risk of future relapse, particularly if weight regain occurs.[60, 62] Three important considerations underlie a definition of remission, the:

- glycaemic threshold at which remission is said to have been achieved (normoglycaemia)
- absence of anti-hyperglycaemic medications
- duration over which glycaemic levels below the specified threshold should be maintained before remission can be diagnosed.[61]

In 2021, an international expert group convened by the ADA proposed a revised definition of T2D remission, namely HbA1c <48 mmol/mol (6.5%) measured at least three months after cessation of glucose-lowering pharmacotherapy.[62] This updates previous definitions proposed by the ADA for complete (HbA1c <6.0% (42 mmol/mol) or fasting glucose <100 mg/dl (< 5.6 mmol/l) of at least one year's duration in the absence of active pharmacologic therapy or ongoing procedures) and partial remission (HbA1c (<6.5%) or fasting glucose 100–125 mg/dl (5.6–6.9 mmol/l) of at least one year's duration in the absence of active pharmacologic therapy or ongoing procedures).[63] This revised HbA1c threshold is consistent with the definition of T2D remission recommended by the Association of British Clinical Diabetologists (ABCD) and the Primary Care Diabetes Society in terms of the recommended HbA1c threshold (<48 mmol/mol (<6.5%)), although the definitions differ in the recommended duration of glycaemic control below the diagnostic threshold for T2D necessary to diagnose T2D remission (3 months for the ADA versus 6 months for the ABCD together with the Primary Care Diabetes Society, respectively).[60] It is noted that there is considerable debate in the literature regarding the optimal duration over which HbA1c levels must be maintained to define remission. Shorter minimum durations have been favoured in recent guidelines with the aim of motivating patients to maintain healthy behaviours and well-being over a longer period.

2.5.2 Diabetes self-management education and support (DSMES)

Building positive health behaviours is an essential component of diabetes care and may comprise nutritional advice,, routine physical activity, smoking cessation counselling and self-management education and support.[64] Self-management

education and support interventions increase the patient's knowledge, skills and confidence in managing their diabetes by providing information and advice on factors that can influence blood glucose levels such as diet, weight management, alcohol, smoking, physical activity, medication and foot care.[58, 65]

The benefits of diabetes structured education from a patient perspective include:

- increased application by the individual of knowledge/understanding of diabetes
- self-empowerment with the person effectively and confidently participating in their own diabetes self-management
- psychological adjustment to living with diabetes
- improved undertaking of diabetes self-management behaviours
- improved clinical outcomes.[66]

DSMES should not be limited to the time of diagnosis. According to guidance from the ADA and the US Centers for Disease Control and Prevention (CDC), access to DSMES at other key times such as annually can help patients manage changing clinical (for example, T2D control above treatment targets, development of T2D-related complications) or personal circumstances that may impact glycaemic control.[67, 68]

Nutrition

For adults with T2D, nutrition therapy is needed to reduce body weight and attain individualised treatment targets including glycaemic, blood pressure and lipids. In Ireland, structured support for weight loss and guidance on appropriate food choices is provided to patients as part of diabetes self-management education and support, delivered individually or in a group setting, depending on an individual patient's needs.[58]

Physical activity

Increased physical activity and a reduction in sedentary behaviour is important for blood glucose management and overall health in individuals with comorbid T2D and obesity by contributing to reductions in HbA1c, blood pressure, and insulin resistance as well as improvements to lipid profiles.[69] Recommendations for physical activity are provided as part of DSMES and vary according to individual characteristics (for example, age or previous activity levels), obesity- or T2D-related health complications (for example, peripheral neuropathy, pre-proliferative or proliferative retinopathy, functional limitations) and treatment goals.[59, 69]

Smoking cessation

As part of DSMES, patients who smoke are provided with smoking cessation advice and referral to a smoking cessation service, where necessary.[58, 70]

2.5.3 Pharmacotherapy

Interventions supporting behaviour change and well-being generally have limited long-term success in maintaining adequate glycaemic and cardiovascular risk factor control as standalone interventions.[59] Pharmacological agents are typically needed to meet individualised treatment targets for the majority of patients.[59]

Pharmacological management of glycaemic control

Pharmacological treatment of diabetes includes glucose-lowering agents (also called anti-diabetes or anti-hyperglycaemic agents) and, or insulin treatment. Given the progressive nature of T2D, anti-hyperglycaemic treatment is typically increased in a stepwise manner in order to maintain glycaemic control. Metformin monotherapy is currently recommended by the ADA[54] and IDF[33] as the first-line pharmacological treatment in people with T2D, followed by dual or triple combinations later in the disease course. Insulin treatment may be necessary if oral anti-hyperglycaemic agents are not effective in controlling blood glucose levels to recommended levels (Figure 2.1).[35]

Some glucose-lowering agents can be associated with weight gain, hepatic, renal or cardiac impairments, among other side effects. For those with comorbid T2D and obesity, medications should be carefully selected to minimise the risk of exacerbating comorbid conditions.[28, 71, 72] Diabetes medications that are associated with modest weight loss or are weight-neutral are preferable in patients with T2D and obesity.[28, 71, 72]

Guidance from the American College of Cardiology (ACC) and the ADA recommend that a decision to initiate one of the suggested therapies should be made through a shared-decision-making approach involving discussion between the patient and clinician with consideration to drug-specific effects and patient factors. [54, 73] Relevant efficacy and patient factors include:

- comorbidities such as atherosclerotic cardiovascular disease (ASCVD) and indicators of at-risk of ASCVD chronic kidney disease (CKD), and heart failure
- hypoglycaemia risk
- effects on body weight
- side effects or contraindications

- cost
- patient preferences.[74]

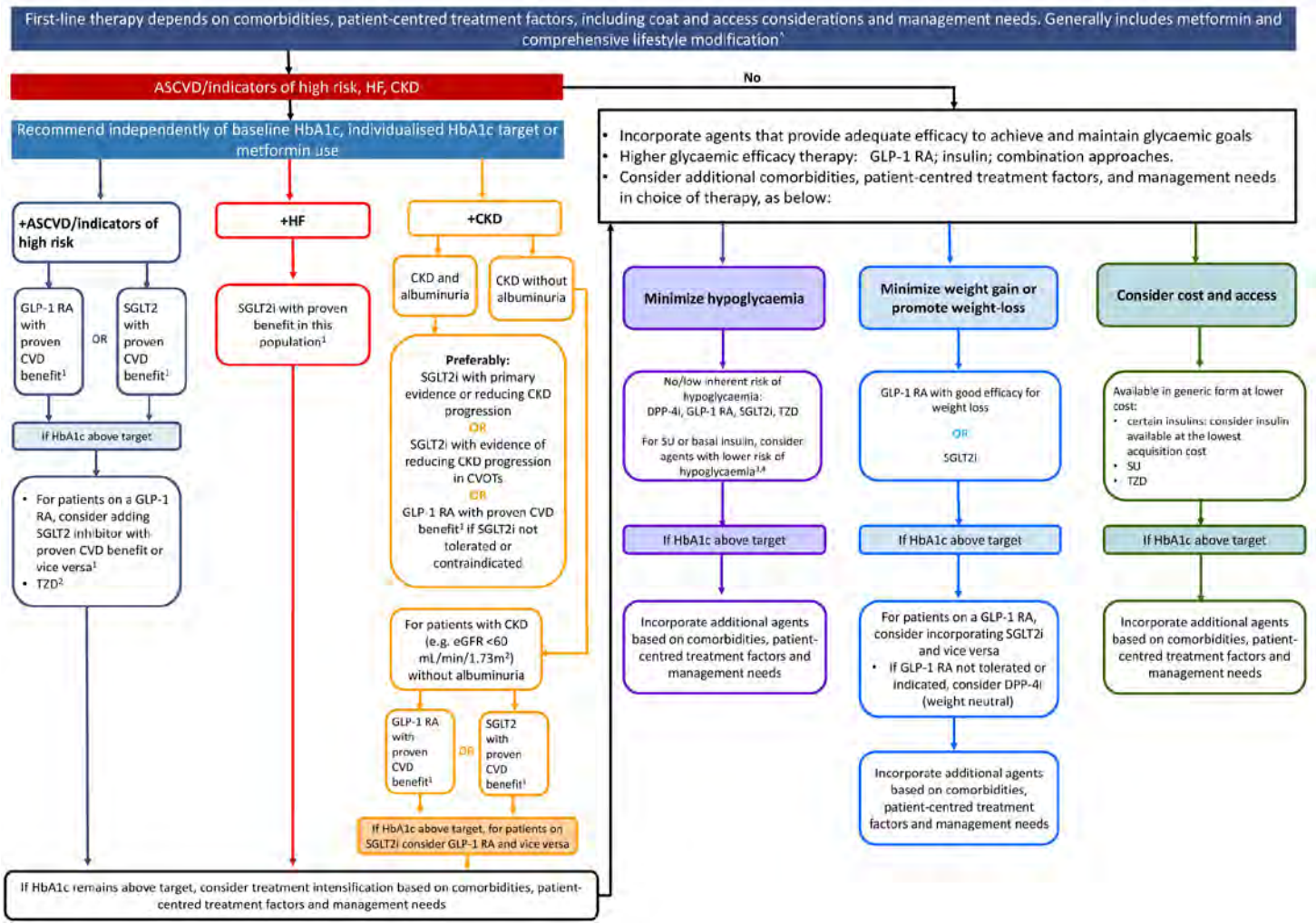
Cardiovascular risk factor reduction

In addition to interventions to support behaviour change, pharmacological cardiovascular risk factor reduction is an important component of T2D management for many patients as conditions such as hypertension and dyslipidaemia frequently coexist in patients with comorbid T2D and obesity.[75] Cardiovascular risk factor reduction can include:

- treatment of hypertension with angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, thiazide-like diuretics, or dihydropyridine calcium channel blockers
- treatment of dyslipidaemia with statins or other lipid-lowering agents
- anti-platelet agents such as aspirin in patients at increased risk of recurrent cardiovascular events (secondary prevention).[75]

Two classes of glucose lowering agents, sodium-glucose co-transporter 2 (SGLT-2) inhibitors and glucagon-like peptide 1 receptor agonists (GLP-1RA), have also been shown to reduce cardiovascular risk in patients with T2D and CVD.[73]

Figure 2.1. Algorithm for anti-hyperglycaemic agent selection with consideration to drug-specific and patient factors



Key: ASCVD - atherosclerotic cardiovascular disease; CKD - chronic kidney disease; CVD - cardiovascular disease; CVOTs - cardiovascular outcomes trials; DPP-4i - dipeptidyl peptidase 4 inhibitor; eGFR - estimated glomerular filtration rate; GLP-1 RA - glucagon-like peptide 1 receptor agonist; HF - heart failure; SGLT2i - sodium–glucose co-transporter 2 inhibitor; SU - sulfonylurea; T2D - type 2 diabetes; TZD - thiazolidinedione.

1 Proven CVD benefit refers to label indication.
2 Low dose may be better tolerated though less well studies for CVD effects.
3 Choose later generation SU to lower risk of hypoglycaemia.
4 Risk of hypoglycaemia: degludec / glargine U-300 <glargine U-100 / detemir <NPH insulin.
5 Consider country- and region-specific cost of drugs.

^For adults with overweight or obesity, lifestyle modification to achieve and maintain ≥5% weight loss and ≥150 min/week of moderate- to vigorous-intensity activity is recommended.

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

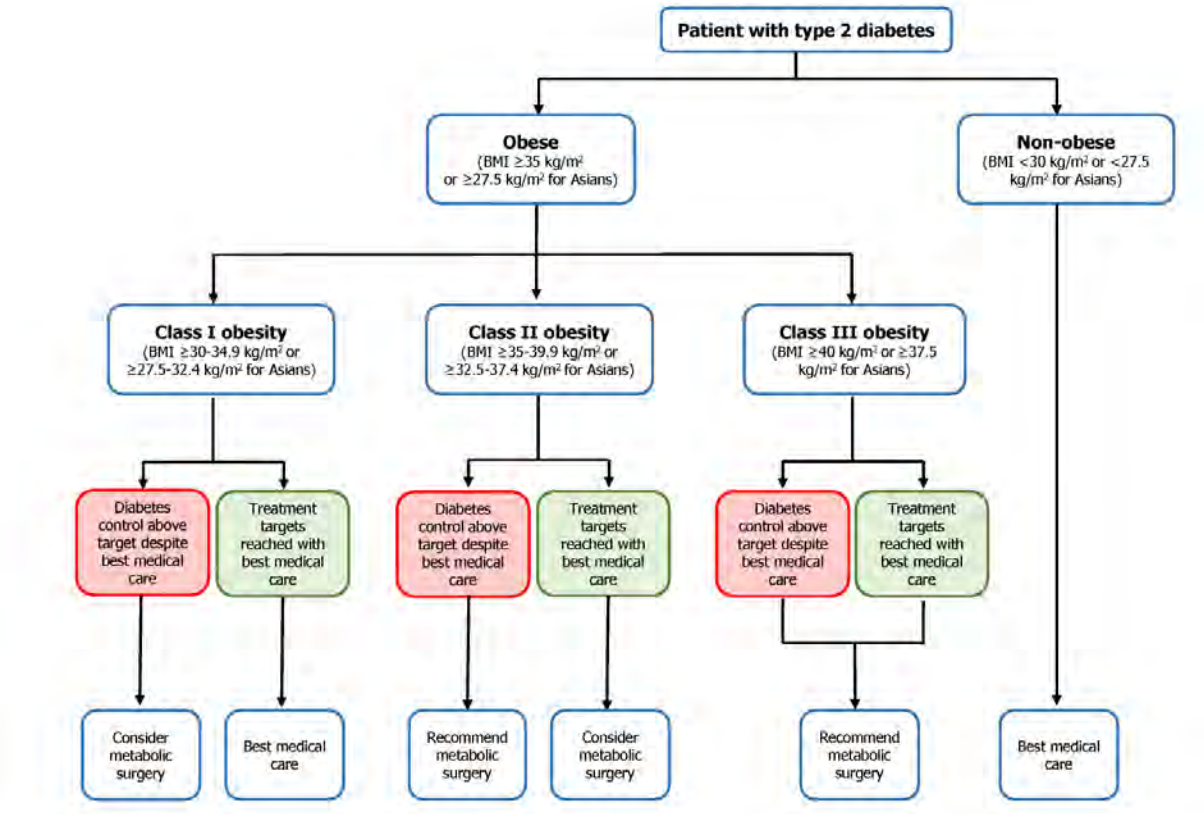
‡ Most patients enrolled in relevant trials were on metformin at baseline as glucose-lowering therapy.

2.5.4 Metabolic surgery

Traditionally, T2D has been treated with oral medication with or without injectable agents. Nevertheless, despite escalation of care along the treatment pathway and use of maximal tolerated doses, some patients have T2D control above treatment targets.

For the purposes of this assessment, metabolic surgery refers to the use of bariatric surgical procedures with the intention of treating metabolic complications in patients with comorbid T2D and obesity (Figure 2.2). The various types of metabolic surgery available in Ireland are described in the following sections. Endoluminal procedures (that is, non-surgical weight-loss interventions performed by entering the gastrointestinal tract that do not require external incisions) are beyond the scope of this assessment.

Figure 2.2 Metabolic surgery in the treatment algorithm for T2D



Traditionally, metabolic surgical procedures have been divided into restrictive, malabsorptive or a combination of both.[76] Restrictive procedures produce early satiety and a consequent reduction in food intake by reducing the capacity or size of the stomach while maintaining the normal continuity of the gastrointestinal tract.[77] Examples of such procedures include laparoscopic adjustable gastric banding (LAGB), and laparoscopic sleeve gastrectomy (LSG).[76] Malabsorptive techniques bypass parts

of the digestive tract and divert biliopancreatic secretions.[76, 77] Any procedure that dramatically alters the structure of the gastrointestinal tract will affect the intake of nutrients. Roux-en-Y gastric bypass (RYGB), one anastomosis gastric bypass (OAGB) and biliopancreatic diversion with duodenal switch (BPD-DS), can be defined as combination procedures, having both restrictive and malabsorptive features (Figure 1.3). It is now recognised that this categorisation represents a substantial oversimplification of the mechanisms of action of metabolic surgery.[76] Beyond the extensive metabolic and anatomical changes that accompany bariatric surgery, inflammatory responses, changes in neural and endocrine signalling, gut microbial factors as well as learned behaviour change contribute to the overall benefits of surgery.[76]

Adjustable gastric banding

Adjustable gastric banding (AGB) is considered a reversible intervention. During this surgery, the surgeon positions an inflatable ring or band around the uppermost part of the stomach, 1-2 cm below the gastro-oesophageal junction, separating the stomach into two parts (Figure 2.3a).[77, 78] The small upper gastric pouch above the band communicates with the rest of the stomach through a narrow channel created by the band.[79] Less food is required to fill the uppermost portion of the stomach, limiting the amount of food that can be eaten.[79] The band is connected to a small device, called a port, placed under the skin.[78, 79] The tightness of the band can be adjusted by injecting or removing saline solution through a subcutaneous port.[78, 79]

While the surgery is less likely to result in nutritional problems, band-related failure or complications in the medium- to long-term (for example, band slippage/migration, erosion) necessitating revision surgery and insufficient weight loss in the long-term have led to a decline in the use of this procedure in some countries.[7, 71, 80]

Sleeve gastrectomy

With sleeve gastrectomy (also known as vertical sleeve gastrectomy or gastric sleeve surgery), most of the stomach is removed, with only a tube-shaped portion, or "sleeve" remaining with a capacity of approximately 100-200 mL (Figure 2.3b).[81-83] This restricts the amount of food that the stomach can accommodate and accelerates gastric emptying.[83] Removing part of the stomach may also affect gut hormones (for example, ghrelin) or other factors such as the gut microbiome that may impact appetite and metabolism.[78, 83] Sleeve gastrectomy can be a valuable option to treat obesity and obesity-related comorbidities, especially in patients for whom there are concerns regarding the risk of post-operative nutritional complications associated with procedures that involve bowel diversion.[7, 82]

Sleeve gastrectomy may be carried out as a standalone procedure, or as a first-stage procedures in patients at high risk of complications from surgery.

Roux-en-Y gastric bypass

A Roux-en-Y gastric bypass (RYGB, often abbreviated to gastric bypass) is carried out in three steps (Figure 2.3c).[78] The stomach is first divided into two sections to create a small pouch with 15-30 mL capacity at the uppermost part of the stomach which results in restriction of food intake.[78, 82] Next, an incision is made in the jejunum (that is, the second part of the small intestine), and the gastric pouch is then directly anastomosed (connected) to the distal end of the jejunum creating a "Roux" limb of typically 100–150 cm.[82] Food enters the small pouch of stomach and then passes into the jejunum, thereby bypassing the majority of the stomach, the duodenum (the first part of the small intestine) and some of the jejunum leading to decreased absorption of nutrients.[78] Finally, bowel continuity is restored by reconnecting the excluded biliopancreatic limb (that is, the excluded proximal end of the jejunum and the remainder of the stomach) to the Roux limb further down the small intestine to allow some stomach acid and digestive enzymes to eventually mix with the food to facilitate digestion and minimise nutritional deficiencies.[82]

RYGB is considered a reasonably challenging procedure to perform from a technical point of view as it requires the formation of two anastomoses.[80]

One anastomosis gastric bypass

The one anastomosis gastric bypass (OAGB, also known as the single anastomosis gastric bypass, mini-gastric bypass (MGB) or omega-loop gastric by-pass) differs from the traditional RYGB which requires two anastomoses, but still combines both restrictive and malabsorptive mechanisms (Figure 2.3e).[80] Although OAGB is a relatively recently developed procedure, it is now considered an acceptable mainstream surgical option.[84]

During an OAGB procedure the upper part of the stomach is divided into a tube. The tubular gastric pouch is then anastomosed to a loop of intestine, thereby bypassing the duodenum, and some of the jejunum.[85] The length of the bypassed portion of the small intestine (the biliopancreatic limb) influences absorption capacity. Variable limb lengths have been investigated in order to identify the optimal balance between weight loss and comorbidity improvement, and long-term nutritional deficiencies.[86, 87]

Patients undergoing OAGB are thought to be at a lower risk of anastomotic leak and perioperative complications in comparison to RYGB, however long-term comparative

data are lacking.[8, 80] The risk benefit-balance for this procedure is not yet fully understood.[80]

Biliopancreatic diversion with duodenal switch

Biliopancreatic diversion with duodenal switch (BPD-DS, sometimes abbreviated to duodenal switch) involves two separate components (Figure 2.3f).[88] The first part is similar to gastric sleeve surgery. A substantial proportion of the stomach is removed, leaving behind a smaller tubular-shaped stomach pouch.[88] The second part of the surgery is similar to the gastric bypass, except a larger portion of the small intestine is bypassed. An incision is made in the duodenum (the first part of the small intestine) just past the outlet of the stomach. The distal (farthest) portion of the small intestine is then connected to the outlet of the tubular-shaped stomach pouch created in the first part of the surgery.[88] Food passes through the newly created stomach pouch and empties directly into the last segment of the small intestine. Approximately 75% of the small intestine is bypassed.[88] The bypassed portion of the small intestine that contains bile and pancreatic enzymes necessary for the digestion and absorption of food is reconnected to the last segment of the small intestine to facilitate digestion and nutrient absorption.[88] The surgery also affects guts hormones in a manner that impacts hunger and satiety as well as blood sugar control.[88]

As food does not mix with bile and pancreatic enzymes until very far down the small intestine, the absorption of calories and nutrients (particularly protein and fat), as well as nutrients and vitamins dependent on fat for absorption (that is, fat soluble vitamins and nutrients), is significantly decreased. While the surgery is very effective, particularly in terms of glycaemic control, it is technically difficult to perform resulting in an increased risk of surgical complications and often leads to nutritional problems making its risk-benefit profile less favourable than that of the other metabolic procedures for most patients.[7, 76, 88] DSS-II recommendations suggest that BPD-DS should be considered only in patients with extreme levels of obesity (for example, BMI 60 kg/m^2) due to the risk of nutritional deficiencies.[7]

New and investigational procedures

Single anastomosis duodenal-ileal bypass with sleeve gastrectomy

Single anastomosis duodenal-ileal bypass with sleeve gastrectomy (SADI-S, also known as one anastomosis duodenal switch (OADS)) was proposed as an alternative to the currently accepted BPD-DS procedure which is technically challenging to perform and can be associated with clinically significant nutritional complications.[89, 90]

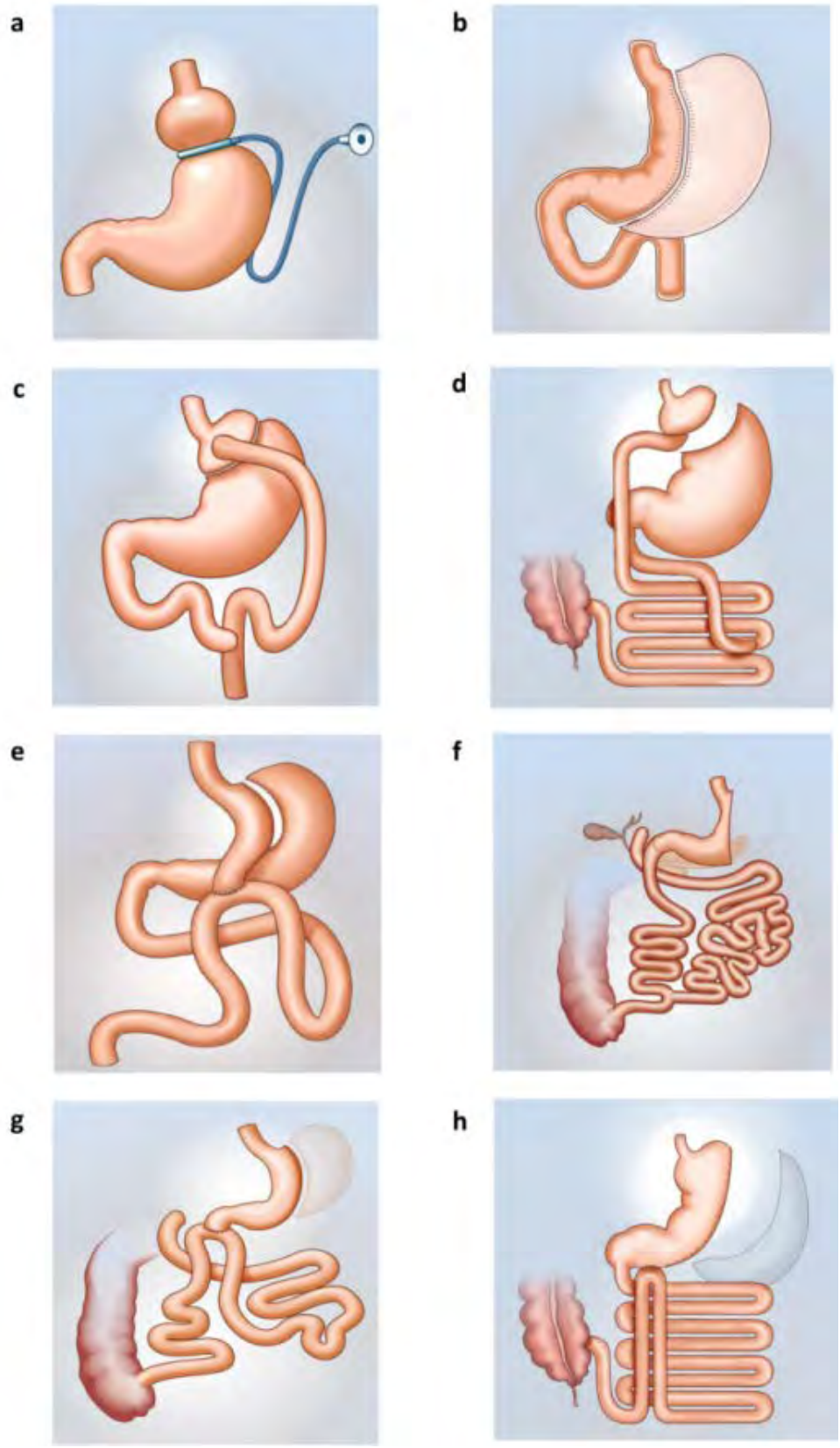
Initially, the size of the stomach is reduced through a sleeve gastrectomy (Figure 2.3g).[91] The duodenum is then divided leaving a short segment of duodenum attached to the pylorus (that is, the opening from the stomach into the duodenum). The distal end of the duodenum is closed off permanently.[91] A loop of small bowel, usually 200 to 300 cm from the ileocaecal valve, is anastomosed to the short segment of duodenum arising from the pylorus to restore gut continuity.[91]

The advantage of conserving the pylorus includes a potential reduction in the risk of post-surgical gastrointestinal disturbances such as dumping syndrome (that is, the contents of the stomach move too quickly into the small intestine resulting in symptoms such as nausea or diarrhoea) or biliary reflux.[92] The single anastomosis may also reduce the risk of surgical complications.[90]

Single anastomosis sleeve ileal bypass

Single anastomosis sleeve ileal bypass (SASI) bypass is a novel procedure in which a sleeve gastrectomy is followed by a single anastomosis between the reduced gastric pouch and the ileum (that is, the final part of the small intestine) (Figure 2.3h).[93] This creates two potential routes for the transit of food; through the newly-created gastro-ileal anastomosis into the final part of the small intestine, and also via the normal route through the duodenum.[94] As the procedure does not exclude any part of the small intestine, the risk of nutritional deficiencies and malabsorption may be decreased relative to other malabsorptive procedures.[94-96]
In SASI bypass, compared to SADI-S, the duodenum is not transected and the anastomosis is created between the gastric pouch and the ileum as opposed to the first part of the small intestine and the ileum.[94]

Figure 2.3 Metabolic surgery procedures



(a) Adjustable gastric banding (AGB); (b) sleeve gastrectomy (SG); (c) Roux-en-Y gastric bypass (RYGB); (d) Distal Roux-en-Y gastric bypass (D-RYGB); (e) One anastomosis gastric bypass (OAGB); (f) Biliopancreatic diversion with duodenal switch (BPD-DS); (g) Single anastomosis duodenal-ileal bypass with sleeve gastrectomy (SADI-S); (h) Single anastomosis sleeve ileal (SASI) bypass.

Reproduced with permission from Haute Autorité de Santé (HAS)[92, 97, 98] and Norwegian Institute of Public Health (NIPH).[18]

Surgical approach

Metabolic surgery can be performed through open or laparoscopic (also known as "keyhole" surgery or minimally invasive surgery) modalities.[78] According to EAES guidelines, laparoscopic surgery is now considered the gold standard approach for bariatric surgery, and should be undertaken in the absence of contra-indications.[8] According to the 2019 IFSO 5th global registry report,[99] which included data from 61 countries, between 2015 and 2018, 99.1% of procedures worldwide were carried out laparoscopically.

The benefits of laparoscopic surgery can include improved peri-operative outcomes (such as, reduced blood loss and pain) compared with open procedures as well as faster post-operative recovery resulting in shorter length of hospital stay.[78, 100]

While the mode of surgery is different for laparoscopic and open bariatric procedures, the techniques used to perform the procedure remain the same.

Choice of procedure

At present, there is no universal "gold standard" metabolic surgery procedure for all patients with comorbid T2D and obesity.[89] Guidance from the EAES published in 2020 has issued procedure-specific recommendations for the use of some well-established bariatric/metabolic surgical procedures in widespread use internationally (RYGB and sleeve gastrectomy).[8] However, for newer or investigational surgical procedures, specific recommendations to inform precise assignment of different procedures to individual patients could not be issued due to the absence of long-term direct comparative evidence.[8]

Selection of the most appropriate procedure for an individual patient is generally influenced by a number of factors including the best available evidence, the clinical experience and expert judgement of the multi-disciplinary team (MDT), the individual patient's medical history (including consideration of the individualised goals of therapy (for example, weight loss with or without a requirement for improved metabolic control)).[101, 102]

In general, increased surgical manipulation of the gastrointestinal tract is associated with improved weight-related outcomes and metabolic endpoints (for example, improvement or remission of T2D).[7] However, there is also a greater risk of post-operative complications with increased surgical complexity.[7] The clinical effectiveness and safety of currently available metabolic surgeries is described in Chapter 4.

2.6 International practice

Treatment algorithms

Treatment algorithms for bariatric surgery have traditionally been reported in obesity management guidelines. In recent years, guidelines from professional societies including the American Diabetes Association (ADA),[9] International Diabetes Federation (IDF)[33] and the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO)[89] have recommended adoption of a comorbidity-centric model for the selection of candidates for bariatric or metabolic surgery as opposed to traditional BMI-based eligibility criteria in order to facilitate prioritisation of access based on clinical need. According to these guidelines, metabolic surgery is recommended for the treatment of T2D and obesity when adequate glycaemic control and risk factor reduction cannot be achieved using non-surgical methods.

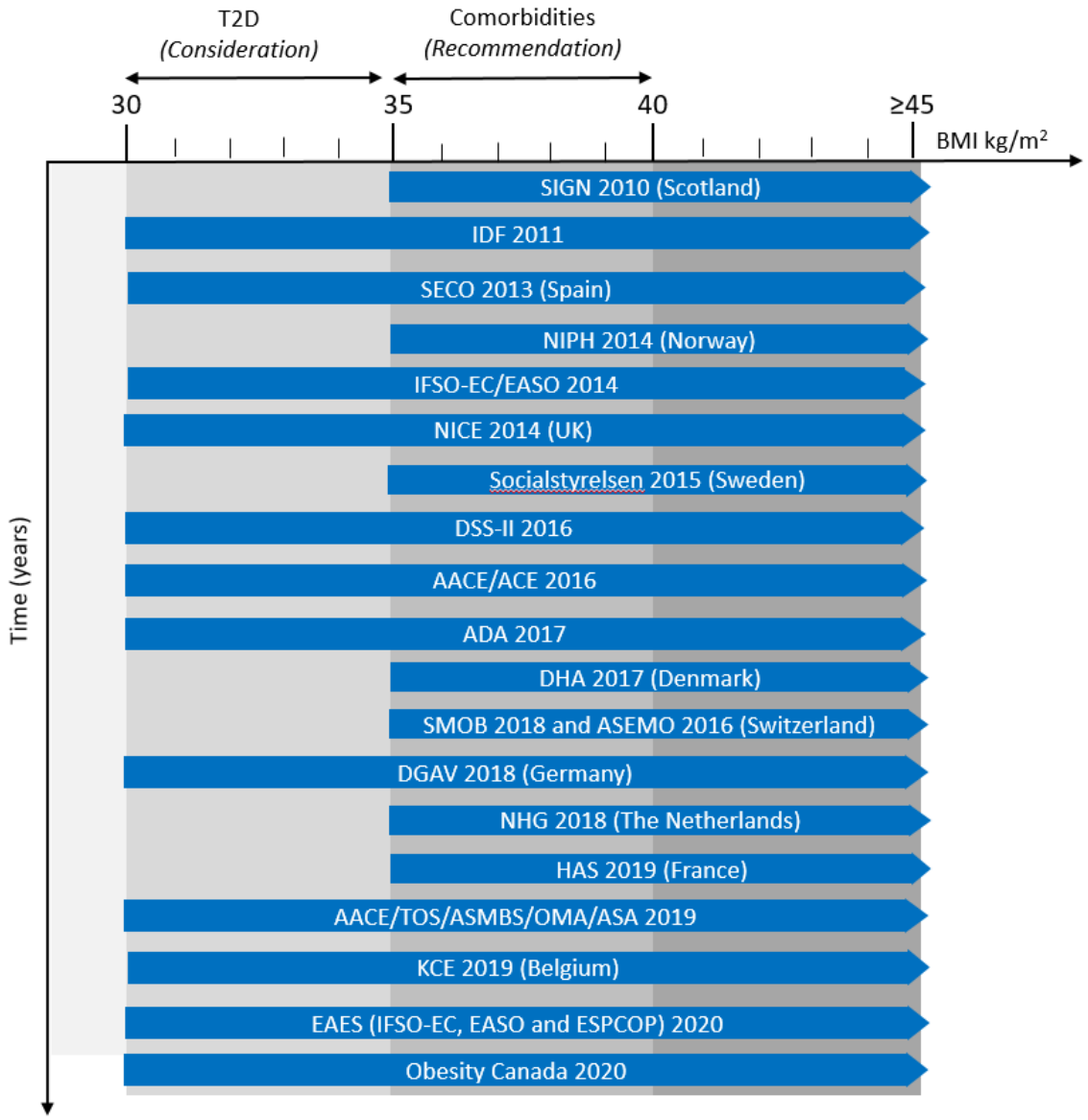
Guidance from England,[10, 11] Scotland,[103] Spain,[104] The Netherlands,[105] Sweden,[106] Norway[107] and Canada[71] specifically refer to metabolic surgery within T2D management guidelines. In France,[108] Switzerland[109] and Denmark[110] metabolic surgery is not described within T2D treatment algorithms. Metabolic surgery has also been recommended for the treatment of patients with T2D and obesity by the Belgian Health Care Knowledge Centre (KCE) within the context of the bariatric surgery services.[12] In Germany, bariatric and metabolic surgery are integrated into a single guideline.[13]

Of note, at the time of writing, assessments were underway by Haute Autorité de Santé in France and Ontario Health in Canada considering metabolic surgery for the treatment ofT2D and obesity.[111, 112]

Indications

The indications for surgery vary between countries and guidelines (Figure 2.4). In line with traditional eligibility criteria for bariatric surgery, guidance from Norway,[113] Sweden,[106, 114] Denmark,[115] Switzerland,[116, 117] France[108] Spain,[118] and The Netherlands[105] recommends access to bariatric or metabolic surgery for those with a BMI ≥40 kg/m or a BMI ≥35 kg/m^2 and obesity-related comorbidities. In England,[10, 11] Germany[13] and Belgium[12] the indications for metabolic surgery have been expanded to include patients with a BMI of 30-34.9 kg/m^2 and recent-onset[10] or inadequately controlled T2D.[13] Guidance from Spain (2013) and Norway (2018) outlined that there was insufficient long-term evidence to routinely recommend the use of metabolic surgery for individuals with T2D and a BMI <35 kg/m^2.[118, 119]

Figure 2.4 Minimum BMI and associated criteria for primary bariatric or metabolic surgery



Key: AACE - American Association of Clinical Endocrinologists; ACE - American College of Endocrinology; ADA - American Diabetes Association; ASEMO - Swiss Association for the Study of Obesity; ASMBS - American Society for Metabolic and Bariatric Surgery; DGAV - German Society for General and Visceral Surgery; DHA - Danish Health Authority; DSS - Diabetes Surgery Summit; EAES - European Association of Endoscopic Surgery; EASO - European Association for the Study of Obesity; ESPCOP - European Society for the Peri-operative Care of the Obese Patient; FHI - Swedish National Institute of Public Health; HAS - Haute Autorité de santé; IDF – International Diabetes Federation; IFSO-EC - European Chapter of the International Federation for the Surgery of Obesity and Metabolic Disorders; KCE - Belgian Health Care Knowledge Centre; NHG - Dutch College of General Practitioners; NICE - National Institute for Health and Care Excellence; NIPH - Norwegian Institute of Public Health; OMA - Obesity Medicine Association; SECO - Spanish Society for Obesity Surgery; SIGN - Scottish Intercollegiate Guidelines Network; SMOB - Swiss Society for the Study of Morbid Obesity and Metabolic Disorders; TOS - The Obesity Society.
* Refractory hypertension listed as an eligibility criterion in patients with class I obesity in EAES 2020 guidelines only.
Recommendations of each agency or society are available in Appendix 1.

2.7 Discussion

T2D is a chronic, metabolic disease associated with significant morbidity and mortality as a result of microvascular and macrovascular complications. The risk of developing vascular complications of diabetes and progression to severe disease can be reduced with tight glycaemic control.

Current treatment for patients with comorbid T2D and obesity includes self-management education and support and multicomponent behavioural interventions (such as, dietary changes, physical activity and smoking cessation advice) and cardiovascular risk factor reduction in addition to anti-diabetes medication(s) with or without insulin. The term lifestyle intervention is widely used in the literature to refer to any intervention that includes components such as nutritional therapy, exercise, smoking cessation, psychological counselling or peer support.[120] However it is recognised that social determinants of health such as access to education, the built environment or social and community context may influence an individual's ability to modify these risk factors. For the purposes of this assessment, the terminology used (for example, behavioural of lifestyle intervention) is consistent with the referenced literature. It is recognised however, that "lifestyle intervention" may not capture the role of a broad range of behavioural, environmental and social factors on the development or progression of obesity and metabolic disease.[121]

Behavioural interventions and pharmacotherapy are not always sufficient to reach individualised T2D treatment targets. Bariatric surgery is typically used for the treatment of obesity and obesity-related comorbidities. The benefits of surgery for patients with comorbid T2D and obesity have led to the coining of the term "metabolic surgery" to describe the use of bariatric surgical procedures in these patients to produce improvements in or remission of T2D, thereby potentially reducing the onset or delaying the progression of T2D-related complications.

A number of bariatric or metabolic procedures are available or in development, each with its own risk-benefit profile (reviewed in Chapter 4). Traditionally, bariatric surgical procedures have been divided into restrictive or malabsorptive procedures or a combination of both mechanisms of action. Restrictive procedures include LAGB, and LSG. Combination procedures include BPD-DS, RYGB and more recently OAGB. It is now recognised that this categorisation represents a substantial oversimplification of the mechanisms of action of bariatric surgical procedures. Beyond the extensive metabolic and anatomical changes that occur as a result of metabolic surgery, inflammatory responses, changes in neural and endocrine signalling, gut microbial factors as well as learned behaviour change contribute to the overall benefits of metabolic surgery.

Although the ADA, IDF and IFSO have recommended the revision of T2D treatment algorithms to incorporate metabolic surgery for carefully selected patients,[7, 122] a number of countries in Europe, including Ireland, have not yet included metabolic surgery as part of the T2D clinical care pathway. Traditional BMI-based selection criteria do not favour access based on the clinical need of an individual patient.[7, 122, 123] Complication-based selection criteria employing weight loss as a tool to treat obesity-related comorbidities and may better predict those who are most likely to benefit from surgery. In European countries, selection of candidates for surgery is still largely based on traditional BMI-centric criteria.

3 Burden of disease

Key points

- Diagnoses of Type 2 diabetes (T2D) are primarily driven by rising levels of overweight and obesity and by the ageing population.
- T2D is more prevalent in males and those with lower socioeconomic status. Onset of illness typically occurs in middle-aged and older adults, with the highest prevalence found in those >75 years of age. Estimates of the size of the population with T2D are subject to considerable uncertainty due to the absence of national data sources such as a national diabetes register, centralised database of electronic medical records or a population-based survey of T2D.
- Estimates from wave 1 (2009 to 2011) of The Irish Longitudinal Study on Ageing (TILDA) indicate that 4.52% (95% CI: 4.00 to 5.12) of adults ≥50 years in Ireland have comorbid T2D and obesity (BMI ≥30 kg/m^2), while the estimated prevalence in the population aged 18 to 49 years is less than 1% according to 2019 Healthy Ireland Survey data.
- While the estimated prevalence of diabetes in Ireland is lower than that reported for other European countries, this is likely related to the lack of up-to-date national estimates on the prevalence of T2D in Ireland.
- There is no internationally accepted definition for T2D control that is above treatment targets despite best medical care. At a population-level, blood glucose levels can be used as a simplified means of approximating the risk of T2D-related complications. Among patients with T2D and obesity enrolled in the Diabetes Cycle of Care programme in Ireland, 32% have glycaemic control above target despite best medical care.
- T2D and obesity are typically characterised by a clustering of metabolic and cardiovascular risk factors including hypertension and dyslipidaemia. As a result, T2D is associated with considerable morbidity. T2D is associated with a two-fold increase in the risk of cardiovascular disease (CVD) compared with the general population. It is estimated that 90% of patients with T2D in Ireland have at least one additional chronic disease.
- People with T2D and obesity have reduced quality of life relative to the general population, particularly for patients with intensive treatment regimes, higher HbA1c levels and or T2D-related complications.

- T2D is associated with a considerable medication burden for patients and increased health service utilisation relative to those without T2D, particularly for patients with T2D-related complications or multimorbidity.
- T2D is associated with an increased risk of all-cause and CVD-mortality relative to those without T2D, although all-cause and CVD-mortality have declined over time. Declining all-cause and CVD-mortality may contribute to relative increases in diabetes-related morbidity, including renal disease, diabetic foot, and retinopathy, with important implications for the burden of T2D on the healthcare system.
- According to the most recent International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) global registry report, patients with T2D and obesity are under-represented among bariatric surgery candidates within existing bariatric surgery services.
- Between 2009 and 2019, the number of procedures carried out per year increased over time, but on average was 74 in the public hospital system. Patients with T2D currently represent approximately 24% of patients undergoing bariatric surgery in Ireland.

3.1 Introduction

Type 2 diabetes (T2D) occurs as a result of the body's inability to respond to or produce insulin, resulting in elevated blood glucose levels (hyperglycaemia) which can cause damage to blood vessels and nerves throughout the body.[35] Patients with T2D with glycaemic and cardiovascular risk factor control above treatment targets are at risk of developing serious complications affecting multiple tissues, organs and systems, including the eyes, kidneys, nerves and cardiovascular system.[35] The risk of developing complications is influenced by the magnitude and duration of hyperglycaemia, as well as the management of additional risk factors such as hypertension or excess body fat.[124]

The objective of this chapter is to describe the epidemiology of T2D, focusing on adults with comorbid obesity, and particularly in Ireland. Estimates of the number of adults with comorbid T2D and obesity who may benefit from access to metabolic surgery are provided, in addition to estimates of the number of adults with diabetes-related complications.

3.2 Risk factors associated with T2D

European data show that multiple behavioural, sociodemographic and genetic factors are associated with an increased risk of developing T2D. These include non-modifiable factors such as older age, family history of T2D, and low socioeconomic status, and modifiable risk factors, such as excess weight, and components of the metabolic syndrome (see Table 3.1).[125]

Table 3.1 Type 2 diabetes risk factors

Modifiable	Non-modifiable
▪ overweight (BMI 25 to 29.9 kg/m^2) or obesity (BMI ≥30 kg/m^2 ▪ abdominal obesity† ▪ high blood pressure ▪ abnormal blood cholesterol/lipid levels ▪ diet ▪ sedentary behaviour or decreased physical activity ▪ smoking	▪ older age ▪ male sex ▪ ethnicity ▪ family history of T2D ▪ history of gestational diabetes ▪ low socioeconomic status ▪ clinical conditions (for example, PCOS)

Key: PCOS – polycystic ovary syndrome; T2D – type 2 diabetes.
† A waist circumference of ≥94 cm and ≥80 cm in Caucasian men and women, respectively, is associated with an increased risk of type 2 diabetes.[126, 127]
Table adapted from Kryou et al. 2020.[125]

Overweight, obesity and cardiometabolic abnormalities

Overweight and obesity, particularly abdominal obesity, are considered the most important modifiable risk factors for prediabetes and T2D.[125, 128, 129] Overweight and obesity can lead to a spectrum of cardiometabolic abnormalities, such as high blood pressure and insulin resistance, which can progress to T2D and cardiovascular disease, depending on the degree, distribution, timing and duration of excess weight gain.[125] The increasing prevalence of obesity worldwide has been associated with an increase in T2D diagnoses.[130]

In Ireland, data from TILDA, a nationally representative sample of adults aged ≥50 years, showed that those with central obesity were over four times more likely to have T2D(RR 4.31; 95% CI: 2.94 to 6.31), relative to those with a normal waist circumference.[131]

Sociodemographic factors

Older age and male sex are associated with an increased risk of T2D.[132-137] In Ireland, data from the 2007 SLÁN study showed that adults aged 55 to 64 years were almost ten times more likely to have diabetes (not reported by type) than those aged 18 to 34 years (OR 9.9 (95% CI: 4.86 to 20.14)).[133] The prevalence of T2D is consistently reported to be higher in men compared with women. In Irish adults ≥50 years (TILDA data), more males (10.3% (95% CI: 9.4 to 11.2%)) than females (6.6% (95% CI: 5.9 to 7.5)) had a diagnosis of T2D.[132] Similarly, in the Cork and Kerry Diabetes and Heart Disease Study, male subjects were two and a half times more likely to have T2D compared with females (OR 2.5 (95% CI: 1.5 to 4.1)).[134]

Social determinants of health are an individual's personal circumstances that impact a person's health and well-being.[138] These can include access to educational and occupational opportunities, social and community context, healthcare access and the environment (for example, access to places to exercise).[125, 139] Many of these factors are linked to a person's socioeconomic status. In Ireland, the prevalence of T2D is higher in those with lower SES.[134, 140] Among those with T2D in a middle-aged Irish population (Cork and Kerry Diabetes and Heart Disease Study), 13.3%, 30.1% and 56.6% were classified as in high, middle and low income classes (defined according to the European Socio-economic Classification System (EseC)), respectively.[134] Data from the 2019 Irish Health Survey indicate that the prevalence of diabetes (data not available by type) was more than double in those classified as 'very disadvantaged' (5%), compared to 'very affluent' persons (2%), according to the Pobal Haase-Pratschke (HP) Deprivation Index.[140]

3.3 Prevalence of diabetes

In Ireland, there is no national diabetes register, database of electronic medical records or population-based survey of diabetes to generate estimates of the burden of disease or the impact of interventions at a national level. In the absence of such national-level data, cross-sectional analyses of nationally representative datasets, or data from individual studies undertaken at various time points, were used here to provide estimates of the prevalence of T2D and T2D-related complications in the Irish adult population over time. Only studies reporting on incidence or prevalence of T2D, or of all diabetes, were considered of potential relevance. Studies reporting on other types of diabetes only (type 1 diabetes, gestational diabetes) were not included.

Data sources from which the estimates were derived include the following:

- Survey of Lifestyle, Attitudes and Nutrition, 2007 (SLÁN)
- The Irish Longitudinal Study on Ageing (TILDA)
- The Cork and Kerry Diabetes and Heart Disease Study
- Healthy Ireland Survey (2019)
- Central Statistics Office (CSO) Irish Health Survey (2019).

In the absence of a national diabetes register for Ireland, data from the Scottish national diabetes register, SCI (Scottish Care Information)-Diabetes were used to estimate the prevalence of T2D irrespective of BMI, and of comorbid T2D and obesity. From an epidemiological perspective, Ireland and Scotland may be considered to be relatively similar, thus data from Scotland may provide an indication of the burden of disease in Ireland.

3.3.1 Prevalence of diabetes in the European Region

The prevalence of diabetes is increasing globally.[141] Developed regions, such as Western Europe, show considerably higher prevalence rates that continue to rise despite public health interventions.[142] Comparison of diabetes prevalence rates, particularly T2D, across countries is challenging as estimates may be influenced by access to diagnostic testing.[143]

Estimates for the prevalence of T2D in the European region derived from different data sources may produce slightly different estimates, potentially due to differences in the timing of studies, or countries, types of diabetes and or age groups considered, although recent estimates for the European Region are broadly consistent. According to the 2017 Global Burden of Disease Study, the estimated

prevalence of T2D in Europe is 8.5%, based on data from France, Germany, Italy, the Netherlands, Russia, Spain, Sweden, Switzerland, Turkey and the UK, and is projected to increase.[142] No major shift in the age distribution was identified from 1990 to 2017.[142] The International Diabetes Federation Atlas 2021 estimated the prevalence of diabetes (type 1 and 2) in Europe to be 9.2%, corresponding to 61 million people.[144] The prevalence is anticipated to increase by 13% by 2045 based on current trends.[144]

3.3.2 Type 1 and type 2 diabetes in Ireland

Based on an analysis of SLÁN 2007 study data, the prevalence of doctor-diagnosed diabetes amongst Irish adults aged >18 years was 3.5% (95% CI: 3.1 to 3.9).[133] More recent estimates from the 2019 Central Statistics Office (CSO) Irish Health Survey (HIS) reported a prevalence of 3% among adults aged 15 years and older.[140] The lower prevalence observed in the CSO HIS may be impacted by the inclusion of children aged 15 to 18 years (in whom the prevalence of T2D is extremely low, thereby lowering the total prevalence) or an artefact arising from the data collection process. As the data collection methods for the CSO HIS do not facilitate identification of undiagnosed T2D, it is likely that the prevalence of diabetes is higher than that reported, given that previous studies conducted in Ireland have reported a considerable proportion of undiagnosed cases.[131, 134, 135]

A 2016 systematic review imputed expected rates of diagnosed diabetes in Ireland based on previous trends. Between 1998 and 2015, the prevalence of self-reported doctor-diagnosed diabetes was projected to remain stable in both men and women aged between 18 and 39 years.[6] However, an upward trend was observed in adults aged ≥40 years.[6] Among adults aged ≤40 years, the prevalence was consistently higher in males than females.

While it was not possible to distinguish between diabetes by type in the aforementioned data sources, it is likely that T2D is driving the reported increase in prevalence as it accounts for 90% of all diabetes cases among adults >40 years.[6] The focus of this assessment is the management of patients with T2D, in particular among those with comorbid obesity.

3.3.3 Prevalence of type 2 diabetes in Ireland

Limited current or historic data are available on the prevalence of T2D in Ireland. The best available national data source of the estimated population with T2D in Ireland is the TILDA study. TILDA is a nationally representative cohort study of over 8,000 community-dwelling adults aged ≥50 years resident in Ireland.[145] The first wave of data collection occurred between 2009 and 2011. Participants completed a

computer-assisted personal interview administered by trained social interviewers and a health assessment.[145] The interview included questions relating to self-reported doctor-diagnosed chronic conditions, such as T2D, and medication use.[145] The health assessment involved collection of objective measures of health status including weight, height and venous blood samples.[145]

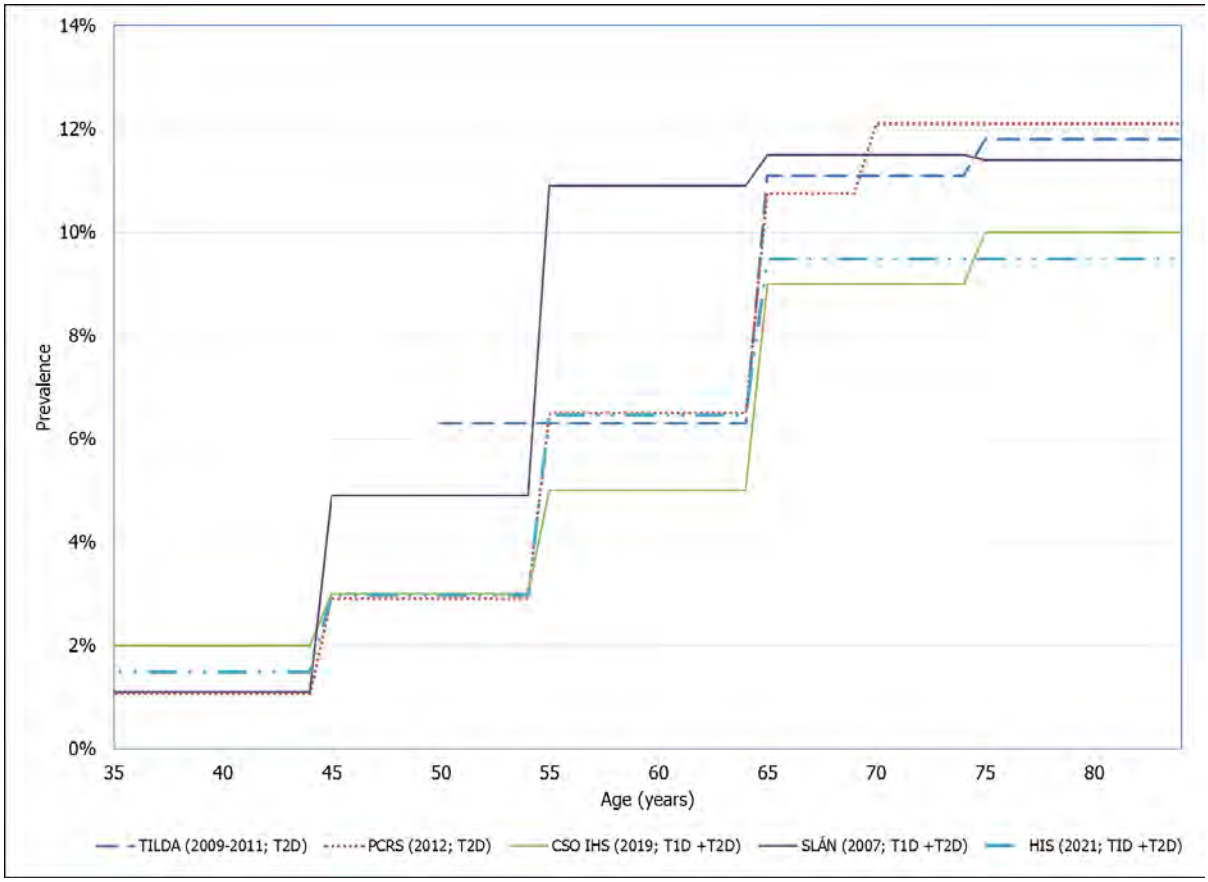
A cross-sectional analysis of TILDA data from wave 1 reported a prevalence of T2D in adults ≥50 years of 8.4% (95% CI: 7.8 to 9.0), and was significantly higher in men (10.3%; 95% CI: 9.4 to 11.2) compared with women (6.6%; 95% CI: 5.9 to 7.5).[132] Other Irish cross-sectional studies in adults >50 years have reported similar prevalence estimates.[134, 146]

Based on a published cross-sectional analysis of dispensing data from the Health Service Executive-Primary Care Reimbursement Service (HSE-PCRS) in 2012, the prevalence of T2D treated with oral anti-hyperglycaemic agents (with or without insulin) was 3.16% (95% CI: 3.15 to 3.18) among the population ≥15 years.[147] The prevalence was higher in men (2.96%; 95% CI: 2.94 to 2.98) than in women (2.04; 95% CI: 2.02 to 2.06). The prevalence increased above the total population average for adults ≥45 years, with the prevalence peaking in adults aged >70 years of age (12.1%; 95% CI: 11.99 to 12.20).[147] Age-specific estimates from TILDA and the PCRS database were consistent (see Figure 3.1).

As elevated blood glucose develops gradually over time, a proportion of the population may go undetected in the early stages of the disease. It is estimated that between 0.9% (95% CI: 0.6 to 1.1) and 3.5% (95% CI: 2.8 to 4.4) of adults aged ≥50 years have undiagnosed T2D in Ireland.[131, 134] Among Irish private health insurance holders aged 45 to 75, the prevalence of undiagnosed T2D was estimated to be 1.8%.[135]

In the absence of up-to-date national data sources, prevalence estimates have been estimated based on simulation modelling to inform health service planning. One simulation study projected that the number of people living with T2D in Ireland will increase from 216,000 in 2020 to 414,000 in 2036 unless an effective diabetes prevention programme is implemented.[148] The rising burden of T2D over time was said to be driven by both the growing and ageing population as well as increases in the incidence of pre-diabetes, of which a proportion will progress to overt T2D. Using data modelled from the Scottish Diabetes Register, it has been estimated that 234,398 people in Ireland are living with T2D, corresponding to 4.9% of the population, based on 2016 CSO population estimates.[149]

Figure 3.1 Prevalence of diabetes in Ireland by age, as reported by several national data sources



Key: Data from The Irish Longitudinal Study on Ageing (TILDA) and the Primary Care Reimbursement Service (PCRS) show estimates for the population with T2D, for the years 2009 to 2011, and 2012, respectively.[132, 147] The Survey of Lifestyle, Attitudes and Nutrition (SLÁN) survey, Central Statistics Office (CSO) Irish Health Survey (HIS) and the 2021 Health Ireland Survey† show the estimated prevalence of diabetes (type 1 and type 2) in 2007 and 2019, respectively.[133, 140, 150]
† Prevalence estimates were weighted by sex based on 2021 CSO population projections.

3.4 Prevalence of obesity

The 2019 Eurostat survey estimated the average obesity prevalence among adults aged ≥18 years in Ireland at 25.9%. In comparison, the European Union (EU) average prevalence was 16.5%.[151] Obesity prevalence was reported to be similar among males (25.7%) and females (26%) in Ireland.[151] Of note, the United Kingdom was not included in the 2019 Eurostat survey; according to data from the 2017 Non-communicable Disease Risk Factor Collaboration (NCD-RisC), the prevalence of obesity among males (29.3%) and females (31.3%) in the UK is higher than Ireland (males 27.3%; females 28.2%).[152]

Data from the NCD-RisC have also been used to estimate the long-term prevalence of obesity in various European countries, including Ireland.[152] Based on trends to 2016, the projected maximum obesity prevalence in Ireland was estimated to reach 36.8% (95% CI: 34.7 to 39.9) in males by 2037 and 35.5% (95% CI: 34.0 to 37.7) in females by 2035.[152]

3.5 Prevalence of type 2 diabetes and obesity

Estimates of the prevalence of obesity among those with T2D vary between countries. However, the prevalence of obesity is consistently higher among those with T2D when compared with the general population. A 2013 systematic review of observational studies found that the prevalence of obesity, as defined by BMI, among patients with T2D in Europe ranged from 33% in Croatia to 64% in the UK. In general, the prevalence of obesity was higher when defined according to waist circumference.[153] Data from the Scottish Diabetes Register indicate that the prevalence of obesity among those with T2D is 55.7%.[154] Similar to the estimate from Scotland, in Ireland the prevalence of obesity among adults with T2D aged ≥50 years has been estimated to be between 54 and 60%, based on data from TILDA and a GP-based study.[131, 132, 155] Among those with comorbid T2D and obesity aged ≥50 years, the population is not evenly distributed across the obesity spectrum, with the majority of this cohort having class I obesity (BMI 30 to 34.9 kg/m2) (see table 3.2).

Table 3.2 Weight distribution by BMI class among the population with T2D aged ≥50 years, by BMI class†

BMI class	Percentage population
Normal weight and overweight (BMI <30 kg/m^2)	41.6 (95% CI: 36.9 to 46.5)
BMI 30 to 34.9 kg/m^2	31.6 (95% CI: 27.1 to 36.5)
BMI 35 to 39.9 kg/m^2	17.7 (95% CI: 14.2 to 21.8)
BMI ≥40 kg/m^2	9.0 (95% CI: 6.5 to 12.5)

Key: BMI – body mass index; CI – confidence interval.
† Methods described in the supplementary appendices.

As noted, not all patients with T2D have comorbid obesity. Estimates of the prevalence of comorbid T2D and obesity will be important to indicate the potential number of people eligible for metabolic surgery. However, it is difficult to estimate the prevalence of comorbid T2D and obesity in Ireland with the available data sources. Based on an analysis of TILDA data, it is estimated that 4.52% (95% CI:

4.00 to 5.12) of adults aged 50 years and older in Ireland have comorbid T2D and obesity (see supplementary appendices for methods). Healthy Ireland Survey data from 2019 indicate that the prevalence of comorbid diabetes and obesity among adults 18 to 49 years in Ireland is 0.35%; however, data are not available by diabetes type.[1](156) Overall, this equates to an estimated 80,347 people based on 2021 CSO projections.

It the absence of a national diabetes register in Ireland, estimates from the Scottish National Diabetes Register are presented to corroborate Irish estimates, under the assumption that these populations are comparable. It was estimated that 3.6% of the population ≥18 years have comorbid T2D and obesity in Scotland (data correct as of 13 January 2022). (154) Applied to the Irish population, this equates to 137,532 people based on 2021 CSO population projections. It is likely that available Irish data underestimate the prevalence of comorbid T2D and obesity due to the reliance of Healthy Ireland Survey data on self-report, and likelihood of an increase in the prevalence of T2D and obesity since wave 1 TILDA data were collected (due to increasing overweight/obesity and the ageing population), and the potential for response bias.

3.6 Estimation of the eligible population for metabolic surgery in Ireland

Not everyone with comorbid T2D and obesity will require metabolic surgery for disease management. Traditionally, bariatric surgery has been indicated for patients with BMI ≥40 kg/m^2 or ≥35 kg/m^2 with comorbidities. However, it is now known that preoperative BMI specifically, as a measurement of obesity, is a relatively poor indicator of metabolic status and thus outcomes of metabolic surgery.(157) With consideration to guidance from the American Diabetes Association (ADA), the second Diabetes Surgery Summit (DSS) and the Model of Care for the Management of Overweight and Obesity in Ireland, metabolic surgery may be *recommended* as a treatment option for adults with T2D and a BMI:(7, 158, 159)

- ≥40 kg/m^2 (class III obesity)
- 35 to 39.9 kg/m^2 (class II obesity)

Metabolic surgery may be *considered* as a treatment option for adults with T2D and a BMI:

- 30 to 34.9 kg/m^2 (class I obesity) for whom T2D control is above treatment targets despite best medical care.

[1]Data were analysed by Danko Stamenic, Postdoctoral Researcher, University College Cork, and provided to HIQA researchers.

Defining T2D control that does not meet treatment targets

As noted, not everyone with comorbid T2D and class I or II obesity will require metabolic surgery for T2D management. Traditional bariatric surgery has been offered to those with a BMI ≥35 kg/m^2, however it is now recommended that indications are expanded to include those with a BMI 30 to 34.9 kg/m^2 and in whom T2D control is not on-target despite best medical care. There is no standardised definition for T2D control that does not meet treatment targets, or a validated HbA1c threshold at which the risk of T2D-complications clearly begins.[160-162] In clinical practice, targets for glycaemic control are typically determined at an individual patient level with consideration to patient and disease factors.[56] Guidance from the ADA, the American College of Physicians (ACP), and the American Association of Clinical Endocrinologists (AACE) together with the American College of Endocrinology (ACE), indicates that targets for glycaemic control should be individualised with consideration to patient and disease characteristics (see table 3.3).[64, 163-165] The age of a patient can impact on how treatment targets are interpreted, with consequent implications for treatment choices. A 2019 systematic review reported that tools for assessing the severity of T2D vary both in terms of the components of T2D management considered (for example, glycaemic control, cardiovascular risk factor reduction, presence of T2D-related complications) and the diagnostic thresholds used. However, in general, the vast majority of tools included measures of diabetes-related complications and/or indicators of glycaemic control.[161] Given the dependence of treatment targets on the specific clinical context, defining the level of T2D control that does not meet treatment targets, in order to inform estimation of the eligible population for metabolic surgery, is challenging.

Table 3.3 Examples of potential HbA1c targets for particular T2D subgroups

Population subgroup	Target HbA1c
▪ Patients without serious comorbidities ▪ Patients at low risk of hypoglycaemia ▪ Patients with new-onset T2D ▪ Patients with a life expectancy of at least 10-15 years	Lower thresholds (i.e., more stringent targets) than for the general population with T2D may be appropriate (e.g. 48 mmol/mol (6.5%))
Most adults with T2D	53 mmol/mol (7%)
Patients for whom the potential harms of tight glycaemic control outweigh the benefits, for example, patients with: ▪ a history of hypoglycaemia ▪ a longer duration of T2D ▪ a limited life expectancy ▪ comorbidities ▪ T2D-diabetes complications ▪ limited access to resources and/or support	Less stringent HbA1C goals (such as, 64 mmol/mol (8%))

Key: HbA1c – glycated haemoglobin; T2D – type 2 diabetes.

HbA1c is a validated and a widely used parameter in clinical trials investigating the impact of public health or pharmacological interventions on T2D management.[166] In general, RCTs of metabolic surgery enrolled participants based on a diagnosis of comorbid T2D and obesity, although some inclusion criteria considered additional clinical characteristics, including duration of diagnosed T2D,[167] or a diagnosis of albuminuria[168] or hypertension[169] at baseline (see chapter 4). A HbA1c target of <53 mmol/mol outlined in clinical practice guidelines for most adults with T2D may not be applicable to the many patients with comorbid T2D and obesity, given the high prevalence of comorbidities in this subgroup. A HbA1c target of >58 mmol/mol (7.5%) has been used in studies of pharmacological interventions,[170, 171] and registry reports.[154, 172] Therefore, with consideration to the underlying evidence, for the purposes of estimating the potentially eligible population, T2D control above treatment target was defined using HbA1c threshold of >58 mmol/mol.

In the international literature the proportion of the population with T2D not meeting treatment targets ranged from 26%[173] to 61%,[174] likely due to differences in the

definition of T2D treatment targets used and population characteristics (see Appendix 2). Assuming a population-level treatment target of <58 mmol/mol (7.5%), to facilitate comparison with Irish Cycle of Care data, estimates from the Scottish National Diabetes Registry indicate that 48.7% of patients have T2D control above treatment target.[175] Data were not available by age group. It is noted that less stringent treatment targets are typically used in older patients with a long history of T2D, which may lead to overestimation of the proportion patients not meeting treatment targets.

Estimates of the proportion of the Irish population with glycaemic control and cardiovascular risk factors above target

The proportion of the population with comorbid T2D and obesity with T2D control above target were estimated using national datasets including the HSE's Diabetes Cycle of Care (CoC) programme and TILDA. In 2017, the estimated prevalence of glycaemic control above the population-level treatment target (HbA1c >58 mmol/mol) among patients with comorbid T2D and obesity enrolled in the Diabetes CoC programme was 32.3%.[176] With consideration to additional markers of T2D control, an estimated 17.4% of those with a BMI of ≥30 kg/m^2 also had both HbA1c and blood pressure above treatment targets (see figure 3.2). The number of patients with glycaemic control above treatment targets increased with increasing BMI class. Of note, data from the Diabetes CoC may not be nationally representative as eligibility is limited to medical card and GP visit card holders. Access to these schemes is mostly means-tested, so that these groups comprise a disproportional number of those with lower socio-economic status. Cross-sectional analysis of TILDA data indicate that 68.4% of people with diabetes have a medical card or GP visit card and are thus covered by the CoC programme.[177] It is possible that the characteristics of the population with T2D who are not covered by the programme may differ from those who are. However, those not enrolled in the programme may be less likely to be considered eligible for surgery due to the known associated between socioeconomic status and health outcomes (see section 3.2). As a result of the considerable proportion of the population with T2D covered by the CoC programme, and the likely increased risk of poorer health outcomes among that population, the bias in the estimates may be limited. The Diabetes CoC data therefore represents the likely upper bound for the proportion of patients with comorbid T2D and obesity with T2D control above treatment targets.

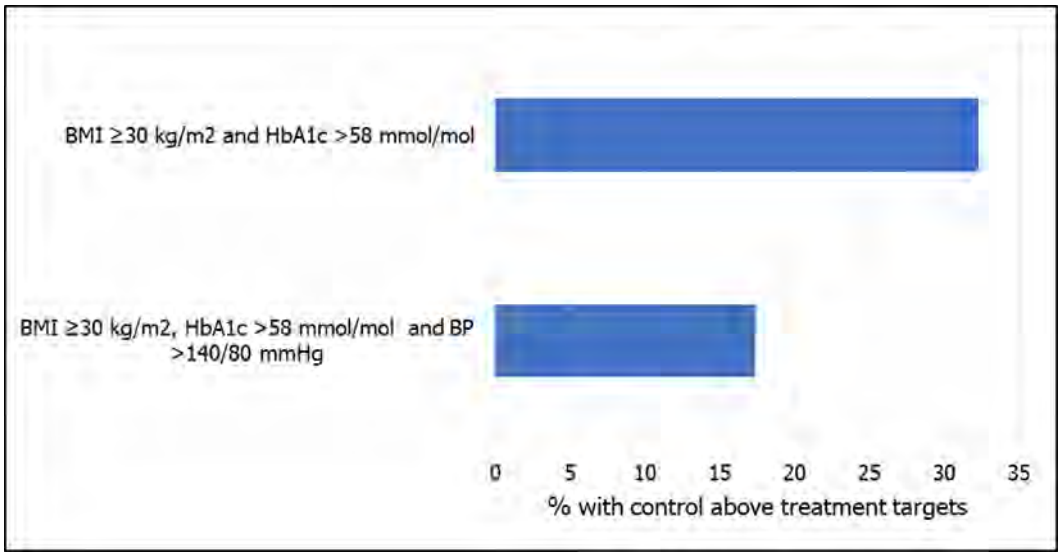
The prevalence of glycaemic control above treatment targets (>58 mmol/mol) was considerably lower among TILDA participants ≥50 years, at 6.0% (see Figure 3.2). However, only a small proportion of those enrolled in TILDA had comorbid T2D and obesity and the population with perceived poor health may be less likely to present

for assessment in clinical research;[178] therefore, estimates derived from this dataset may not be applicable to the broader population with comorbid T2D and obesity.

The proportion of the population with cardiovascular risk factors above treatment targets was similar across both datasets. Nineteen percent and 48% of T2D patients did not have total cholesterol <5 mmol/litre and blood pressure ≤140/80 mmHg, respectively, in the diabetes CoC dataset.[176] Among TILDA participants with comorbid T2D and obesity, approximately 16.4% and >46.3% did not meet treatment targets for total cholesterol and blood pressure, respectively (see Figure 3.3).[176]

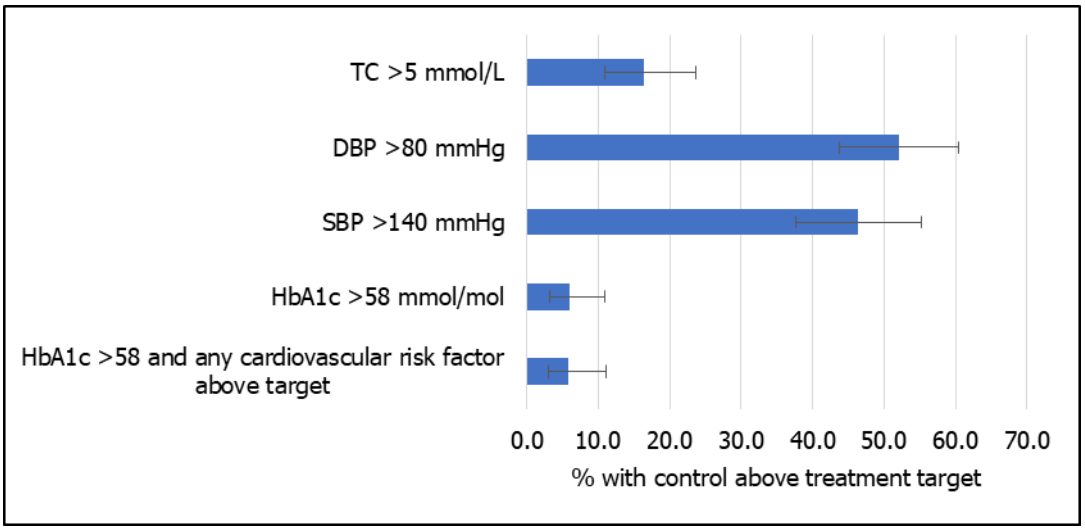
In both datasets, the number of patients not meeting treatment targets for both glycaemic and cardiovascular control was considerably less compared with each target considered individually.[176]

Figure 3.2 Percentage of people enrolled in the Diabetes Cycle of Care with cardio-metabolic risk factors above target



Key: BMI – body mass index (kg/m^2); BP – blood pressure (mmHg); HbA1c – glycated haemoglobin (mmol/mol).

Figure 3.3 Percentage of people aged ≥50 years with comorbid T2D and obesity and with cardio-metabolic risk factors above target †



Key: DBP – diastolic blood pressure; HbA1c – glycated haemoglobin; SBP – systolic blood pressure; TC – total cholesterol.
† Treatment targets have been applied to facilitate comparison with Diabetes Cycle of Care data and UK National Diabetes Audit data at a population-level.
Error bars denote the 95% confidence interval.

Table 3.4 outlines the population potentially eligible for metabolic surgery, based on measures of T2D status, obesity and T2D control (for the population with a BMI ≥30 to <35 kg/m^2). Prevalence estimates were derived from TILDA (first wave) and the Healthy Ireland Survey (fifth wave), described in section 3.4. Based on the best available evidence, it is estimated that 50,863 to 63,449 people may be eligible for surgery with consideration to T2D status and obesity only. In clinical practice, not all patients would be considered surgical candidates (for example, due to comorbidities or age), or would wish to undergo metabolic surgery.

Table 3.4 Estimated size of the population potentially eligible for metabolic surgery

Variable	Prevalence (95% CI)	Population (n)†‡
Adults ages ≥50 years		
T2D and BMI ≥35 kg/m^2	2.1 (95% CI: 1.7 to 2.5)	33,727
T2D and BMI ≥30 to <35 kg/m^2	2.5 (95% CI 2.0 to 2.9)	39,919
Estimation of the population with class I obesity (BMI ≥30 to <35 kg/m^2) and control above treatment targets		
T2D control above target (worst case scenario)§	61.2%	24,430
T2D control above target (best case scenario)¶	32.3%	12,894
Total (worst case scenario)		58,158
Total (best case scenario)		46,621
Adults ages ≥18 to 49 years		
Diabetes and obesity (BMI ≥30 kg/m^2)	0.3††	6,701
T2D and BMI ≥35 kg/m$^{2\#}$	-	3,068
T2D and BMI ≥30 to 34.9 kg/m$^{2\#}$	-	3,632
Estimation of the population with class I obesity (BMI ≥30 to <35 kg/m^2) and control above treatment targets		
T2D control above target and BMI ≥30 to <35 kg/m^2 (worst case scenario)§	61.2%	2,223
T2D control above target and BMI ≥30 to <35 kg/m^2 (best case scenario)¶	32.3%	1,173
Total (worst case scenario)		5,291
Total (best case scenario)		4,241
Total population (worst case scenario)		63,449
Total population (best case scenario)		50,863

Key: BMI – body mass index; T2D – Type 2 diabetes.
† Estimates of the size of the eligible population assume that there is no age limit on eligibility for metabolic surgery. Surgical candidates would be subject to pre-operative screening to determine eligibility.
‡ Population estimates are based on Central Statistics Office (CSO) population projections for 2021 based on the 2016 census.[179]
§ Worst case scenario is based on the estimated prevalence of T2D control above target from the 2018-2019 UK National Diabetes Audit data (HbA1c value ≤ 58mmol/mol, blood pressure ≤140/80 and, and is receiving statins (where indicated)).[174]
¶ Best case scenario is based on the estimated prevalence of glycaemic control above target in adults enrolled in the Diabetes Cycle of Care programme.[176]
†† It was assumed that 87.9 % of diabetes cases were T2D in the population aged 18 to 49 years.[149]
# The distribution of obesity by class was estimated using the TILDA data and applied to the Healthy Ireland Survey data on the population aged 18 to 49 years. While this may overestimate those with class two obesity and higher, it is noted that the population aged less than 50 years will only represent a small proportion of those eligible for surgery, and hence introduce little bias into our estimates.

3.7 Morbidity

T2D is a systemic disease affecting a number of body tissues, organs and systems. People with T2D can experience long-term complications including damage to the eyes (retinopathy), nerves (neuropathy), kidneys (nephropathy) and the heart and circulatory system (cardiovascular disease).

The prevalence of T2D complications is influenced by patient characteristics including duration of disease, age, socioeconomic and comorbidity status as well as healthcare system characteristics including access to healthcare services, and adherence to treatment. Intensive glycaemic control can reduce the risk of developing or slow the progression of vascular complications, and therefore the risk of diabetes-related morbidity and mortality.[180]

Estimates of the burden of disease for the population with comorbid T2D and obesity in Ireland were not available. Data reported were derived from the general population with T2D as this represents the best available evidence, and as is likely indicative of the burden of disease in the population with comorbid T2D and obesity. However, those with comorbid T2D and obesity may have a greater burden of disease given the association between obesity and adverse cardiovascular and metabolic outcomes.[181]

3.7.1 Multimorbidity

Obesity and T2D are related multifactorial, complex diseases that frequently coexist. Both diseases, either individually or as comorbid conditions, are typically characterised by a clustering of metabolic and cardiovascular risk factors including hypertension and dyslipidaemia.[182] The relationship between T2D, obesity and cardiovascular disease (CVD) is a result of complex interplay between multiple risk factors that promote atherosclerotic disease.[36, 182]

As a result of the underlying pathological process leading to the development of T2D, patients with T2D in Ireland and elsewhere in Europe tend to have multimorbidity (typically defined as the co-occurrence of two or more chronic conditions in an individual).[183] An Irish cluster randomised controlled trial (RCT) (2006 to 2007) based in general practice reported that 90% of patients with T2D have at least one other chronic condition, and 25% had four or more additional chronic conditions.[155] Circulatory problems were the most commonly reported comorbidity, with a prevalence of 73.8%. Hypertension was the most prevalent condition, reported in two thirds of patients with T2D.[155] Similarly, hypertension was reported to be the most prevalent condition recorded among patients attending primary care in the UK and Finland.[184-186] Ninety-three percent of patients attending

Finnish primary care centres between 2011 and 2019 had at least one other chronic disease in addition to T2D.[186] Older age and deprivation are reported to be the leading drivers of multimorbidity in patients with T2D.[187]

The risk of multimorbidity increases as BMI increases.[188] A pooled analysis from studies conducted across the USA and Europe indicated that compared with those with a healthy BMI (20.0 to 24.9 kg/m^2), participants with a BMI of 30 to 34.9 kg/m^2 (class I obesity), and higher than 35.0 kg/m^2 (class II obesity) were 4.5 (95% CI: 3.5 to 5.8), and 14.5 (95% CI: 10.1 to 21.0) times more likely, respectively, to develop cardiometabolic multimorbidity (that is, developing at least two out of the following three conditions: type 2 diabetes, coronary heart disease, and stroke).[188]

3.7.2 Macrovascular complications

T2D is associated with an increased risk of CVD and CVD-mortality. According to the Framingham Heart Study, the absolute risk of CVD and CVD-mortality is two- and three-fold greater, respectively, among persons with diabetes relative to those without diabetes.[189, 190] A trend towards a reduction in CVD-mortality over the 55-year follow-up period was identified in both those with and without T2D.[190] However, more recent estimates from the UK Clinical Practice Research Datalink (CPRD) database (2004 to 2010) indicate that the risk of CVD-mortality among patients with T2D remains three-fold greater compared with those without T2D.[191]

In 2018, 36.9% of patients with T2D recorded in the UK CPRD database had CVD.[192] The pooled prevalence of CVD among people with T2D in Europe was found to be lower at 30% according to a 2018 systematic review, which may be expected given the higher prevalence of obesity in the UK compared with other European countries.[152] In some studies, obesity was associated with increased risk of CVD among people with T2D, although the relationship was not found to be linear.[193, 194]

The number of cardiovascular risk factors above treatment targets greatly influences the risk of cardiovascular disease among patients with T2D. Analysis of patients with T2D recorded in the Swedish National Diabetes Register between 1998 and 2012 demonstrated a stepwise increase in the hazard ratios for cardiovascular events for each additional risk factor (elevated glycated haemoglobin level, elevated LDL cholesterol, albuminuria, smoking, and elevated blood pressure) that was not within the target range.[195] For example, the risk of myocardial infarction was 1.5 (95% CI: 1.4 to 1.7) times higher for adults aged 55 to <65 years with two risk factors above treatment targets relative to the general population without T2D. For the same age group, the relative risk of myocardial infarction increases to 4.8 (95% CI: 3.8 to 6.2) in the presence of five risk factors above treatment targets.[195]

National and regional estimates of CVD prevalence among those with T2D in Ireland demonstrate a large burden of disease. Among TILDA participants with T2D, the overall prevalence of self-reported macrovascular complications (including myocardial infarction, heart failure, stroke or transient ischemic attack) was 15.1% (95% CI: 12.2 to 18.4), and was higher among men (17.8%; 95% CI: 14.3 to 23.1) than women (11.4%; 95% CI: 7.7 to 16.4).[132] During the period 2010 to 2011, cardiovascular disease (defined as diagnosis of myocardial infarction, heart failure, angina, aortic aneurysm, hardening of the arteries, stroke or any other heart trouble) was reported among 22.2% and 28.4% of undiagnosed and diagnosed T2D cases, respectively, in the Cork and Kerry Diabetes and Heart Disease Study.[196] A second cross-sectional study carried out in Cork published in 2015 also reported a high prevalence of vascular complications in the coronary (17.8% ischaemic heart disease), cerebral (5.2% cerebrovascular disease) and peripheral (12.9% peripheral vascular disease) vascular systems.[197] Among private health insurance patients with undiagnosed T2D, the prevalence of CVD was estimated to be considerably lower at 8.4% between 2009 and 2012.[135] The lower prevalence in this population subgroup is likely attributable to less severe T2D in the undiagnosed population, and ownership of private health insurance which is likely a marker of higher socioeconomic status.

3.7.3 Microvascular complications

Among adults ≥50 years with T2D in Ireland, the overall prevalence of microvascular complications is 26.0% (95% CI: 22.5 to 29.9), with no gender-specific differences identified.[132] Evidence of T2D-related complications for the population <50 years in Ireland is limited. Young adults with a shorter duration of disease may be less likely to present with T2D-related complications. However, young adults with T2D control above treatment targets are at risk of developing T2D-related complications in the future.

Neuropathy was the most frequently reported microvascular complication (14.6%; 95% CI: 11.4 to 18.2)) among adults ≥50 years with T2D in Ireland.[132] The West of Ireland Diabetes Foot Study published in 2013 reported that 23 to 25% of patients with T2D had symptoms of neuropathy, depending on the test used.[198]

Pooled prevalence estimates of diabetic retinopathy (irrespective of severity) in Europe range from 18.75% (95% CI: 13.69 to 25.12) to 25.7% (95% CI: 22.8 to 28.8).[199, 200] Up-to-date data for Ireland are available from the National Diabetic Retinal Screening Programme, Diabetic RetinaScreen, which commenced in 2013 with the aim of offering free diabetic retinopathy screening and treatment to people with diabetes (T1D or T2D) aged ≥12 years. In 2019, 23.2% of those presenting for screening had evidence of background retinopathy, which is broadly consistent with

pooled prevalence estimates from European studies Europe. A proportion of the population with diabetic retinopathy are at risk of progression to visual impairment or blindness. Pre-proliferative retinopathy, proliferative retinopathy and age-related macular degeneration were detected in 0.1%, 0.3% and 0.3% of the screened cohort in Ireland in 2019, respectively.[201] The number of cases of retinopathy detected is not available by diabetes type.[201] The estimated pooled prevalence of clinically significant diabetic retinopathy in European countries ranges from 3.70 (95% CI: 2.20 to 6.20) to 5.29% (95% CI: 4.18 to 6.68).[199, 200] The reasons for the lower estimated burden of clinically significant retinopathy detected by RetinaScreen relative to estimates reported in other European countries is unclear, but may be related to the clinical characteristics of the population presenting for screening. In Ireland, in 2019, 72.9% of those invited to attend agreed to participate in screening. No data are available for those who declined an invitation.

Other estimates for the Irish population indicate a considerably lower burden of diabetic retinopathy. In patients with T2D aged ≥50 years in Ireland, retinopathy was reported in 8.2% (95% CI: 6.2 to 10.9) of the population.[132] Similarly, a prevalence of 11% was reported in the 8-year Diabetes Watch Programme cohort at enrolment between 2005 and 2013.[202] The reasons for the lower prevalence of retinopathy in the TILDA dataset and Diabetes Watch Programme when compared with pooled estimates from other European countries are unclear, but may be related to differences in the definitions used (for example, non-proliferative retinopathy, proliferative retinopathy) or changes in diagnostic methods over time with consideration to the higher prevalence of background retinopathy detected by Diabetic RetinaScreen in recent years.

In addition to damage to the nerves and eyes, elevated HbA1c levels are associated an increased risk of kidney damage.[203] Proteinuria and kidney damage were prevalent in 6.1% (95% CI: 4.3 to 8.6%) and 5.1% (95% CI: 3.4 to 7.6) of adults ≥50 years in Ireland, respectively.[132] Between 2008 and 2009, an Irish prospective observational study reported that 21% of participants had evidence of moderate or severe renal dysfunction (that is, eGFR 15– 59 ml/min/1.73 m^2), however data were not available by diabetes type.[198] Damage to the nephrons in the kidneys can lead to progressive loss of renal function resulting in chronic kidney disease (CKD), described in the following section.

3.7.4 Chronic kidney disease

Over time, elevated blood glucose levels and hypertension can cause damage to blood vessel clusters in the kidneys resulting in kidney damage. Obesity, diabetes, hypertension and dyslipidaemia have been shown to be independently associated

with CKD.[204] Therefore, individuals with multiple risk factors may be particularly at risk. In the UK, people with T2D have a 3.6 times increased risk of end-stage renal disease compared with the general population.[205]

According to the 2017 Global Burden of Disease study, the age-standardised incidence of T2D-related CKD in Ireland is 0.027% (95% uncertainty interval (UI): 0.023 to 0.032). The age-standardised mortality rate and disability-adjusted life years (DALYs) attributable to T2D-related CKD were 0.0015% (95% UI: 0.0012 to 0.0019) and 0.030% (95% UI: 0.025 to 0.036), respectively.[206] The aging population and high BMI were identified as key drivers of the increased burden of CKD between 1990 and 2017 in high sociodemographic index (SDI) regions such as Ireland.[206] A cross-sectional analysis of patients with diabetes attending primary care in Cork estimated the prevalence of CKD to be 5.5%.[197]

3.7.5 Diabetic foot problems

Peripheral neuropathy and tissue ischemia resulting from peripheral vascular disease (PVD) are two contributing factors in the development of foot ulcers (that is, an open non-healing wound in the skin) in patients with diabetes. Once a foot ulcer develops there is a high risk of disease progression that may lead to complications such as infection and limb amputation.

Eighteen to 40% of participants in the West of Ireland Diabetes Foot Study (2008 to 2009) had evidence of vascular impairment, depending on the assessment method used, with 11% at high risk of future ulceration using the Scottish Intercollegiate Guidelines Network (SIGN) risk stratification system (data not available by diabetes type).[198] The prevalence of foot ulceration was approximately 4% in both TILDA (2009 to 2011) and the West of Ireland Diabetes Foot Study.[132]

A comparable prevalence of foot ulceration in other European countries has been reported. A 2016 systematic review reported a pooled mean prevalence of diabetic foot ulceration of 5.1% (95% CI: 4.1 to 6.0%), with a higher prevalence among patients with T2D compared with T1D.[207]

Data from the Hospital In-Patient Enquiry (HIPE) system indicate that in 2009 there were 175.7 diabetes-related amputations per 100,000 people with diabetes (0.2%).[208] Similar rates were reported in the UK NDA for the period 2017 to 2018. The incidence of major and minor amputation in patients with T2D (or other diabetes not including T1D) was 0.1% and 0.2%, respectively.[205] Across Europe there is considerably variation in the rate of lower extremity amputations (LEAs). A review of international trends in diabetes complications including LEAs noted a decline in total LEA incidence which was said to be driven largely by declines in

major LEAs (defined as loss of lower limb through or above the ankle).[209] In general, smaller relative declines have been reported for minor LEAs.[209]

3.7.6 Quality of life

T2D and obesity independently or as comorbid conditions are associated with a reduction in quality of life (QoL) relative to the general population.

Analysis of the 2003 Health Survey for England demonstrated that having T2D or obesity, as individual conditions, significantly reduce health-related quality of life (HRQoL).[210] Having both conditions resulted in considerably lower (QoL) than either condition individually.[210]

Patients with T2D control above treatment targets have lower QoL when compared with those meeting treatment targets.[211] European studies have shown that complex treatment regimens including multiple daily injections, higher HbA1c levels, medications that promote weight gain and the presence of T2D-related complications are associated with a decrease in QoL in patients with T2D.[211-215] Thus, short-term changes in HbA1c can have an immediate impact on QoL for patients with T2D, in addition to the effect on the development or progression of T2D-related complications.[211]

3.7.7 Mortality

Although reductions in all-cause mortality among those with T2D have been observed over time , excess risk relative to those without T2D remains high.[216] A 55-year follow-up of the Framingham Heart Study participants from 1950 to 2005 revealed that the risk of all-cause mortality decreased over time from approximately a two-and-a-half-fold excess risk to a two-fold excess risk in patients with diabetes versus without diabetes.[190]

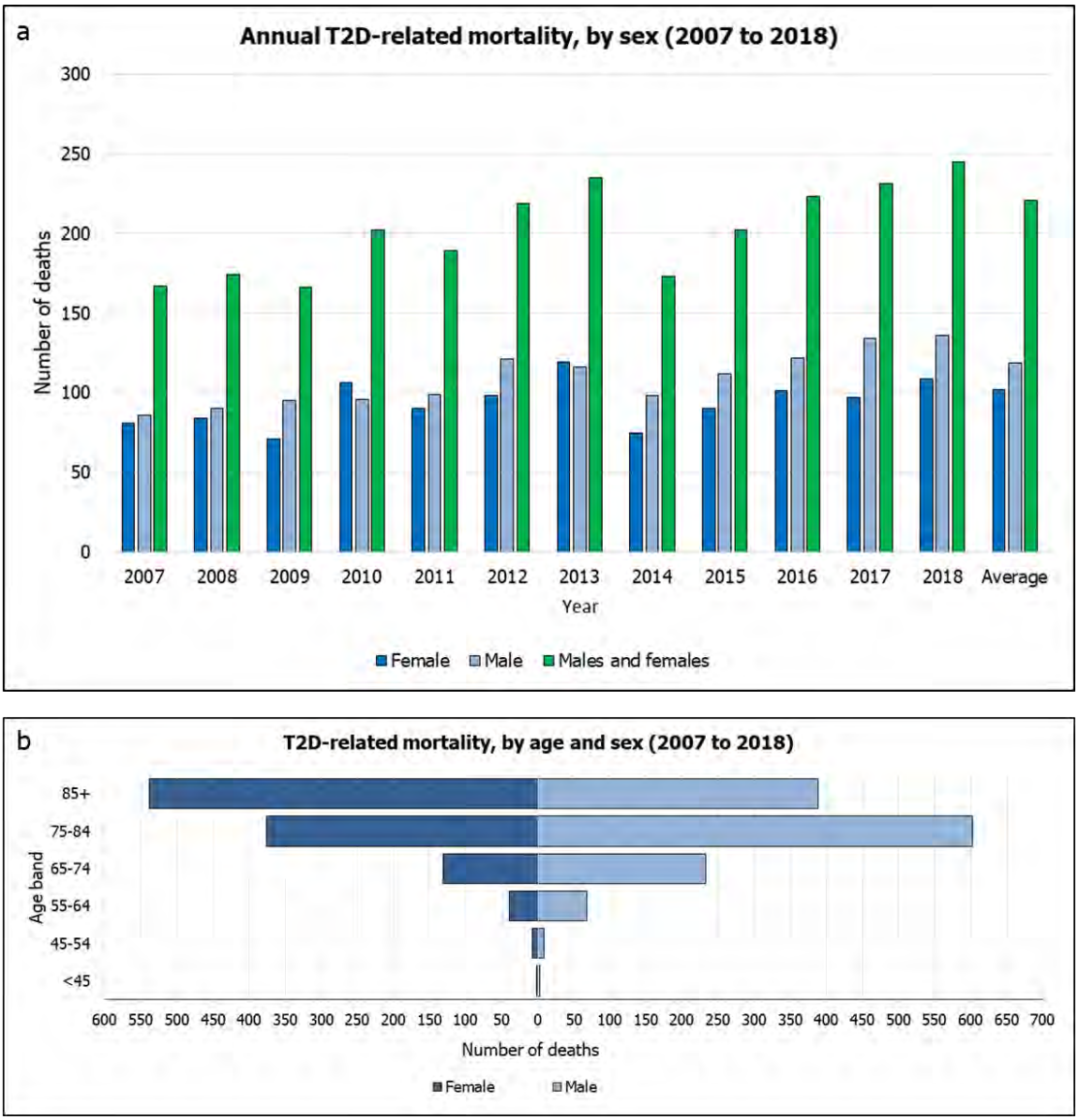
For those with T2D, the presence of risk factors above treatment target has been associated with an additional increased risk. Analysis of adults with T2D registered in the Swedish National Diabetes Register from 1998 to 2012 showed that the risk of all cause-mortality increased in the presence of risk factors not within the target range (elevated HbA1c, elevated LDL-cholesterol, albuminuria, smoking and elevated blood pressure) and with younger age at onset.[195] For example, for adults aged 55 to <65 years with T2D and two risk factors outside the target range, the hazard ratio for excess mortality relative to matched controls was 1.32 (95% CI: 1.27 to 1.38).[195]

National estimates

Data on T2D-related mortality were obtained from the Central Statistics Office (CSO) for the period 2007 to 2018. In Ireland, T2D-related mortality is highest in females aged ≥85 years, and in males aged 75 to 84. On average, between 2007 and 2018, T2D-related mortality rate was higher in males than in females (Figure 3.4, a).

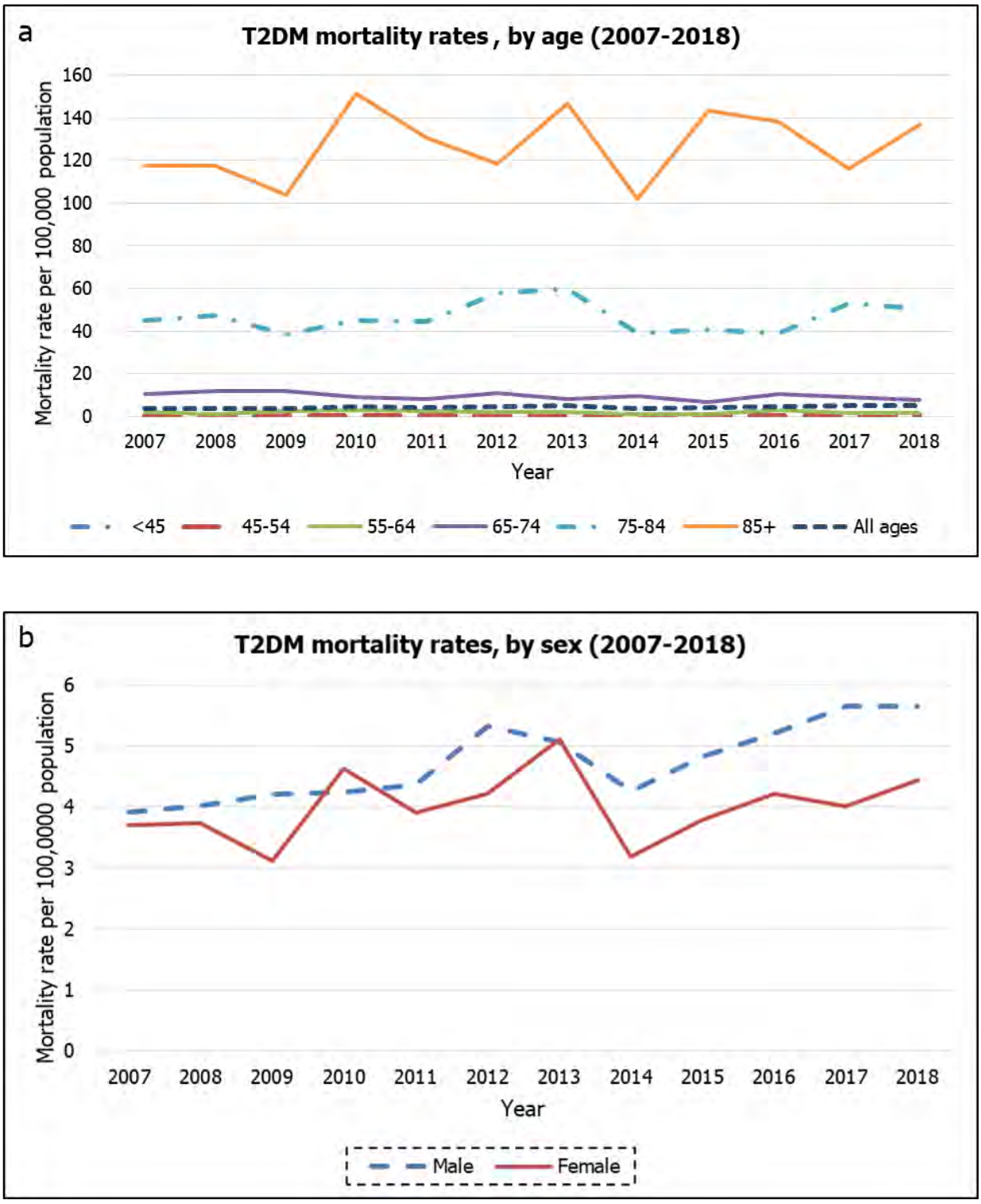
The incidence of T2D-related mortality increases with age (Figure 3.4, b). Between 2007 and 2018, the mean T2D-related mortality rate was approximately 4 per 100,000 population. Between 2007 and 2018, the mean age-specific mortality rate for those aged 75 to 84 and ≥85 years was 47 and 127 per 100,000 population, respectively (Figure 3.5, a); mean age-specific mortality was higher in males than females (Figure 3.5, b).

Figure 3.4 T2D-related mortality (2007 to 2018)



Key: Total number of T2D-related deaths recorded by the Central Statistics Office (CSO) by age and sex from 2007 to 2018 (panel a). Number of T2D-related deaths recorded by the CSO by sex from 2007 to 2018 (panel b).

Figure 3.5 T2D-related mortality per 100,000 population (2007 to 2018)



Key: T2D-related mortality rate per 100,000 population by age band between 2007 and 2018 (panel a). Annual T2D-related mortality rate per 100,000 population by sex between 2007 and 2018 (panel b). Population estimates were based on Central Statistics Office (CSO) projections for 2021.[179]

Life expectancy

Changes to treatment pathways over time, including improvements in pharmacotherapy, patient education and monitoring for T2D-related complications have translated into improvements in life-expectancy for those with T2D;[217, 218] however, life expectancy remains reduced for those with T2D relative to the general population, particularly for those with T2D-related complications.

In the UK, T2D is associated with an average of 1.7 life years lost per person compared with those without T2D.[219] A population-based cohort study conducted in Scotland during 2012 to 2014 showed that life expectancy in people with T2D was significantly reduced relative to those without T2D at all ages and levels of socioeconomic status (except deprived men aged 80 to 89).[220] Younger age at disease onset was associated with a greater reduction in life expectancy. Differences in life expectancy ranged from -5.5 years (95% CI: -6.2 to -4.8) to 0.1 years (95% CI: -0.2 to 0.4) for women aged 40 to 44 years in the second most-deprived quintile of the Scottish Index of Multiple Deprivation (SIMD), and for men aged 85 to 89 years in the most-deprived quintile, respectively.[220]

In the Netherlands, there were no differences in life expectancy for people with T2D compared with the general population,[217] however, the presence of albuminuria (HR 1.72; 95% CI: 1.26 to 2.35) and cardiovascular disease (HR 1.71; 95% CI: 1.23 to 2.37) in those with T2D increased the risk of shorter life expectancy.[217]

In Germany and the Netherlands it has been shown that the time spent with T2D increases with increases in total life expectancy.[221, 222] In the Netherlands, compared to those with normal weight, men and women with T2D and obesity lived 2.8 (95% CI: 0.1 to 6.1) and 4.7 (95% CI: 0.6 to 9.0) fewer years without diabetes, respectively.[221] The additional years lived with morbidity may have important implications for health service utilisation and healthcare costs.[221, 222]

Relationship between glycaemic control and mortality risk

Several European studies have reported an increased risk of all-cause mortality with both low and high HbA1c values. A retrospective cohort study of patients ≥65 years initiating insulin therapy obtained from UK primary care practice data reported a U-shaped relationship between all-cause mortality and HbA1c; the highest mortality risks of 31% and 40% were significantly associated with the lowest (<6.5%: aHR 1.31; 95% CI: 1.10 to 1.56) and highest (≥11.5%: aHR 1.40; 95% CI: 1.01 to 1.96) HbA1c categories, respectively.[223] The lowest all-cause mortality risk was observed in the HbA1c range of 6.5 to 7.4%. A large population-based registry study in

Denmark reported an increased risk of all-cause mortality of 22% for individuals at a HbA1c ≥7% and 44% for those with a HbA1c ≥9.0%.[224]

3.7.8 Healthcare service use

Management of T2D and its related complications is associated with increased health service utilisation and a substantial economic burden. According to an analysis of TILDA data, adults ≥50 years with diabetes have 1.49 (95% CI: 1.10 to 1.88) additional GP visits annually compared with those without diabetes.[225] Diabetes was associated with an 87% increase in outpatient visits, a 52% increase in hospital admissions and a 33% increase in emergency department attendances.[225] Diabetes was also significantly associated with an approximately 60% increased odds of attending an optician (OR 1.58; 95% CI: 1.27 to 1.96) or public health nurse (OR 1.57; 95% CI: 1.17 to 2.10).[225] Of note, requirements for monitoring and regular follow-up likely contribute to the increased resource use in primary care and potentially in terms of out-patient appointments, and does not necessarily reflect the burden on the healthcare system associated with the management of T2D-related complications.

Evidence from Ireland is consistent with data from the UK reporting high healthcare utilisation among those with T2D. For the period 2017 to 2018 in England and Wales, people with diabetes accounted for around 25 to 30% percent of emergency admissions for CVD complications.[205] During the same period, people with T2D accounted for 40 to 70% of emergency admissions for amputations and renal replacement therapy.[205] A retrospective cohort study of a large secondary care provider in the UK showed that although the prevalence of T2D in the cohort was reported to be 7% in 2012, diabetes and its associated complications accounted for approximately 31% of secondary care costs.[226]

The presence of additional chronic conditions has a significant impact on the treatment and management of T2D. In a cohort of patients with T2D attending general practice in Ireland, the median number of GP visits in the previous 12 months increased significantly with the number of chronic conditions.[155] The median numbers of GP visits were three and eight for those with one and nine or more chronic conditions, respectively.[155] Similarly, the number of comorbidities (elevated HbA1c, elevated LDL-cholesterol, albuminuria, smoking and elevated blood pressure) and age at T2D onset were shown to be associated with the risk of hospitalisation for heart failure relative to matched controls among patients recorded in the Swedish National Diabetes Register between 1998 and 2012.[195] The hazard ratio ranged from 1.17 (95% CI: 1.08 to 1.27) for patients with T2D aged ≥80 years

with one risk factor above the target range to 11.35 (95% CI: 7.16 to 18.01) for patients with T2D aged <55 years with all five risk factors above target.[195]

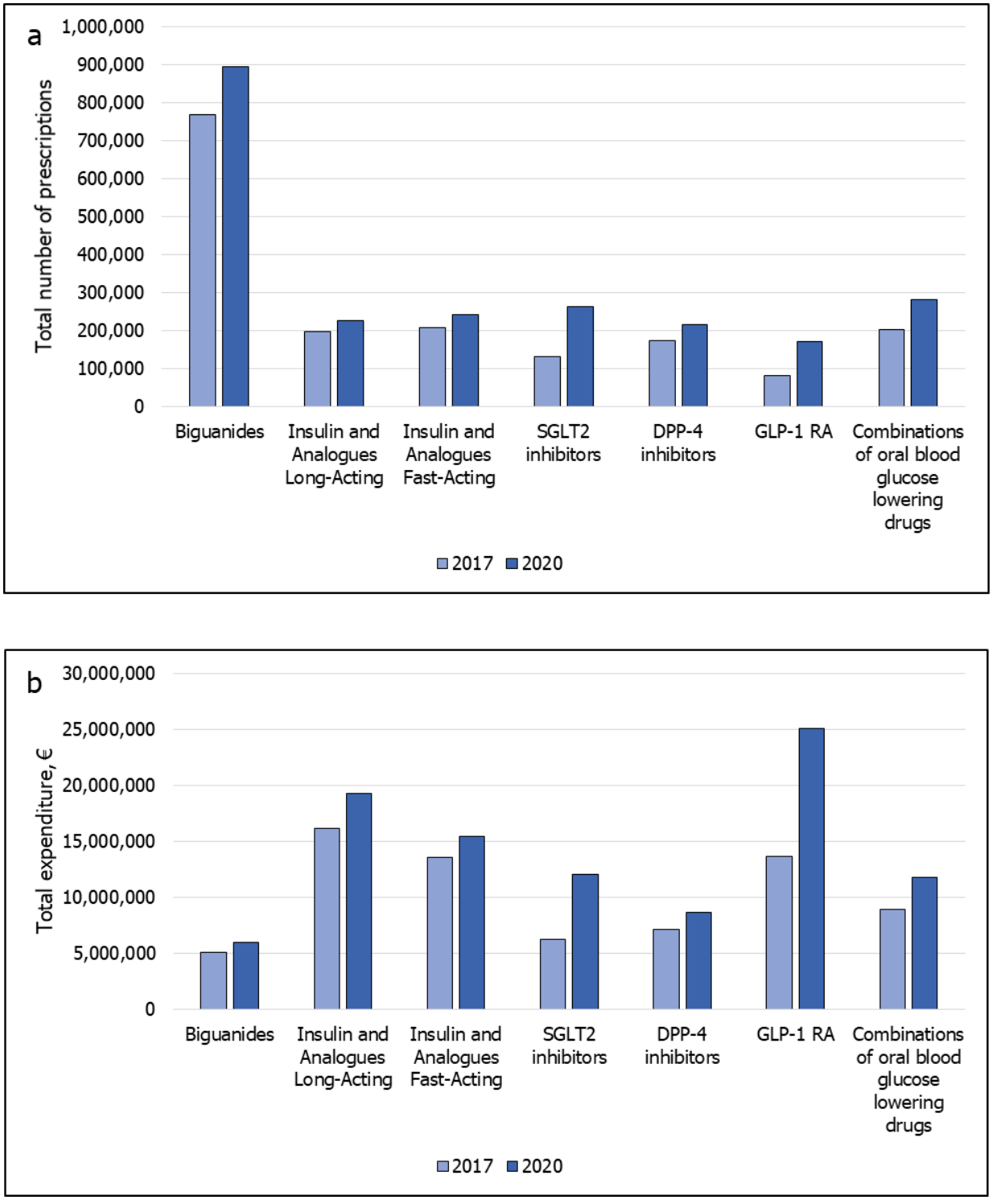
3.7.9 Medication use

In 2020 in Ireland, on average, 276,694 diabetes medications were prescribed monthly under both the Long Term Illness (LTI) and General Medical Services (GMS) schemes. The number of drugs prescribed by diabetes type is not recorded in the Primary Care Reimbursement Service (PCRS) database.

Diabetes is associated with a considerable medication burden for patients and an associated economic burden to society. An analysis of national pharmaceutical expenditure reported an increase in expenditure on blood glucose-lowering medications between 2012 and 2015.[227] The increase was said to be attributable to increased prescription of newer drug classes, including DDP-4 inhibitors, GLP-1 analogues and SGLT2 inhibitors, used in the treatment of T2D as recommended by the ADA.[74, 227] Between 2017 and 2020, prescribing of newer diabetic agents under the LTI scheme continued to increase resulting in further increases in expenditure on blood glucose-lowering medications (Figure 3.6). Given that T1D is managed with insulin,[228] increasing costs associated with changing patterns in the prescription of oral anti-hyperglycaemic agents can be attributed to the treatment of T2D.

In addition to anti-hyperglycaemic medications, patients with T2D and comorbidities require additional medication. Among a cohort of patients with T2D attending Irish general practices, polypharmacy increased significantly with the number of chronic conditions.[155] Just over half the patients were prescribed six or more medications.[155] Those with only one condition (that is, T2D only) were prescribed a mean of 3.4 medications.[155] Of those with undiagnosed and diagnosed T2D in the Cork and Kerry Diabetes Study, 44.4% and 64.7%, were taking medication for hypertension, and 48.6% and 65.7% were taking cholesterol-lowering agents, respectively.[196] A similar proportion of the population with undiagnosed T2D were reported to be taking anti-hypertensive medication in the Diabetes Mellitus and Vascular health initiative (DMVhi) study (45.4%).[135]

Figure 3.6 Most commonly prescribed anti-hyperglycaemic medications under the long term illness scheme in 2017 and 2020 by drug class



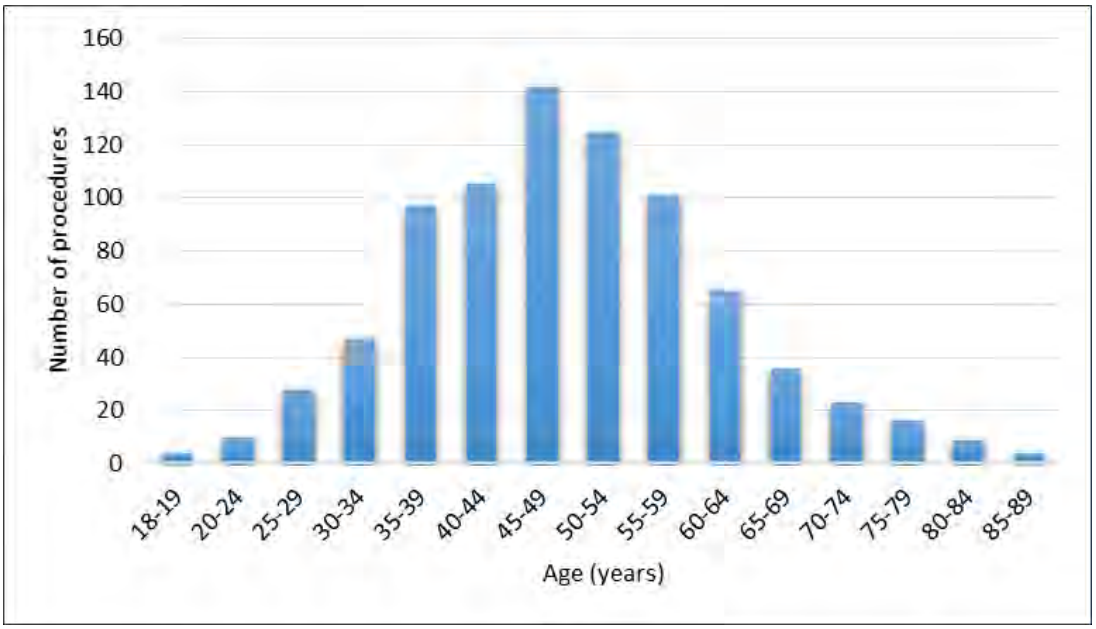
Key: Total number of prescriptions by drug class (panel a). Total expenditure by drug class (panel b). Data were extracted from the Health Service Executive (HSE) Primary Care Reimbursement Service (PCRS) database.[229] Data cannot be used to estimate the prevalence of diabetes as patients may be prescribed >1 drug.

3.8 Bariatric surgery in Ireland

Data regarding bariatric surgery procedures carried out in the Irish public healthcare system were collated using the Hospital Inpatient Enquiry (HIPE) database. Between 2009 and 2019, 70% of patients accessing bariatric surgery through the bariatric surgery programme were aged between 35 and 59 years (Figure 3.7).

Due to delays accessing surgery as a result of limited capacity within the bariatric surgery service, increasing access to surgery may result in a decrease in the age profile of surgical candidates through a reduction in the time interval between referral and surgery.

Figure 3.7 Age profile of bariatric surgery cases between 2009 and 2019 among adults >18 years†



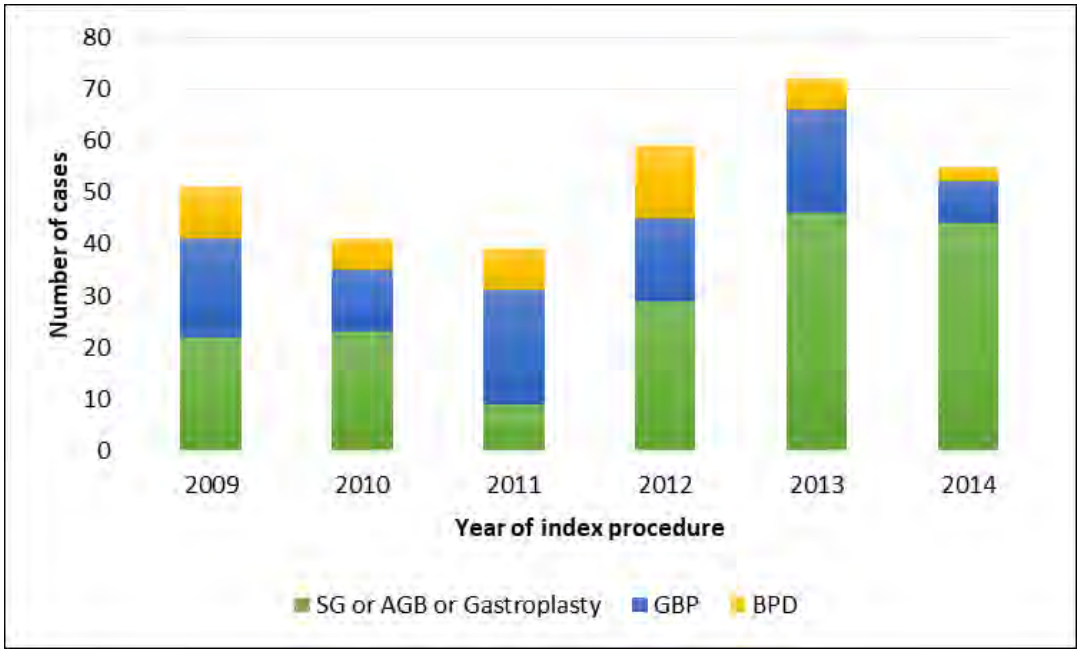
†Reported cases may include a small proportion of cases undergoing partial gastrectomy for benign or malignant disease.

Between 2009 and 2019, 810 cases (2009-14: 316; 2015-19: 494), including 812 (2009-14: 317; 2015-19: 495) procedures were recorded in adults ≥18 years in Irish public acute hospitals. Bariatric surgery is also undertaken in the private hospital system in Ireland, however data on the number of procedures carried out is not available.

Prior to 2015, all gastric restrictive procedures (for example, laparoscopic adjustable gastric banding (LAGB), sleeve gastrectomy or gastroplasty) were recorded using a single code. Therefore, it is not possible to differentiate between AGB, sleeve gastrectomy and gastroplasty. Gastric bypass (primarily RYGB) and sleeve

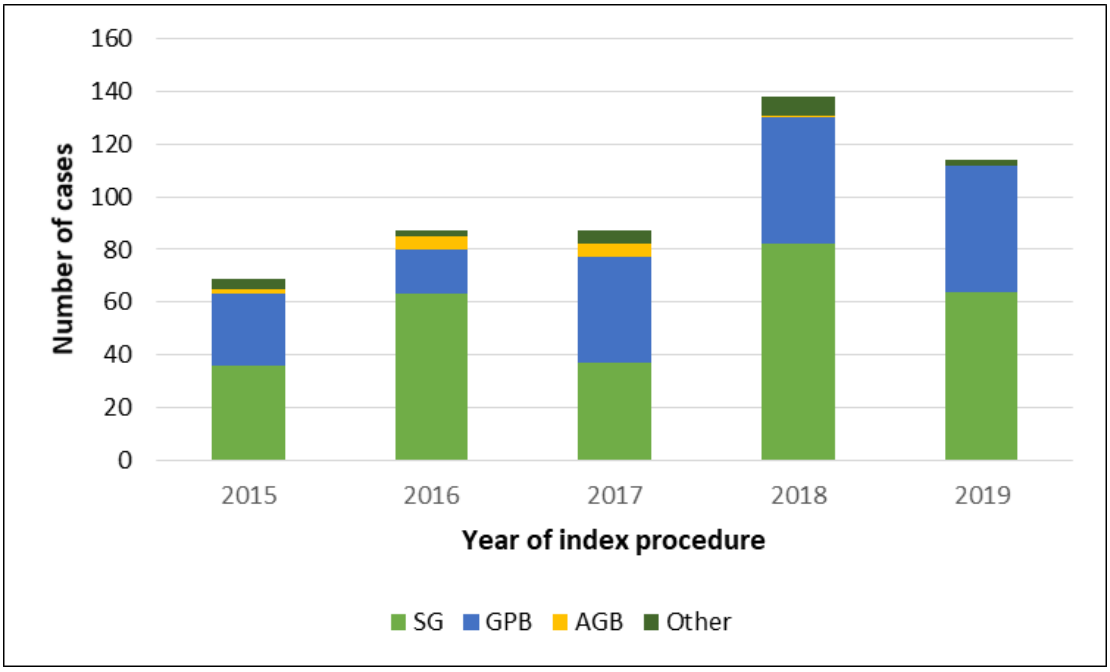
gastrectomy are the most commonly reported bariatric procedures in public acute hospitals in Ireland, accounting for 36% and 57%, respectively, of all bariatric surgeries performed in Ireland between 2015 and 2019 (Figure 3.9). Data from HIPE indicate that AGB accounted for 3% of all bariatric procedures carried out between 2015 and 2019. BPD represented a small proportion of total procedures carried out annually during this period. No gastric banding procedures were reported in acute public hospitals in Ireland after 2018.

Figure 3.8 Number of primary bariatric surgery procedures performed by procedure type between 2009 and 2014 among adults aged ≥18 years*



Key: AGB – adjustable gastric banding; BPD – biliopancreatic diversion; GBP – gastric bypass (mostly Roux-en-Y); SG – sleeve gastrectomy.
*Prior to 2014, all gastric restrictive procedures were recorded in the Hospital Inpatient Enquiry System (HIPE) using a single code. It is not possible to disaggregate the number of adjustable gastric banding, sleeve gastrectomy or gastroplasty procedures performed prior to 2015. Reported cases may include a small proportion of cases undergoing partial gastrectomy for benign or malignant disease.

Figure 3.9 Number of primary bariatric surgery procedures performed by procedure type between 2015 and 2019 among adults aged ≥18 years*



Key: AGB – adjustable gastric banding; GBP – gastric bypass (mostly Roux-en-Y); SG – sleeve gastrectomy.
* Other procedures include biliopancreatic diversion, gastroplasty, ileal-interposition and duodenal-jejunal bypass. Reported cases may include a small proportion of cases undergoing partial gastrectomy for benign or malignant disease.

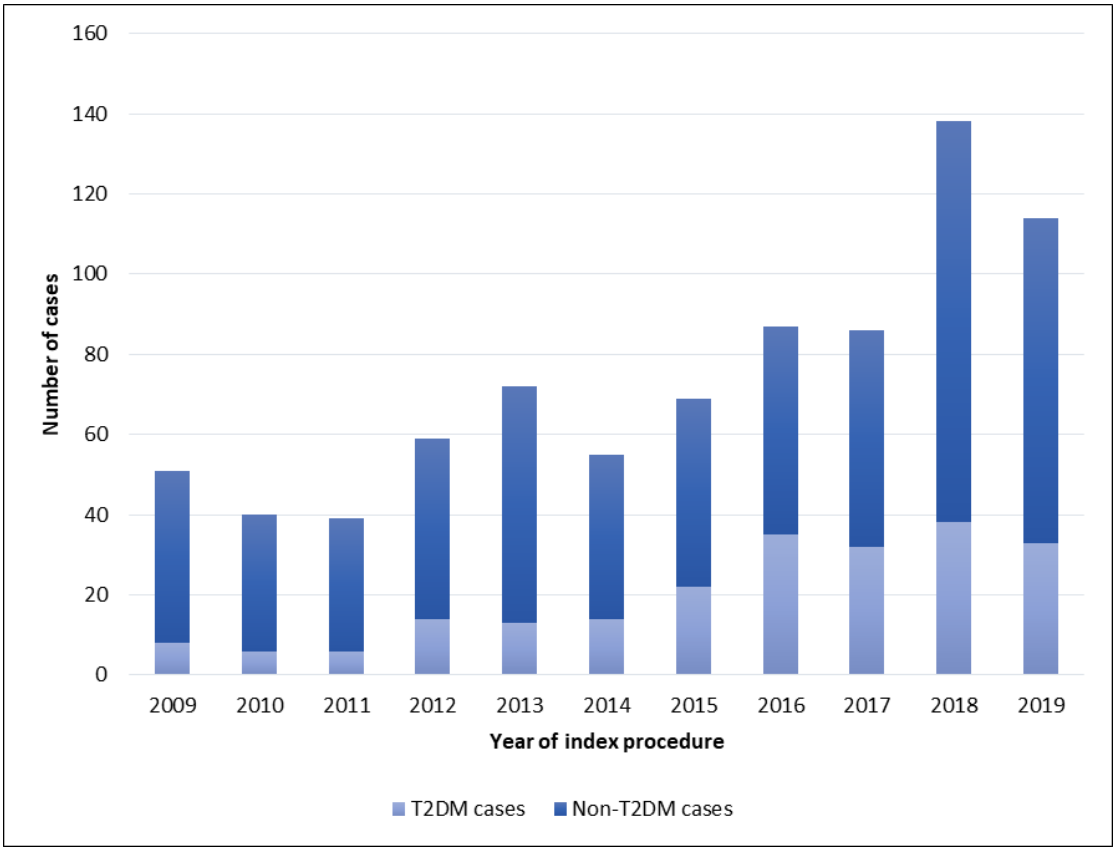
Access to bariatric surgery

At present, access to bariatric surgery services in Ireland is provided exclusively through the National Clinical Programme for Obesity or accessed privately. The eligibility criteria for bariatric surgery have been expanded to adopt a complication-based approach to selection of candidates, as opposed to traditional BMI-based criteria.[230] In addition to patients with a BMI ≥40 kg/m^2 and patients with BMI ≥35 kg/m^2 who have obesity-related comorbidities, patients with a BMI ≥30 kg/m^2 and severe obesity-related comorbidities are eligible for surgery.

At present, patients with comorbid T2D and obesity access surgery through the bariatric surgery service. The proportion of cases with T2D undergoing surgery is inconsistent from year-to-year, as there is no dedicated access for these patients. According to HIPE data, the proportion of cases with a diagnosis of T2D undergoing bariatric surgery gradually increased, from 16% of all cases in 2009 to 40% in 2016 (Figure 3.10). From 2016 to 2019, despite an increase in the total number of procedures being performed, the number of cases with a diagnosis of T2D accessing surgery remained relatively constant. On average, between 2009 to 2019, patients with a diagnosis of T2D represented 24% of cases who underwent a primary

bariatric surgery Data on the pre-operative clinical characteristics of those undergoing bariatric surgery are not available such as BMI, cardiovascular risk factors or HbA1c.

Figure 3.10 Cases with and without T2D undergoing primary bariatric surgery between 2009 and 2019 among adults aged ≥18 years



3.9 International practice

3.9.1 Access to surgical treatment of T2D

According to the fifth International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) global registry report, despite guidelines recommending the use of metabolic surgery for the management of patients with comorbid T2D and obesity above treatment targets despite best medical care, these patients remain under-represented among bariatric surgical candidates.[99] Between 2015 and 2018, the majority of countries reported that 10 to 30% of those undergoing primary bariatric surgery required medication for T2D management at baseline. In European countries including France, Ireland, Norway, Poland, Portugal, Sweden and the United Kingdom, on average 16.9% of bariatric surgery candidates had T2D at

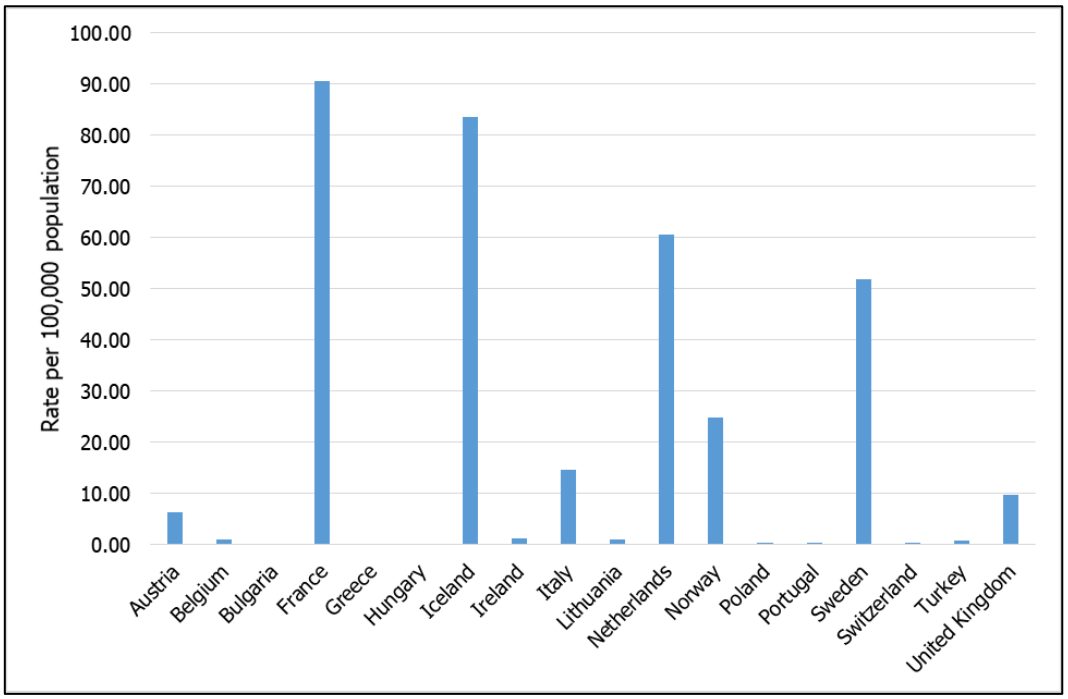
baseline. In contrast, over 50% of bariatric surgery candidates in Austria required medication for T2D prior to surgery during the same period.[99]

3.9.2 Global bariatric surgery trends

According to the IFSO 2019 Global Registry Report, there is a general trend towards a reduction in the rates of AGB and RYGB procedures being performed and a concomitant increase in the number of SG procedures carried out globally.[99] Globally, SG was the most commonly performed procedure (58.6%) between 2015 and 2018, followed by RYGB (31.2%).[99] However, these trends may change, pending the results of ongoing clinical studies of newer and alternative procedures. In particular, the uptake of OAGB appears to be increasing. Of note, the data reported includes patients undergoing both bariatric and metabolic surgery. Trends in the overall population with obesity may not be reflective of usage patterns for patients undergoing metabolic surgery for the treatment of comorbid T2D and obesity.

The number of bariatric surgical procedures performed between 2015 and 2018 varied widely across Europe, despite similar rates of obesity, taking differences in the total eligible population into account (Figure 3.11).[99] In Austria, Belgium, Bulgaria, Greece, Hungary, Ireland, Lithuania, Poland, Portugal, Switzerland, Turkey and the United Kingdom, on average, less than 10 procedures per 100,000 population per year were carried out during the period 2015 and 2018. On average, between 15 and 25 surgeries per 100,000 population per year were carried out in Italy and Norway, respectively, during the same period. In excess of 50 surgeries per 100,000 population were carried out in France, Iceland, the Netherlands and Sweden between 2015 and 2018. [99, 231] Of the data reported in the IFSO Global Registry Report, it is unclear what proportion of the bariatric surgery operations were undertaken within publicly funded healthcare systems.

Figure 3.11 Number of surgical procedures per 100,000 population in selected European countries†‡



† The absolute number of surgeries in European countries was identified from the 2019 IFSO global registry report, and expressed as the rate per 100,000 population based on population estimates available from the Organisation for Economic Co-operation and Development (OECD).[99, 232]
‡ In some cases the absolute number of surgeries reported in the 2019 IFSO report may be an underestimate due to missing data. The level of bariatric surgical activity in France is based on a 2018 national report.[99]

3.10 Discussion

The prevalence of T2D and obesity is rising globally, particularly in Western Europe.[142, 152] While the prevalence of diabetes in Ireland has been estimated to be lower when compared with other European countries this is likely related to the lack of up-to-date national estimates on the prevalence of T2D in Ireland.

Obesity and T2D, individually or as comorbid conditions, are associated with a clustering of cardiometabolic risk factors leading to considerable morbidity. CVD is the leading cause of morbidity and mortality for people with T2D.[233] Given the clinical burden associated with CVD complications in patients with T2D, there has been an increased focus on the joint management of T2D and CVD in T2D treatment algorithms.[194] Improvements in the management of patients with T2D have translated into relative reductions in CVD and CVD-mortality over time.[190, 217, 218] However, in the context of rising T2D prevalence and increased life expectancy, this may not translate into a reduction in the burden of T2D on the healthcare system.[216] Due to improved survival and potentially earlier onset linked to rising

obesity levels, people are living for longer with T2D resulting in a shift in the disease burden from mortality to morbidity. In this way, prevention and management of T2D-related complications is one of the greatest challenges facing public health systems. Management of T2D and treatment of T2D-related complications is associated with a considerable healthcare and economic burden.[225, 226] Increased disease severity is associated with more frequent interactions with the health service, suggesting that reductions in cardio-metabolic risk factors and avoiding the progression of T2D-related complications could provide substantial cost savings through improved clinical outcomes and lower resource use.[225, 226]

There was considerable variation in the prevalence of retinopathy reported in the Irish population compared with European-level estimates.[132, 199, 200] Differences may be attributable to variation in approach to measuring microvascular complications (for example self-report versus direct measurement). The prevalence of microvascular complications in the TILDA dataset is based on self-report which likely explains the lower prevalence in Ireland relative to other European estimates.

According to the fifth IFSO global registry report, patients with comorbid T2D and obesity are under-represented among bariatric surgery candidates within existing bariatric surgery services, with less than 20% of surgical candidates requiring medication for T2D pre-operatively in European counties (for which data were available).[99] This suggests that changes in clinical guidelines recommending metabolic surgery for the treatment of comorbid T2D and obesity have not yet translated into changes in clinical practice. In Ireland, between 2009 and 2019, on average, cases with a diagnosis of T2D represented 24% of all cases who underwent a primary bariatric surgery procedure.

Limitations

Limited epidemiological evidence was available for the population with comorbid T2D and obesity. Estimates of morbidity were based on the general population with T2D in the absence of estimates for the target population of this assessment. Thus, it is possible that the prevalence estimates for T2D-related complications presented here underestimate the burden of T2D-related complications among people with comorbid T2D and obesity, and in particular the burden of cardiovascular complications, due to the known association between obesity and cardiovascular risk.[188]

Countries with similar ethnicity, demography and environmental factors may have different rates of T2D and T2D-related complications. Through a comparison of TILDA data and Northern Ireland Cohort for the Longitudinal Study of Ageing (NICOLA) data, it has been shown that people in Northern Ireland reported

substantially more complications related to diabetes, although rates of healthcare utilisation are similar.[234] From the available evidence it is not possible to identify causal mechanisms behind differences in the severity of T2D, although it could be due to societal factors or differences in access to care. In general, estimates of the prevalence of T2D microvascular complications vary considerably between countries, possibly attributable to methodological differences such as the diagnostic test used or characteristics of the population agreeing to participate in clinical research, or population-level differences including the duration of diabetes, the degree of glycaemic control, age and comorbidities. In the absence of Irish-specific data, estimates obtained from the international literature were based on populations with a similar burden of obesity and T2D relative to Ireland, and are thus likely generalisable to the Irish population. However, some differences may exist.

In the context of increasing obesity levels and the ageing population, prevalence estimates derived from wave one of TILDA are likely an underestimate of the total population ≥50 years with T2D and obesity. Furthermore, estimates for the population aged 18 to 49 years with T2D from the Healthy Ireland survey are based on self-report only and therefore do not capture those with undiagnosed T2D. However, given that the target population for this assessment is those with class I obesity and T2D control above target, and those with class II or III obesity who are likely to have multimorbidity and thus require routine access to healthcare services,[188] those eligible for metabolic surgery in Ireland would be unlikely to go undetected. The estimates used in this assessment may not be suitable for estimating the size of the population eligible for interventions targeting the broader population with T2D, including those with undiagnosed T2D. In addition, older age is not considered an absolute contra-indication for bariatric/metabolic surgery,[235] thus an upper age limit for metabolic surgery was not applied in estimating the potential size of the population eligible for surgery. In clinical practice, potential surgical candidates would be subject to pre-operative screening to identify contraindications to metabolic surgery including inability to comply with lifelong behavioural changes, untreated psychiatric illness including drug/alcohol dependency or limited life expectancy.[235] Thus, the total size of the population suitable for metabolic surgery is less than that presented.

Estimation of the size of the population with T2D control above treatment targets and a BMI ≥30 to 39.9 kg/m^2 was challenging. Firstly, estimation of the size of the population with T2D control above treatment targets is highly dependent on the definition used. Optimal management of T2D and obesity requires consideration of glycaemic control, weight loss, and cardiovascular risk factor reduction in addition to patient-specific characteristics such as age and comorbidity status.[56, 75, 159] However, many estimates of the size of the population with T2D control above

treatment targets identified in the international literature were based on glycaemic control only which may limit their clinical utility.[173, 236-238] In addition, treatment targets identified in the literature were designed to document the proportion of the population meeting treatment targets to facilitate sensitive monitoring of the effectiveness of the overall T2D treatment pathway, rather than estimation of the population eligible for metabolic surgery.[174, 176] Within populations identified as not meeting treatment targets, data on prescribed pharmacological treatments were not reported, therefore, a proportion of these patients may be successfully managed with treatment intensification. Given the challenges associated with defining T2D control above treatment targets, a range of definitions were applied in this assessment to reflect the complexity of T2D treatment. Secondly, the characteristics of the population studied influence estimates of proportion of the population meeting treatment targets. The characteristics of patients managed by the CoC programme may differ from the overall population with T2D in Ireland as only those with a medical card or GP visit card are eligible to be managed as part of the CoC.[239] The direction of bias related to estimates derived from the Cycle of Care programme is unclear. Those enrolled in the programme typically have lower socioeconomic status which may affect access to care and health behaviours, which are likely risk factors for more severe disease in the population with T2D. However, estimates of T2D control above treatment target (based on HbA1c <58 mmol/mol) derived from the CoC programme were lower when compared with estimates from the National Diabetes Registry in Scotland, which could suggest those enrolled in a programme with systematic follow-up may receive better quality of care. In addition, the proportion of those with T2D above treatment targets and a BMI ≥30 to 39.9 kg/m^2 may vary according to age, however, estimates of the prevalence of T2D control above treatment targets were not available by age band. Estimates derived from the international literature may not be directly applicable to the Irish context due to difference in patient and healthcare system characteristics, but can be used to corroborate estimates derived from the Irish population. In the absence of a standardised definition of T2D control above treatment targets,[161] a plausible range of estimates of the potential burden of T2D control above treatment targets in the population with T2D and a BMI ≥30 to 39.9 kg/m^2 has been provided.

Conclusion

Diabetes places a significant burden on the individual patient, the healthcare system and wider society. The increasing prevalence of comorbid T2D and obesity, the large burden of morbidity related to cardiometabolic risk factors in this population and the associated high healthcare utilisation indicates that the burden of comorbid T2D and obesity on the Irish healthcare system will continue to rise unless more effective public health measures can be identified and implemented.

4 Systematic review of clinical effectiveness and safety

Key points

- A systematic review was undertaken to assess the clinical effectiveness and safety of metabolic surgery for the treatment of comorbid type 2 diabetes (T2D) and obesity. Twenty-four randomised controlled trials (RCTs) enrolling 1,712 participants were included that compared metabolic surgery with best medical care or another metabolic surgery.
- Trials generally included short- to medium-term follow-up data. Ten RCTs reported a maximum of 12 months follow-up, while 6 reported up to five years or longer. Mean age ranged from 37 to 56 years. Fourteen RCTs compared one or more metabolic surgeries with best medical care. Four RCTs had three arms.
- Evidence was retrieved for 11 metabolic surgery procedures including:
  - three in routine clinical use for the treatment of obesity (Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG) and one anastomosis gastric bypass (OAGB))
  - two that are not widely used (biliopancreatic diversion (BPD) and laparoscopic adjustable gastric banding (LAGB))
  - four variations of RYGB (laparoscopic silastic ring-RYGB (LSR-RYGB), metabolic RYGB (mRYGB), small pouch RYGB and large pouch RYGB
  - two newer procedures that are not widely adopted (greater curvature plication (GCP) and sleeve gastrectomy with transit bipartition (SG-TB)).
- There was considerable variability in remission rates between RCTs. Remission rates were highly dependent on the definition used and the length of follow-up. In general, metabolic surgery was associated with significantly increased the probability of T2D remission (defined as HbA1c <6.5% (48 mmol/mol) without pharmacological management) relative to best medical care up to five years' follow-up. An additional 25 participants per 100 followed in the RYGB group were in T2D remission relative to best medical care at five years (RD 0.25, 95% CI: 0.13 to 0.38, four RCTs GRADE=low). SG increased cases of T2D remission by an additional 23 participants per 100 followed at five years (RD= 0.23, 95% CI: 0.11 to 0.36, one RCT, GRADE=low) compared with best medical care.
- While surgery was associated with a statistically significant increase in the number of patients in T2D remission, the effect reduced over time indicating that a proportion of those in T2D remission relapsed. However, glycaemic

control as measured with HbA1c remained significantly improved relative to best medical care in the long term irrespective of the procedure.

- The effect of metabolic surgery on T2D is mainly mediated through reductions in HbA1c and BMI. Metabolic surgery resulted in improvements in some, but not all cardiovascular risk factors relative to best medical care, although not all participants had dyslipidaemia or hypertension at baseline. Where pharmacological management of cardiovascular risk factors was indicated, metabolic surgery was associated with a reduction in medication use relative to best medical care.
- For the majority of metabolic outcomes there was no evidence of significant differences between surgeries, although the evidence base was limited for most comparisons other than RYGB versus SG. There was a trend towards a greater reduction in BMI for participants randomised to RYGB compared with SG, however the difference was not statistically significant at all time points.
- Based on limited evidence, metabolic surgery may be associated with an improvement in nephropathy in participants with albuminuria at baseline compared with best medical care. There was no significant difference in the incidence or progression of retinopathy or neuropathy. Investigation of the impact of metabolic surgery on macrovascular disease was not possible due to the sample sizes and relatively short duration of follow-up of included RCTs.
- Metabolic surgery may be associated with improvements in quality of life (QoL) relative to best medical care measured using validated instruments. This effect was largely due to changes in physical rather than mental health domains in some studies. In general, for head-to-head comparisons of surgeries there were no differences in improvement in QoL from baseline.
- No surgery-related mortality was reported in the trials. RCTs were not powered to detect differences in the rate of surgery-related adverse events; however, where reported they were generally not associated with long-term morbidity.
- Limited evidence were available for other potential adverse events including gastroesophageal reflux, dumping syndrome and gallstones. A limited number of RCTs reported nutritional deficiencies during the post-operative period. However, data were generally not reported in the context of clinical manifestations or adherence to prescribed micronutrient supplementation making interpretation challenging.
- The main issues identified during risk of bias assessment related to blinding and attrition. The evidence base is constrained by the small sample sizes of included RCTs and the limited head-to-head evidence between surgical procedures.

4.1 Introduction

The aim of this chapter is to review the clinical effectiveness and safety of metabolic surgery for the treatment of patients with comorbid T2D and obesity.

4.2 Methods

A number of systematic reviews have been conducted in recent years on the topic of metabolic surgery for the treatment of T2D. However, existing reviews differ in terms of the population (for example, BMI category),[240] the types of procedures,[240, 241] or outcomes considered (microvascular outcomes, macrovascular outcomes)[242-244] or methodological approach (for example, minimum duration of follow-up, head-to-head comparisons of surgical procedures).[245-248] No single systematic review in line with the inclusion criteria for this review was identified. An overview of reviews was not considered appropriate as RCT evidence published in 2020[168] and 2021[249] identified during scoping was not captured by existing reviews.

4.2.1 Review protocol

This systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria and registered with the international prospective register of systematic reviews (PROSPERO) with the registration number CRD42021264699.

4.2.2 Research question

The specific question for this systematic review was developed to reflect the outcomes associated with bariatric surgery specifically in a population with comorbid T2D and obesity. Relevant clinical and safety outcomes were identified using core outcome sets for bariatric/metabolic surgery,[250, 251] in addition to T2D-specific outcomes.[252] The PICO (Population, Intervention, Comparator, Outcomes) framework used to formulate the research question is presented in Table 4.1. Only studies in which all participants in the study had a diagnosis of T2D at baseline were included.

Table 4.1 Inclusion criteria set out in the PICOS framework

Population	Adults ≥ 18 years of age with type 2 diabetes and obesity†
Intervention	Metabolic surgery procedures in current use, performed either as open or laparoscopic procedures
Comparator	▪ Non-surgical treatment (optimal medical management including oral or injectable antidiabetic agents and/or insulin) ▪ Other metabolic surgery procedures in current use, performed either as open procedures or laparoscopically
Outcomes	**Primary outcomes:** ▪ Diabetes status o Glycaemic endpoints (e.g., HbA1c, fasting plasma glucose, T2D remission, T2D improvement) o T2D medication use (oral hypoglycaemic medication and insulin) ▪ Mortality (30 day and long-term) ▪ Safety outcomes o Any major or minor technical complications associated with the surgery (e.g., leaks, fistula, strictures, ulcers at anastomosis, internal hernia, gastric band slippage or erosion, intra-operative organ injury, wound infection) o Any post-operative clinical complications (e.g., dysphagia/regurgitation, dumping syndrome, clinically significant nutritional deficiency‡) o Any re-operation/re-intervention **Secondary outcomes:** ▪ BMI change ▪ Health-related quality of life indicators and diabetes-specific measures using a validated instrument (e.g., EQ-5D score, SF-36 score, KCCQ score, BAROS) ▪ Healthcare utilisation or resource use o Hospital length of stay o Outpatient care o Hospital admission/re-admission *Diabetes-related complications* ▪ Lower limb ulceration; major or minor amputation ▪ End-stage renal disease ▪ Cardiovascular risk reduction o Cardiovascular events (e.g., MI, stroke) o Medication use (e.g., antihypertensives, statins, aspirin) ▪ Microvascular complications o Incidence of microvascular complications of T2D (retinopathy, nephropathy, neuropathy) o Resolution or improvement in microvascular complications (e.g., reduction in albuminuria, interventional therapy for retinopathy such as anti-VEGF treatment or the use of medication for neuropathy or nephropathy)
Study design	Randomised and non-randomised controlled trials§

Key: BAROS – Bariatric Analysis and Reporting Outcome System; BMI – Body mass index; EQ-5D - EuroQoL-5 Dimension; HbA1c – Haemoglobin A1c; KCCQ - Kansas City Cardiomyopathy Questionnaire; MI – myocardial infarction; SF-36 – Short Form 36-item Survey; T2D – Type 2 Diabetes.
† Suboptimal or inadequate glycaemic control as defined by study authors.
‡ Clinically significant nutritional deficiency is defined is any lack of essential vitamins and/or minerals secondary to post-operative intestinal malabsorption resulting in clinical manifestations including but not limited to microcytic anaemia, megaloblastic anaemia, neurologic abnormalities, osteoporosis, fractures, ocular xerosis, night blindness symptoms, ophthalmoplegia, peripheral neuropathy and easy bleeding as reported by the

European Association for the Study of Obesity (EASO) and the British Obesity and Metabolic Surgery Society (BOMSS) (see appendix 1).
§ Subsequently excluded due to challenges association with identification of nRCTs during screening.

Exclusion criteria

- reviews, conference abstracts, case reports, or any studies without a comparator group
- before and after studies, not directly comparing surgery with a no-surgery group
- studies in which only a sub-group of the population had a diagnosis of T2D
- studies that include revision procedures (unless disaggregated data are available)
- studies reporting on endoscopic procedures intended for temporary benefit (for example, intragastric balloons)
- surgeries that remove fat (for example, liposuction or abdominoplasty), excess skin or any cosmetic procedures
- articles reporting data on participants <18 years of age (unless disaggregated data are available).

4.2.3 Search strategy

The search string was developed in consultation with a librarian from the Royal College of Surgeons in Ireland (RCSI) and is presented in Appendix A3.1.

Electronic searches were conducted in Medline (via Ovid), Embase and the Cochrane library. Searches of electronic databases were carried out on 24 May 2021 and were supplemented by a search of grey literature including Google Scholar, national and HTA electronic sources (Appendix A3.1). The WHO International Clinical Trials Registry Platform and ClinicalTrials.gov were searched for ongoing or prospective trials. Reference lists of included studies were searched for potentially relevant citations. No date restrictions were applied to the search.

4.2.4 Study selection

Titles and available abstracts were independently screened by two reviewers. The full text of potentially eligible articles were retrieved and independently assessed for eligibility by two reviewers according to the inclusion criteria outlined in Table 4.1, with any disagreements resolved through discussion, or if necessary, a third reviewer. The study selection process is presented on a PRISMA flow diagram (Figure 4.1).

Although originally planned for inclusion, non-randomised controlled trials were not included due to difficulties associated with systematically identifying this type of study design during screening. A list of studies excluded during full text review is presented in Appendix A3.2. Typically, studies were excluded for more than one reason, but the first reason identified is reported.

4.2.5 Data extraction

Data extraction was conducted independently by two reviewers using a standardised, pre-piloted electronic data extraction form. Disagreements were resolved through discussion. The following data was extracted from studies:

- Study details: author, year, country of origin, study design, length of follow-up and funding source.
- Participant details: population size (including attrition rate), population demographics at baseline (age; sex; comorbidities; glycaemic control; BMI; duration of T2D) and eligibility criteria.
- Intervention details: procedure (laparoscopic or open), follow-up care (frequency and type).
- Outcome details: In addition to the criteria listed in Table 4.1, definitions of outcomes (for example, T2D remission, early vs late adverse event, minor vs major adverse event) were extracted, where reported. Adverse events and serious adverse events were reported as defined in the primary studies.

In the case of missing data, the study authors were contacted. Where follow-up data from a single trial was published across a number of publications reporting at different time points, multiple-imputation-based analyses were extracted, where available, to account for loss to follow-up.

Only RCTs that defined microvascular complications (that is, nephropathy, neuropathy, and retinopathy) as primary or secondary outcomes were included in the clinical effectiveness estimates. Microvascular complications reported as adverse events were not extracted due to the absence of information on the diagnostic methods used and the lack of systematic measurement in all participants. Macrovascular events (for example, stroke and myocardial infarction) were extracted where defined as an adverse event.

4.2.6 Data synthesis

T2D remission was synthesised in line with the 2021 revised definition of T2D remission proposed by an international expert group convened by the American

Diabetes Association (ADA), that is, “HbA1c <6.5% (48 mmol/mol) measured at least 3 months after cessation of glucose-lowering pharmacotherapy”.(62) To account for studies reporting in line with previous definitions of T2D remission (partial remission or full remission defined as HbA1c <6.5% (fasting glucose 100 to 125 mg/dL (5.6 to 6.9 mmol/L)) or <6% (<100 mg/dL (5.6 mmol/l), respectively), for at least one year's duration in the absence of active pharmacologic therapy or ongoing procedures), evidence in relation to “any T2D remission” was synthesised in accordance with the following ranking system, developed in consultation with clinical experts on the EAG:

1. HbA1c <6.5% without pharmacological therapy (updated definition)
2. HbA1c <6% with or without pharmacological therapy
3. HbA1c <6% without pharmacological therapy (previously full remission).

The duration of glycaemic control below the diagnostic threshold for T2D, necessary to diagnose T2D remission, was not reported in many RCTs and was thus not included in the definition applied in this systematic review.

Calculation of the odds ratio (OR) or risk ratio (RR) requires application of a continuity correction (that is, adding 0.5 to the number of events or non-events in the intervention and comparator group) to individual RCTs with zero events in one or both arms. However, for the outcome T2D remission, it was observed that the continuity correction biased the estimate towards the null and overestimated variance.(253) Given the very low likelihood of achieving T2D remission in the best medical care group, the risk difference (RD) was presented in addition to the RR, to assist the interpretation of T2D remission estimates.

For continuous data, where appropriate, data were converted to the mean and standard deviation for analysis. If not reported, standard deviations were calculated from standard errors or confidence intervals using the following formulae:

$$SD = SE \times square\ root\ n\ (n = number\ of\ participants)$$

$$SE = (upper\ 95\%\ confidence\ interval - lower\ 95\%\ confidence\ interval) / (2 \times 1.96)$$

Where the mean difference between baseline and follow-up was not reported, it was estimated by simulation of the mean and SD at baseline and follow-up. Where only the median and interquartile range (IQR) were reported, the mean was estimated by summing the median, lower limit and upper limit of the IQR and dividing this sum by three. The SD was then derived by assuming that the width of the IQR was approximately normally distributed. In each case, the change from baseline was

estimated by repeatedly simulating (n=5,000 simulations) the difference between the baseline and follow-up according to a pseudo-random probability. Due to differences in the reporting of continuous outcome measures across studies (for example, units of measurement (mg/dL or mmol/mol) and expression of change scores (absolute or percentage)) the standardised mean difference (SMD) was calculated for the effect size. While this complicates interpretation, it allows for the maximum number of studies to be included in a single comparison. In a number of studies it was unclear if the analysis was adjusted for known prognostic covariates such as HbA1c or BMI. In the context of this systematic review, randomisation was assumed to sufficiently account for confounders to facilitate pooling of outcomes.

Where studies were sufficiently homogenous in terms of participants, interventions and outcomes, meta-analysis was used to generate a pooled effect estimate. Meta-analyses were performed using the meta package (version 4.19-1) in R Studio. Clinical heterogeneity was assessed by reviewing inter-study variability in terms of the study population characteristics, interventions and outcome measurements. Results for both fixed effects and random effects meta-analyses were computed. Preference was given to random effects meta-analysis, due to the variability in RCT populations at baseline. In cases where three or fewer studies where available for a comparison, the fixed effect estimate was used as it was considered that there were insufficient data to support a reliable estimate of between-study variance using a random effects model. Statistical heterogeneity (a consequence of clinical or methodological heterogeneity) was assessed using the I^2 statistic, with an I^2 of between 30% and 60% interpreted as moderate heterogeneity, 50% to 90% as substantial heterogeneity, and 75% to 100% as considerable heterogeneity, in line with Cochrane methodology.[254]

Medication use data were reported heterogeneously across included RCTs including differences in classification by indication (for example, anti-hyperglycaemic agents, anti-hypertensive medication), by drug class (for example, SGLT2 inhibitors), by number of anti-hyperglycaemic medications (that is monotherapy, dual therapy or triple therapy), or by mean change from baseline in the number of agents used. To facilitate synthesis of the available data, the following medications were selected for analysis as exemplars: no T2D medication, insulin, anti-hypertensive and lipid-lowering agents. The groupings ‘no T2D medication’ and ‘insulin use’ can be considered indicative of treatment intensity or a proxy for disease severity. The pooled risk difference was calculated for each medication group at baseline and at follow-up. The impact of length of follow-up on medication use was investigated through meta-regression, although the ability to detect evidence of time trends was limited by the small number of studies available for some comparisons.

Follow-up was defined and categorised according to short-term (<1 year), medium term (1-5 years) or long-term (>10 years) in line with previous studies.[246, 255] Due to variation in the type of metabolic surgery procedures and length of follow-up across studies, subgroup analyses were not possible.

Surgical morbidity and mortality were reported in line with the core outcome set (COS) for bariatric and metabolic surgery, supplemented with input from clinical experts.[250] Technical complications outlined in the COS are listed in Appendix A3.11. Complications unrelated to metabolic surgery were not included. To minimise the possibility of including adverse events unrelated to metabolic surgery, only technical complications occurring up to one year post-surgery (or up to two years in RCTs where data from earlier time points were not available) are reported. The risk of post-surgical adverse events was expressed as the proportion of participants experiencing any technical complication among participants undergoing a procedure. Participants may have had more than one adverse event. The adverse events 'any hypoglycaemic episode' and 'severe/serious hypoglycaemia' were reported as defined by the study authors.

4.2.7 Quality appraisal and grading of the evidence

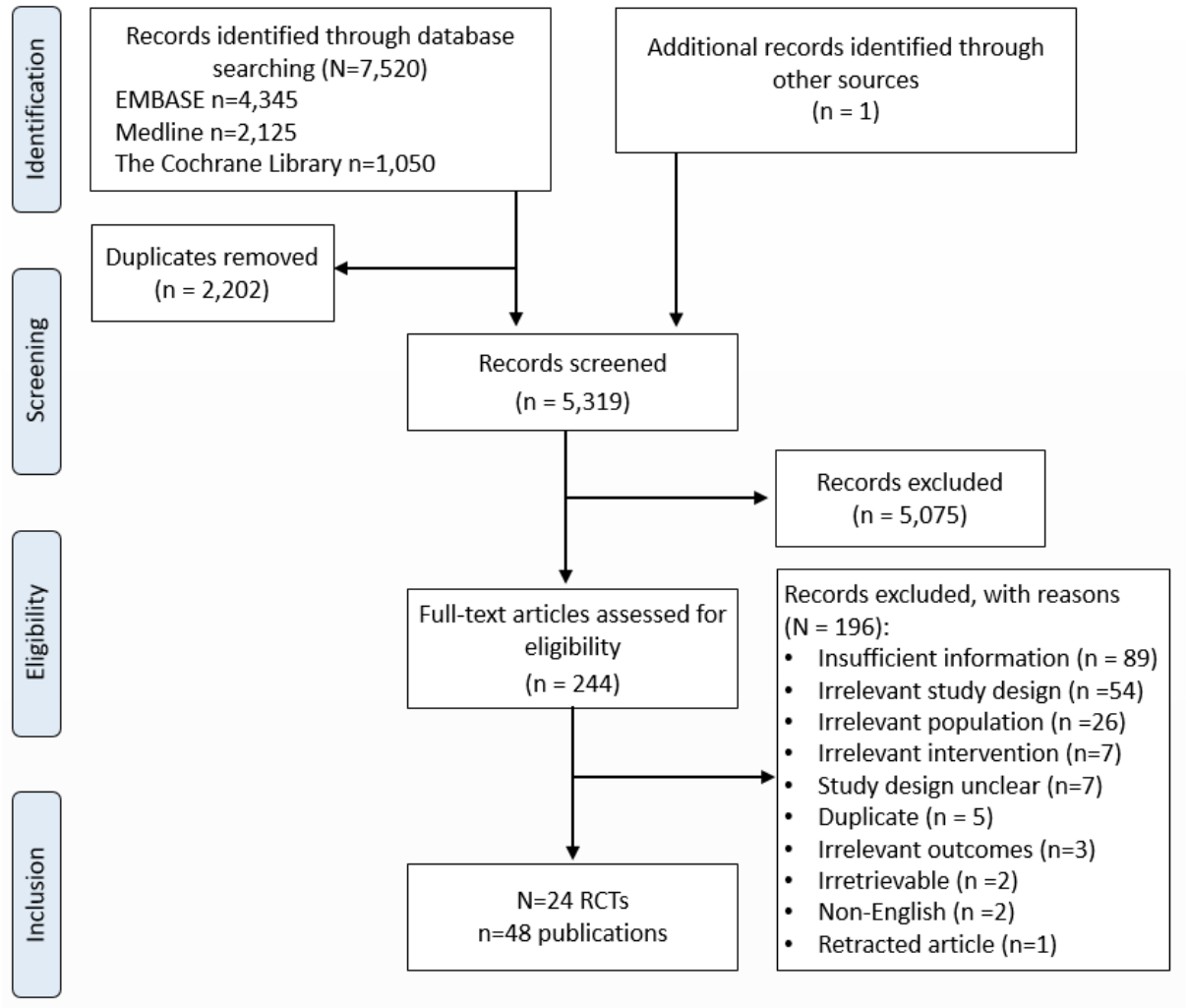
The methodological quality of RCTs was assessed using the Cochrane risk of bias (RoB) 1.0 tool. The RoB 2.0 tool was not applied due to insufficient guidance on the selection of key outcomes for quality appraisal for systematic reviews with multiple outcomes of interest and the documented challenges associated with its application.[256, 257]

The GRADE approach was used to assess the quality of the overall body of evidence for primary outcomes (that is, T2D remission and safety).[258] The five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) were interpreted by two reviewers to assess the quality of the body of evidence for each outcome of interest. Summary of findings tables were generated using the GRADEpro® software. Of note, grading of the body of evidence was only undertaken for primary outcomes fulfilling all elements of the PICO (population, intervention, comparator, outcomes) framework. Technical complications of metabolic surgery were not grading due to the absence of an appropriate comparator.

4.3 Results

After removal of duplicates, 5,319 title and abstracts were assessed for eligibility. Two hundred and forty-four articles required full-text review. Twenty-four randomised controlled trials reported across 48 publications fulfilled the inclusion criteria. An overview of the study selection process is presented in Figure 4.1.

Figure 4.1 PRISMA flow diagram of study selection process



4.3.1 Characteristics of included studies

Twenty-four RCTs reported across 48 publications enrolling 1,712 participants were included in this systematic review (Table 4.2). The majority of included studies were single centre RCTs. Six RCTs were carried out in each of the United States[259-264] and Asia,[169, 265-269] five in Europe,[249, 270-273] two in South America,[168, 274] and one in each of Australia[167] Israel,[275] and New Zealand.[276] Two were multicentre RCTs, of which one was conducted in the United States and Taiwan.[277, 278] Fourteen RCTs compared one or more metabolic surgeries with best medical care.[167-169, 261, 262, 272-274, 279-284] Of these, in ten RCTs, best medical care included intensive T2D management comprising pharmacological management in line with best practice guidelines, an energy-restricted diet and prescribed exercise,[167, 169, 261, 262, 272, 273, 279-284] typically as part of a programme in the first year of the trial, or up to two years in two RCTs.[167, 282]

Ten RCTs reported follow-up data up to one year post-surgery.[169, 261, 262, 265, 267, 271-273, 275, 276] Eight RCTs reported up to medium term follow-up data (two to three years).[167, 168, 263, 264, 266, 268, 274, 277] Five RCTs reported results up to five years post-surgery.[259, 260, 269, 270, 278] Only one RCT reported follow-up data ten years post-surgery with 20 participants in each of the surgical and best medical care arms.[249] Two RCTs enrolled males only.[273, 274]

Studies differed in the mean duration of T2D (that is, time from diagnosis) prior to surgery. In eleven RCTs the mean duration was less than seven years.[167, 265, 266, 268, 271-273, 275, 277, 283, 285] In ten RCTs the mean duration of T2D was greater than seven years, up to a maximum mean duration of 11.4 (SD 4.8) years,[168, 169, 261, 274, 279-282, 284, 286] while in two RCTs the mean duration of T2D prior to surgery was not reported.[262, 267] Nine RCTs were conducted in populations with class II obesity (35 to 39.9 kg/m^2) at baseline.[167, 259-261, 266, 267, 272, 280, 281] In eight studies, the mean BMI at baseline was in the class I obesity range (30 to 34.9 kg/m^2),[168, 169, 262, 265, 268, 269, 274, 278] however of these, five studies included Asian populations for whom lower BMI thresholds are typically used to indicate obesity-related health risk.[169, 265, 268, 269, 278] Insulin use at baseline ranged from zero to 100%.

Twenty three of the 24 RCTs reported the primary outcome of HbA1c,[167-169, 261, 262, 265-268, 271-277, 279-286] 22 reported T2D remission,[167-169, 261, 262, 265, 266, 268, 271, 273-277, 279-286] and 18 reported anti-hyperglycaemic medication use.[167, 168, 261, 262, 267, 268, 271, 274-277, 279-281, 283-286] Nineteen of 24 RCTs reported on mortality.[169, 240, 259-262, 266, 268-271, 274-291]

Table 4.2 Characteristics of included randomised controlled trials[†]

Author, year	Country	Follow-up	Intervention / Comparator	Number of participants (n)		Population characteristics (years (SD))	T2D status at baseline	Baseline BMI (kg/m²)	Comorbidities
Azevedo 2018	Brazil	2 years	LSG+TB	Baseline	10	**Age:** 45 (10.0) **Sex:** 100% male	**HbA1c (%):** 9.3 (2.1) **Duration:** 7.5 (2) **Insulin use:** 100%	33.4 (2.6)	NR
				Year 2	10				
			Medical therapy	Baseline	10	**Age:** 56 (7.0) **Sex:** 100% male	**HbA1c (%):** 8 (1.5) **Duration:** 8.5 (3.2) **Insulin use:** 100%	30.3 (2.1)	NR
				Year 2	10				
Casajoana 2017; 2021	Spain	5 years	Long limb RYGB[†]	Baseline	15	**Age:** 51.1 (7.7) **Sex:** 53% female	**HbA1c (%):** 7.4 (2.0) **Duration:** 4.5 **Insulin use:** 33%	38.7 (2.0)	Hypertension: 66.7% Dyslipidaemia: 73.3%
				Year 1	15				
				Year 5	14				
			SG	Baseline	15	**Age:** 49.2 (9.1) **Sex:** 66.7% female	**HbA1c (%):** 7.89 (1.71) **Duration:** 10.0 **Insulin use:** 40%	39.0 (1.7)	Hypertension: 73.3% Dyslipidaemia: 80%
				Year 1	14				
				Year 5	14				
			GCP	Baseline	15	**Age:** 49.7 (8.1) **Sex:** 80% female	**HbA1c (%):** 8.1 (2.2) **Duration:** 6.9 **Insulin use:** 40%	40.7 (1.3)	Hypertension: 80% Dyslipidaemia: 86.7%
				Year 1	15				
				Year 5	14				
Cohen 2020 (MOMS)	Brazil	2 years	LRYGB	Baseline	51	**Age**: 52.5 (7.6) **Sex**: 45% female	**HbA1c (%):** 8.8 (1.9) **Duration:** 10 (6 to 12)[‡] **Insulin use:** 39%	32.5 (1.9)	Dyslipidaemia: 59%
				Year 1	46				
			Best medical treatment	Baseline	49	**Age**: 50.2 (7.5) **Sex**: 45% female	**HbA1c (%):** 8.94 (1.96) **Duration:** 9 (5 to 13) [‡] **Insulin use:** 24%	32.6 (2.1)	Dyslipidaemia: 37%
				Year 1	46				
Courcoulas 2014; 2015, 2020	United States	5 years	RYGB	Baseline	24	**Age:** 46.3 (7.2) **Sex:** 79%	**HbA1c (%):** 8.7 (2.2)	35.5 (2.6)	Hypertension: 50% Dyslipidaemia: 58%
				Year 1	18				

(TRIABETES)				Year 2	18		**Duration:** 7.4 (4.5) **Insulin use:** 50%		
				Year 5	16				
			LAGB	Baseline	22	**Age:** 47.3 (7.0) **Sex:** 82% female	**HbA1c (%):** 7.9 (2.2) **Duration:** 6.1 (4.3) **Insulin use:** 36%	35.5 (3.4)	Hypertension: 59% Dyslipidaemia: 73%
				Year 1	19				
				Year 2	17				
				Year 5	20				
			Lifestyle Weight-loss intervention	Baseline	23	**Age:** 48.3 (4.7) **Sex:** 83% female	**HbA1c (%):** 7.0 (0.8) **Duration:** 5.7 (5.6) **Insulin use:** 26%	35.7 (3.3)	Hypertension: 70% Dyslipidaemia: 65%
				Year 1	14				
				Year 2	14				
				Year 5	14				
Cummings 2016 (CROSSROADS)	United States	1 year	LRYGB	Baseline	23	**Age**: 52 (8.3) **Sex**: 80% female	**HbA1c (%):** 7.7 (1.0) **Duration:** 11.4 (4.8) **Insulin use:** 60%	38.3 (3.7)	Hypertension: 80% Dyslipidaemia: 87%
				Year 1	15				
			Intensive lifestyle and medical management	Baseline	20	**Age**: 54.6 (6.3) **Sex**: 58.8% female	**HbA1c (%):** 7.3 (0.9) **Duration:** 6.8 (5.2) **Insulin use:** 47%	37.1 (3.5)	Hypertension: 94.1% Dyslipidaemia: 82.4%
				Year 1	17				
Dixon 2008	Australia	2 years	LAGB	Baseline	30	**Age**: 46.6 (7.4) **Sex**: 50% female	**HbA1c (%):** 7.8 (1.2) **Duration:** <2 **Insulin use:** 3%	37 (2.7)	Hypertension: 93% MetS: 97%
				Year 2	26				
			Conventional Therapy	Baseline	30	**Age**: 47.1 (8.7) **Sex**: 57% female	**HbA1c (%):** 7.6 (1.4) **Duration:** <2 **Insulin use:** 0%	37.2 (2.5)	Hypertension: 90% MetS: 97%
				Year 1	29				
Ding 2015; Simonson 2019 (SLIMM-T2D)	United States	3 years	LAGB	Baseline	23	**Age**: 50.6 (12.6) **Sex**: 50% female	**HbA1c (%):** 8.4 (1.1) **Duration:** 10.4 (5.6) **Insulin use:** 72%	36.4 (3.0)	Not reported
				Year 1	18				
				Year 3	16				
			Intensive medical	Baseline	22	**Age**: 51.4 (7.5) **Sex**: 41% female	**HbA1c (%):** 8.1 (1.2)	36.7 (4.2)	Not reported
				Year 1	22				

			diabetes and weight management	Year 3	17		**Duration:** 8.4 (4.2) years **Insulin use:** 18%		
Halperin 2014; Simonson 2018 (SLIMM-T2D)	United States	3 years	LRYGB	Baseline Year 1 Year 3	22 19 16	**Age**: 50.7 (7.6) **Sex**: 68% female	**HbA1c (%):** 8.2 (1.4) **Duration:** 10.6 (6.6) **Insulin use:** 79%	36.0 (3.5)	Not reported
			Lifestyle with intensive medical management	Baseline Year 1 Year 3	21 17 12	**Age**: 52.6 (4.3) **Sex**: 53% female	**HbA1c (%):** 8.83 (1.01) **Duration:** 10.2 (6.1) **Insulin use:** 42%	36.5 (3.4)	Not reported
Hofso 2019; 2021 (OSEBERG)	Norway	1 year	LSG	Baseline Year 1	55 54	**Age:** 47.1 (10.2) **Sex:** 58% female	**HbA1c (%):** 7.9 (6.9 to 9.9) † **Duration:** 6.3 (5.5) **Insulin use:** 20%	42.1 (5.3)	Hypertension: 65% Dyslipidaemia: 51%
			LRYGB	Baseline Year 1	54 53	**Age:** 48.2 (8.9) **Sex:** 74% female	**HbA1c (%):** 7.6 (6.8 to 8.5) † **Duration:** 6.6 (6.5) **Insulin use:** 20%	42.4 (5.4)	Hypertension: 69% Dyslipidaemia: 39%
Ikramuddin 2013; 2015; 2016; 2018 (Diabetes Surgery Study)	United States and Taiwan	5 years	LRYGB	Baseline Year 1 Year 2 Year 3 Year 5	60 57 56 55 55	**Age**: 49 (95% CI: 47 to 52) **Sex**: 63% female	**HbA1c (%):** 9.6 (9.4 to 9.9) **Duration:** 8.9 (95% CI: 7.3 to 10.4) **Insulin use:** 62%	34.9 (95% CI: 34.2 to 35.7)	Hypertension: 68% Dyslipidaemia: 65%
			Lifestyle and medical management	Baseline Year 1 Year 2 Year 3 Year 5	60 57 54 46 43	**Age**: 49 (95% CI 47 to 51) **Sex**: 57% female	**HbA1c (%):** 9.6 (9.3 to 9.9) **Duration:** 9.1 (95% CI 7.7 to 10.5) **Insulin use:** 43%	34.3 (33.5 to 35.1)	Hypertension:73% Dyslipidaemia:68%
Katsogiannos 2019 (Bariglykos)	Sweden	6 months	LRYGB	Baseline 6 months	14 13	**Age:** 55.0 (9.0) **Sex:** 77% female	**HbA1c (%):** 7.2 (1.1) **Duration:** 4.0 (3.0) **Insulin use:** NR	36.8 (4.0)	Not reported
			Standard	Baseline	7	**Age:** 49.0 (5.0)	**HbA1c (%):** 6.62	36.2 (4.0)	Not reported

			medical treatment	6 months	6	**Sex:** 33% female	(0.89) **Duration:** 4 (4) **Insulin use:** NR		
Keidar 2013	Israel	1 year	LRYGB	Baseline	22	**Age:** 51.5 (8.3) **Sex:** 42% female	**HbA1c (%):** 7.7 (1.3) **Duration:** 5.4 (5.0) **Insulin use:** 21%	42.0 (4.8)	Not reported
				Year 1	19				
			LSG	Baseline	19	**Age:** 47.7 (11.7) **Sex:** 50% female	**HbA1c (%):** 8.3 (1.8) **Duration:** 6.7 (5.3) **Insulin use:** 22%	42.5 (5.5)	Not reported
				Year 1	18				
Lee 2011; 2014	Taiwan	5 years	LSAGB	Baseline	30	**Age:** 44.6 (8.6) **Sex:** 73% female	**HbA1c (%):** 10.0 (1.8) **Duration:** 5.8 (5.7) **Insulin use:** 3%	30.2 (2.2)	Hypertension: 53% Dyslipidaemia: 53%
				Year 1	30				
				Year 5	24				
			LSG	Baseline	30	**Age:** 46.4 (8.1) **Sex:** 69% female	**HbA1c (%):** 9.9 (1.8) **Duration:** 6.9 (5.3) **Insulin use:** 23%	31.0 (2.8)	Hypertension: 57% Dyslipidaemia: 57%
				Year 1	30				
				Year 5	24				
Liang 2013	China	1 year	LRYGB	Baseline	31	**Age:** 50.8 (5.4) **Sex:** 29% female	**HbA1c (%):** 10.5 (1.2) **Duration:** 7.4 (1.7) **Insulin use:** 100%	30.3 (1.4)	Hypertension: 100%
				Year 1	NR				
			Usual care + Exenatide	Baseline	34	**Age:** 50.9 (5.9) **Sex:** 29% female	**HbA1c (%):** 10.5 (1.5) **Duration:** 7.2 (1.8) **Insulin use:** 100%	30.5 (1.0)	Hypertension: 100%
				Year 1	NR				
Mingrone 2012; 2015, 2021	Italy	10 years	LRYGB	Baseline	20	**Age:** 43.9 (7.6) **Sex:** 60% female	**HbA1c (%):** 8.6 (1.4) **Duration:** 6.0 (1.2) **Insulin use:** 45%	44.9 (5.2)	Not reported
				2 years	19				
				5 years	19				
				10 years	20				
			BPD	Baseline	20	**Age:** 42.8 (8.1) **Sex:** 50% female	**HbA1c (%):** 8.9 (1.7) **Duration:** 6.0 (1.3) **Insulin use:** 50%	45.1 (7.8)	Not reported
				2 years	19				
				5 years	19				
				10 years	20				
			Medical	Baseline	30	**Age:** 43.5 (7.3)	**HbA1c (%):** 8.5	45.6 (6.2)	Not reported

			therapy	2 years	18	**Sex:** 50% female	(1.2) **Duration:** 6.1 (1.2) **Insulin use:** 55%		
				5 years	15				
				10 years	15				
Murphy 2018	New Zealand	1 year	LSR-RYGB	Baseline	56	**Age:** 46.6 (6.7) **Sex:** 59% female	**HbA1c (mmol/L):** 64.5 (18.1) **Duration:** <5 years: 46.4% 5-10 years: 23.2% >10 years: 30.4% **Insulin use:** 30%	42.2 (6.2)	Not reported
				Year 1	56				
			LSG	Baseline	58	**Age:** 45.5 (6.4) **Sex:** 45% female	**HbA1c (mmol/L):** 61.9 (12.8) **Duration:** <5 years: 41.3% 5-10 years: 32.8% >10 years: 25.9% **Insulin use:** 28%	41.9 (5.9)	Not reported
				Year 1	53				
Parikh 2014	United States	6 months	Surgery (LAGB; LSG; RYGB)	Baseline	29	**Age:** 46.8 (8.1) **Sex:** 79% female	**HbA1c (%):** 7.7 (1.4) **Duration:** NR **Insulin use:** 34%	32.8 (1.7)	Not reported
				6 months	20				
			Medical weight management	Baseline	28	**Age:** 53.9 (8.4) **Sex:** 79% female	**HbA1c (%):** 7.9 (1.3) **Duration:** NR **Insulin use:** 39%	32.4 (1.8)	Not reported
				6 months	24				
Picu 2020 (CREDOR)	Romania	1 year	LSG	Baseline	20	**Age**: 46.0 (5.9) **Sex**: 0% female	**HbA1c (%):** 8.8 (1.6) **Duration:** 5.4 (2.9) **Insulin use:** NR	41.2 (4.8)	Not reported
				Year 1	19				
			Conventional therapy (Diet and diabetes treatment)	Baseline	21	**Age**: 48.7 (6.8) **Sex**: 0% female	**HbA1c (%):** 8.4 (1.5) **Duration**: 6.3 (4.5) **Insulin use:** NR	41.5 (5.6)	Not reported
				Year 1	15				
Ren 2015	China	1 year	Small pouch LRYGB	Baseline	38	**Age:** 45.1 (5.5) **Sex**: 61% female	**HbA1c (%):** 9.7 (1.6) **Duration:** 5.1 (2.3) **Insulin use:** 34%	33.7 (0.9)	Hypertension: 74% Dyslipidaemia:89% MetS: 92%
				Year 1	36				

			Large pouch LRYGB	Baseline	38	**Age:** 44.4 (5.8) **Sex:** 53% female	**HbA1c (%):** 9.5 (1.4) **Duration:** 4.9 (2.3) **Insulin use:** 29%	33.6 (1.0)	Hypertension: 71% Dyslipidaemia: 87% MetS: 95%
				Year 1	33				
Schauer 2012; 2015; 2017 (STAMPEDE)	United States	5 years	LRYGB	Baseline	50	**Age**: 48.3 (8.4) **Sex**: 58% female	**HbA1c (%):** 9.3 (1.4) **Duration:** 8.2 (5.5) years **Insulin use:** 44%	37.0 (3.3)	Hypertension: 70% Dyslipidaemia: 88% MetS: 45% GERD: 34%
				Year 1	50				
				Year 3	48				
				Year 5	49				
			LSG	Baseline	50	**Age**: 47.9 (8.0) **Sex**: 78% female	**HbA1c (%):** 9.5 (1.7) **Duration:** 8.5 (4.8) years **Insulin use:** 44%	36.2 (3.9)	Hypertension: 60% Dyslipidaemia: 80% MetS: 94% GERD: 38%
				Year 1	49				
				Year 3	49				
				Year 5	47				
			Intensive medical management	Baseline	50	**Age**: 49.7 (7.4) **Sex**: 62% female	**HbA1c (%):** 8.9 (1.4) **Duration:** 8.9 (5.8) years **Insulin use:** 44%	36.8 (3.0)	Hypertension: 60% Dyslipidaemia: 84% MetS: 92% GERD: 39.5%
				Year 1	41				
				Year 3	40				
				Year 5	38				
Tang 2016	China	2 years	LSG	Baseline	40	**Age:** 36.6 (8.0) **Sex:** 64.7% female	**HbA1c (%):** 7.4 (1.8) **Duration:** 5.1 (4.1) **Insulin use:** NR	38.4 (8.6)	Hypertension: 35.3% Dyslipidaemia: 32.4%
				Year 2	34				
			LRYGB	Baseline	40	**Age:** 40.4 (12.3) **Sex:** 47.4% female	**HbA1c (%):** 7.4 (1.8) **Duration:** 6.5 (4.1) **Insulin use:** NR	37.8 (5.6)	Hypertension: 42.1% Dyslipidaemia: 26.3%
				Year 2	38				
Wallenius 2020	Sweden	2 years	LRYGB	Baseline	29	**Age:** 49.1 (9.2) **Sex:** 48% female	**HbA1c (%):** 7.9 (1.5) **Duration:** 5.5 (4.1) **Insulin use:** 32%	39.5 (3.7)	Hypertension: 80% Dyslipidaemia:88%
				Year 1	25				
				Year 2	22				
			LSG	Baseline:	31	**Age:** 47 (10.7) **Sex:** 46% female	**HbA1c** (%): 8.2 (1.9) **Duration:** 5.0 (3.7) **Insulin use:** 13%	40.8 (4.1)	Hypertension: 67% Dyslipidaemia: 96%
				Year 1	24				
				Year 2	22				
Yan 2021	China	1 year	LGBP	Baseline	84	**Age**: 43.4 (12.0) **Sex**: 47% female	**HbA1c (%):** 8.3 (1.3)	35.7 (4.5)	Not reported
				Year 1	77				

						Duration: NR **Insulin use:** NR		
			LSG	Baseline	85	**Age**: 44.6(11.8) **Sex**: 46% female	**HbA1c (%):** 8.4 (1.4) **Duration:** NR **Insulin use:** NR	36.2 (4.8)	Not reported
				Year 1	80				
Yang 2021	China	3 years	LSG	Baseline:	32	**Age**: 40.4 (9.4) **Sex**: 71.9% female	**HbA1c (%):** 8.5 (1.2) **Duration:** 4.0 (1.7) **Insulin use:** 47%	31.8 (3)	Hypertension: 31.2% Dyslipidaemia: 65.6%
				Year 1	28				
			LRYGB	Baseline	32	**Age**: 41.4 (9.3) **Sex**: 59.4% female	**HbA1c (%):** 8.9 (1.3) **Duration:** 4.2 (1.9) **Insulin use:** 56%	32.3 (2.4)	Hypertension: 37.5% Dyslipidaemia: 56.2%
				Year 1	27				

Key: BMI – body mass index; BPD – biliopancreatic diversion; CI – confidence interval; GCP – greater curvature plication; GERD – gastro-eosophageal reflux disease; HbA1c – glycated haemoglobin; (L)AGB – (laparoscopic) adjustable gastric banding; (L)GBP – (laparoscopic) gastric bypass; (L)RYGB – (laparoscopic) Roux-en-Y gastric bypass; (L)SAGB – (laparoscopic) single anastomosis gastric bypass/one anastomosis gastric bypass/mini gastric bypass; (L)SG –(laparoscopic) sleeve gastrectomy; MetS – metabolic syndrome; (L)SG+TB – (laparoscopic) sleeve gastrectomy with transit bipartition; SR-LRYGB – silastic ring (laparoscopic) Roux-en-Y gastric bypass; T2D – type 2 diabetes.
† Continuous data are presented as the mean (SD) unless otherwise stated.
‡ Median (interquartile range)

4.3.2 Clinical effectiveness

For clinical outcomes, the focus of the assessment was on Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) procedures, given that these are the most commonly performed procedures in Ireland and globally.[99]

4.3.2.1 T2D remission

Twenty-two of 24 RCTs reported on the outcome T2D remission, at time points ranging from one to ten years post-surgery. Of these, one study did not report the cut-point used and was thus excluded from the quantitative synthesis.[169] Definitions of T2D remission varied across RCTs in terms of the glycaemic cut-point used, the requirement for cessation of medication and the duration of time without pharmacological management. Studies typically applied more than one definition of T2D remission. For the purposes of this systematic review, in line with updated guidance, T2D remission is reported as HbA1c ≤6.5 % without T2D medication,[62] with 11 trials applying this definition.

As included RCTs reported results for T2D remission in line with the previously recommended definitions of partial and complete remission, data for “any T2D remission” and “full remission” are also presented in the supplementary appendix A3.4 (see Methods).

Metabolic surgery compared with best medical care

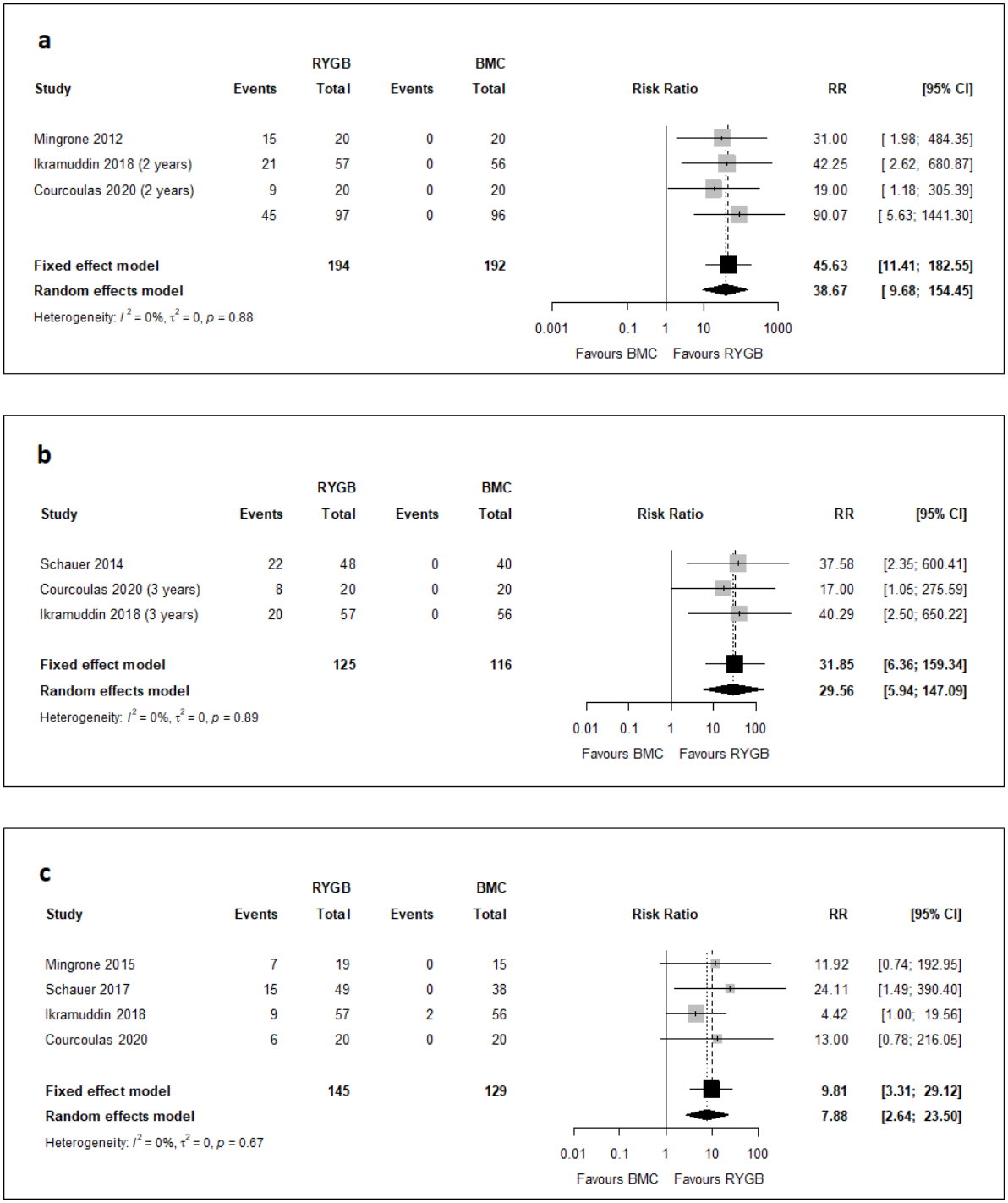
An additional 25 participants per 100 followed in the RYGB group were in T2D remission relative to best medical care at five years (95% CI: 13 to 38, GRADE=low) (Figure 4.2 and Table 4.3). Based on data from one RCT, the treatment effect was not statistically significant at ten years follow-up (RR=4.50, 95% CI: 0.58 to 34.97; RD=0.19, 95% CI: -0.02 to 0.41, GRADE=low). Of note, no participant treated with best medical care experienced T2D remission during follow-up. In one RCT, two participants randomised to best medical care crossed over to RYGB three years post-randomisation and were included in the best medical care estimates for the intention-to-treat analysis resulting in a reduction in the magnitude of the observed treatment effect.[278]

SG increased T2D remissions by an additional 29 and 23 participants per 100 followed at three (RR=23.78; 95% CI: 1.46 to 386.69; RD=0.29; 95% CI: 0.16 to 0.42, GRADE=moderate) and five years (RR=18.69, 95% CI: 1.14 to 307.22; RD= 0.23, 95% CI: 0.11 to 0.36, GRADE=low) relative to best medical care (Table 4.3).

Laparoscopic adjustable gastric banding (LAGB) was associated with a statistically significant increase in the probability of T2D remission when T2D remission was assessed using absolute risk differences, but not relative risk differences at two, three and five years' follow-up (Table 4.3). Biliopancreatic diversion (BPD) was associated with a significant increase in the probability of T2D remission at two, five and ten years' follow-up (Table 4.3).

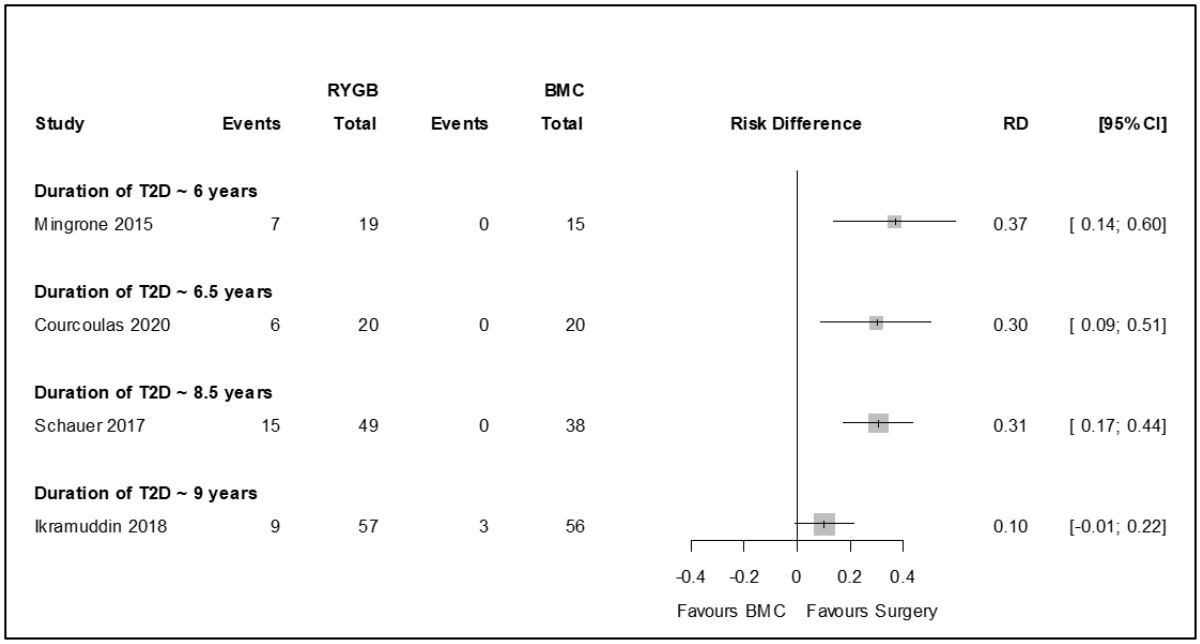
Insufficient data were available to facilitate planned subgroup analysis according to duration of T2D at baseline for the majority of comparisons. However, there was a trend towards increased probability of T2D remission with shorter duration of T2D for the comparison RYGB versus best medical care (Figure 4.3).

Figure 4.2 Efficacy of RYGB compared with best medical care for T2D remission at (a) 2 years', (b) 3 years' and (c) 5 years' follow-up†



Key: BMC – best medical care; RR – relative risk or risk ratio; RYGB - Roux-en-Y gastric bypass.
† Where imputed data for earlier time points were reported in subsequent publications, imputed results are presented.

Figure 4.3 Impact of duration of T2D on the probability of T2D remission for RYGB versus best medical care at 5 years' follow-up



Key: BMC – best medical care; RR – relative risk or risk ratio; RYGB - Roux-en-Y gastric bypass; T2D – type 2 diabetes.

Table 4.3 Effect of metabolic surgery compared with best medical care on T2D remission†

Comparison	Number of RCTs	Author, year	Surgery (n)	Comparator (n)	Relative risk (95% CI)	P value‡	I^2 (95% CI)	Risk Difference (95% CI)	P value‡	I^2 (95% CI)
One year follow-up										
RYGB v BMC	2	Cummings 2016; Courcoulas 2020 (1 year)	39	40	15.06 (3.01 to 75.41)	**0.001**	0.0%	0.52 (0.35 to 0.68)	**<0.0001**	0.0%
LAGB v BMC	2	Ding 2015; Courcoulas 2020 (1 year)	40	45	8.79 (1.12 to 69.12)§	**0.0388**	0.0%	0.17 (0.05 to 0.29)§	**0.0054**	74.1% (0.0 to 94.2)
Two years follow-up										
RYGB v BMC	3	Courcoulas 2020 (2 years); Ikramuddin 2018 (2 years) Mingrone 2012	97	96	30.79 (6.22 to 152.50)	**<0.0001**	0.0% (0.0 to 89.6)	0.47 (0.37 to 0.56)	**<0.0001**	80.2% (37.7 to 93.7)
LAGB v BMC	1	Courcoulas 2020 (2 years)	21	20	12.41 (0.74 to 206.86)	0.0794	NA	0.29 (0.08 to 0.49)	**0.0054**	NA
BPD v BMC	1	Mingrone 2012	20	20	39.00 (2.52 to 604.71)	**0.0088**	NA	0.95 (0.82 to 1.08)	**<0.0001**	NA
Three years follow-up										
RYGB v BMC	3	Courcoulas 2020 (3 years); Schauer 2014; Ikramuddin 2018 (3 years)	125	116	31.85 (6.36 to 159.34)	**<0.0001**	0.0% (0.0 to 89.6)	0.40 (0.31 to 0.49)	**<0.0001**	0.0% (0.0 to 89.6)
LAGB v BMC	1	Courcoulas 2020 (3 years)	21	20	12.41 (0.74 to 206.86)	0.0794	NA	0.29 (0.08 to 0.49)	**0.0054**	NA
SG v BMC	1	Schauer 2014	49	40	23.78 (1.46 to 386.69)	**0.0259**	NA	0.29 (0.16 to 0.42)	**<0.0001**	NA

Five years follow-up										
RYGB v BMC	4	Mingrone 2015; Courcoulas 2020; Schauer 2017; Ikramuddin 2018	145	129	7.88 (2.64 to 23.50)	**0.0002**	0.0% (0.0 to 84.7)	0.25 (0.13 to 0.38)	**<0.0001**	58.1 (0.0 to 86.1)
LAGB v BMC	1	Courcoulas 2020	21	20	8.59 (0.49 to 150.00)	0.1405	NA	0.19 (0.01 to 0.37)	**0.0389**	NA
SG v BMC	1	Schauer 2017	47	38	18.69 (1.14 to 307.22)	**0.0404**	NA	0.23 (0.11 to 0.36)	**0.0003**	NA
BPD v BMC	1	Mingrone 2015	19	15	20.00 (1.28 to 312.60)	**0.0327**	NA	0.63 (0.40 to 0.86)	**<0.0001**	NA
Ten years follow-up										
RYGB v BMC	1	Mingrone 2021	20	18	4.50 (0.58 to 34.97)	0.1505	NA	0.19 (-0.02 to 0.41)	0.0794	NA
BPD v BMC	1	Mingrone 2021	20	18	9.00 (1.27 to 63.54)	**0.0276**	NA	0.44 (0.20 to 0.69)	**0.0003**	NA

Key: BMC – best medical care; BPD – biliopancreatic diversion; (L)AGB – (laparoscopic) adjustable gastric banding; (L)RYGB – (laparoscopic) Roux-en-Y gastric bypass; (L)SG – (laparoscopic) sleeve gastrectomy.
† T2D remission is defined as HbA1c <6.5% without T2D medication.
‡ P <0.05 is considered statistically significant. Bold values denote statistical significance.
§ Tests for statistical significance yield different results under fixed or random effects meta-analysis due to the presence of significant heterogeneity.

Metabolic surgery compared with other metabolic surgeries

Eight head-to-head surgical comparisons were identified, reporting at one to ten years post-surgery, namely:

- LRYGB versus LSG (n=3)
- LRYGB versus LAGB (n=1)
- LRYGB versus BPD (n=1)
- Laparoscopic one-anastomosis gastric bypass (LOAGB) versus LSG (n=1)
- Laparoscopic silastic-ring (LSR)-RYGB versus LSG (n=1)
- Metabolic (m)RYGB (characterised by a longer biliopancreatic limb length) versus SG (n=1)
- mRYGB versus greater curvature plication (GCP) (n=1)
- SG versus greater curvature plication (GCP) (n=1).

At one year follow-up in one RCT, there was a statistically significant increase in the probability of T2D remission in the LOAGB group versus LSG (RR=2.00, 95% CI: 1.35 to 2.97; RD=0.47, 95% CI: 0.27 to 0.67, GRADE=moderate), which was sustained at five years' follow-up, with an additional 30 participants per 100 followed in T2D remission in the LOAGB group relative to LSG (RR=2.00; 95% CI: 1.07 to 3.71; RD=0.30, 95% CI: 0.06 to 0.54, GRADE=low).[269, 285]

At one year follow-up, mRYGB, was associated with a statistically significant increase in the probability of T2D remission versus SG (RR=1.63; 95% CI 1.08 to 2.47; RD=0.40, 95% CI: 0.14 to 0.66) and GCP (RR=1.82, 95% CI: 1.14 to 2.91; RD=0.47, 95% CI: 0.21 to 0.73), which was sustained at five years post-surgery for mRYGB versus SG (RR=2.80, 95% CI: 1.35 to 5.80; RD=0.60, 95% CI: 0.33 to 0.87) and mRYGB versus GCP (RR=7.00, 95% CI: 1.91 to 25.62; RD=0.80, 95% CI: 0.59 to 1.01) based on the results of a single RCT.[270, 286]

For all other comparisons, including RYGB versus SG, there was no significant difference in the probability of being in T2D remission between surgeries at any length of follow-up (Table 4.4).

Table 4.4 Comparative effectiveness of metabolic surgeries on T2D remission†

Comparison	Number of RCTs	Author, year	Surgery (n)	Comparator (n)	Risk ratio (95% CI)	P value‡	Risk difference (95% CI)	P value‡
One-year follow-up								
RYGB v LAGB	1	Courcoulas 2020 (1 year)	24	22	1.83 (0.83 to 4.04)	0.1331	0.23 (-0.05 to 0.50)	0.1030
LOAGB v LSG	1	Lee 2011	30	30	2.00 (1.35 to 2.97)	**0.0006**	0.47 (0.27 to 0.67)	**<0.0001**
LSR-RYGB V LSG	1	Murphy 2018	56	53	1.05 (0.83 to 1.31)	0.6973	0.03 (-0.13 to 0.20)	0.6967
mRYGB V SG	1	Casajoana 2017	15	15	1.63 (1.08 to 2.47)	**0.0207**	0.40 (0.14 to 0.66)	**0.0021**
mRYGB V GCP	1	Casajoana 2017	15	15	1.82 (1.14 to 2.91)	**0.012**	0.47 (0.21 to 0.73)	**0.0004**
SG v GCP	1	Casajoana 2017	15	15	1.13 (0.60 to 2.11)	0.7133	0.07 (-0.29 to 0.42)	0.7119
Two years' follow-up								
RYGB v SG	1	Tang 2016	38	34	0.76 (0.54 to 1.05)	0.0974	-0.19 (-0.40 to 0.03)	0.086
RYGB v LAGB	1	Courcoulas 2020	20	21	1.58 (0.69 to 3.62)	0.2845	0.16 (-0.13 to 0.46)	0.269
RYGB V BPD	1	Mingrone 2012	20	20	0.79 (0.60 to 1.04)	0.0888	-0.20 (-0.41 to 0.01)	0.065
Three years' follow-up								
RYGB v SG	2	Schauer 2014; Yang 2015	75	77	1.24 (0.98 to 1.58)	0.0791	0.12 (-0.01 to 0.25)	0.0712

RYGB v AGB	1	Courcoulas 2015	20	21	1.40 (0.59 to 3.32)	0.445	0.11 (-0.17 to 0.40)	0.438
Five years' follow-up								
RYGB v SG	1	Schauer 2017	49	47	1.31 (0.67 to 2.55)	0.4303	0.07 (-0.10 to 0.25)	0.4246
RYGB v LAGB	1	Courcoulas 2020	20	21	1.58 (0.52 to 4.77)	0.4213	0.11 (-0.15 to 0.37)	0.4123
RYGB V BPD	1	Mingrone 2015	19	19	0.58 (0.30 to 1.15)	0.1211	-0.26 (-0.57 to 0.04)	0.0927
LOAGB v LSG	1	Lee 2014	30	30	2.00 (1.08 to 3.72)	**0.0284**	0.30 (0.06 to 0.54)	**0.014**
mRYGB V SG	1	Casajoana 2021	15	15	2.80 (1.35 to 5.80)	**0.0056**	0.60 (0.33 to 0.87)	**<0.0001**
mRYGB V GCP	1	Casajoana 2021	15	15	7.00 (1.91 to 25.62)	**0.0033**	0.80 (0.59 to 1.01)	**<0.0001**
SG v GCP	1	Casajoana 2021	15	15	2.50 (0.57 to 10.93)	0.2235	0.20 (-0.09 to 0.49)	0.1826
Ten years' follow-up								
RYGB V BPD	1	Mingrone 2021	20	20	0.50 (0.21 to 1.21)	0.1212	-0.25 (-0.54 to 0.04)	0.091

Key: BMC – best medical care; BPD – biliopancreatic diversion; CI – confidence interval; GCP – greater curvature plication; (L)AGB – (laparoscopic) adjustable gastric banding; (L)GBP – (laparoscopic) gastric bypass; (L)RYGB – (laparoscopic) Roux-en-Y gastric bypass; (L)OAGB – (laparoscopic) one anastomosis gastric bypass/single anastomosis gastric bypass/mini gastric bypass; (L)SG –(laparoscopic) sleeve gastrectomy; LSR-RYGB – (laparoscopic) silastic ring Roux-en-Y gastric bypass.
† T2D remission is defined as HbA1c <6.5% without T2D medication.
‡ P <0.05 is considered statistically significant. Bold values denote statistical significance.

Implications of the diagnostic threshold used on estimates of T2D remission

The probability of being in T2D remission was increased relative to best medical care where estimates were reported in line with the updated definition of T2D remission (that is, HbA1c <6.5% without pharmacological management) when compared with the previous ADA definition (that is, HbA1c <6% without pharmacological management).

Using the updated definition, at five years' follow-up random effects meta-analysis indicated that an additional 25 (RD 0.25, 95% CI: 0.13 to 0.38) participants per 100 followed were in T2D remission in the RYGB group relative to best medical care (Table 4.3).[259, 260, 278, 290] When the more conservative definition was applied, the number of additional cases of T2D remission was reduced to 12 per 100 participants followed (RD 0.12, 95% CI: 0.06 to 0.18), based on fixed effects meta-analysis (Supplementary Appendix A3.4).[259, 278, 290]

Similarly, at five years' follow in the STAMPEDE trial, SG was associated with an additional 23 (RD 0.23, 95% CI: 0.11 to 0.36) cases of T2D remission per 100 participants followed relative to best medical care when an HbA1c threshold of 6.5% was used, compared with an additional 15 (RD 0.15, 95% CI: 0.04 to 0.26) per 100 participants followed relative to best medical care using the previous ADA definition.[259]

T2D medication use

Eighteen RCTs reported data in relation to T2D medication use, although there was considerable variation in reporting.[167, 168, 261, 262, 267, 268, 271, 274-277, 279-281, 283-286] Therefore, changes in the number of participants taking insulin and no anti-hyperglycaemic medications and are reported as exemplars.

There was a statistically significant increase in the proportion of patients not taking any medication for T2D treatment at one to two years follow-up for RYGB (RD=0.86; 95% CI: 0.70 to 1.02) and SG (RD=0.51; 95% CI: 0.37 to 0.65) relative to best medical care (Table 4.5). However, both showed a statistically significant trend towards a decreasing risk difference over time. RYGB and SG were associated with a reduction in the number of patients taking insulin of 35 and 30 participants per 100 followed, respectively, at one to two years follow-up relative to best medical care, with no evidence of a change in trends over time. There was no evidence of a difference between RYGB and SG in terms of cessation of T2D medication or insulin use over time. LAGB resulted in a statistically significant increase in the proportion of patients not on any T2D medication relative to best medical care, but did not result in a statistically significant reduction in insulin use (Table 4.5).

Of note, there were few trials available for most of the comparisons, limiting the ability to detect trends over time.

Table 4.5 Risk differences for T2D medication usage by intervention and comparator combination[†‡]

Comparison	Intervention/comparator combination			
	RYGB vs BMC	SG vs BMC	LAGB vs BMC	RYGB vs SG
No T2D medication				
Baseline	RD = -0.01 (95% CI: -0.06 to 0.04, p = 0.684, n = 3)	RD = -0.00 (95% CI: -0.07 to 0.06, p = 0.899, n = 1)	RD = -0.02 (95% CI: -0.13 to 0.09, p = 0.705, n = 2)	RD = -0.02 (95% CI = -0.10 to 0.07, p = 0.669, n = 2)
First follow-up	RD = 0.86 (95% CI: 0.70 to 1.02, **p < 0.001**, n = 3)	RD = 0.51 (95% CI: 0.37 to 0.65, **p < 0.001**, n = 1)	RD = 0.53 (95% CI: 0.38 to 0.69, **p < 0.001**, n = 2)	RD = 0.11 (95% CI: -0.05 to 0.26, p = 0.167, n = 2)
All follow-up	Decreasing risk difference over time (**p < 0.001**, n = 9)	Decreasing risk difference over time (**p < 0.001**, n = 3)	No change over time (p = 0.790, n = 4)	No change over time (p = 0.532, n = 4)
Insulin				
Baseline	RD = 0.06 (95% CI: -0.05 to 0.18, p = 0.244, n = 5)	RD = -0.06 (95% CI: -0.27 to 0.14, p = 0.549, n = 1)	RD = 0.02 (95% CI: -0.11 to 0.15, p = 0.771, n = 2)	RD = 0.05 (95% CI: -0.04 to 0.14, p = 0.310, n = 5)
First follow-up	RD = -0.35 (95% CI: -0.45 to -0.26, p < 0.001, n = 5)	RD = -0.30 (95% CI: -0.47 to -0.13, p < 0.001, n = 1)	RD = -0.04 (95% CI: -0.17 to 0.10, p = 0.587, n = 2)	RD = -0.02 (95% CI: -0.08 to 0.03, p = 0.388, n = 5)
All follow-up	No change over time (p = 0.420, n = 11)	No change over time (p = 0.957, n = 3)	No change over time (p = 0.328, n = 4)	No change over time (p = 0.932, n = 8)

Key: BMC – best medical care; CI – confidence interval; (L)AGB – (laparoscopic) adjustable gastric banding; (L)RYGB – (laparoscopic) Roux-en-Y gastric bypass; (L)SG – (laparoscopic) sleeve gastrectomy; RD – risk difference; T2D- type 2 diabetes.

† Negative value means a reduced risk of medication usage for the intervention relative to the comparator. For 'no T2D medication', a positive value means an increased proportion of participants not on any anti-hyperglycaemic medication relative to best medical care. Fixed effect meta-analysis was used when fewer than three RCTs were available.

‡ P <0.05 is considered statistically significant. Bold values denote statistical significance.

4.3.2.2 HbA1c

All RCTs reported on change in HbA1c from baseline to follow-up.[167, 169, 240, 261, 262, 265-268, 271-275, 277, 279-286]

Metabolic surgery compared with best medical care

Pooled random effects meta-analysis indicated that RYGB resulted in a statistically significant decrease in HbA1c relative to best medical care at one year follow-up (SMD=-0.84; 95% CI: -1.14 to -0.53, I^2=47.0%, Figure 4.4a), although evidence of moderate statistical heterogeneity was observed across RCTs.[169, 261, 279, 281, 282, 284] The reduction in HbA1c remained statistically significant at five years post-surgery (SMD=-0.73; 95% CI: -1.08 to -0.37, I^2=46.4%, GRADE=moderate, Figure 4.4b).[259, 260, 278, 290] At ten years post-surgery, based on results from one RCT, LRYGB was associated with a reduction in HbA1c compared with best medical care (SMD=-0.78; 95% CI: -1.48 to -0.08), although the difference may not be clinically significant.[249] Where undertaken, there was evidence of moderate to substantial heterogeneity across trials in the pooled analysis. It should be noted that the statistical heterogeneity reflects uncertainty in the magnitude but not the direction of effect.

Insufficient data were available for pooling for the comparison SG with best medical care. At one, three and five years' follow-up SG was associated with a significantly greater reduction from baseline in HbA1c compared with best medical care.[259, 273, 284, 291] The magnitude of the difference did not change between three (SMD=-0.82; 95% CI -1.26 to -0.39, GRADE=moderate,) and five years (SMD=-0.82; 95% CI: -1.27 to -0.38, GRADE=moderate,) post-surgery in one RCT.[259, 291]

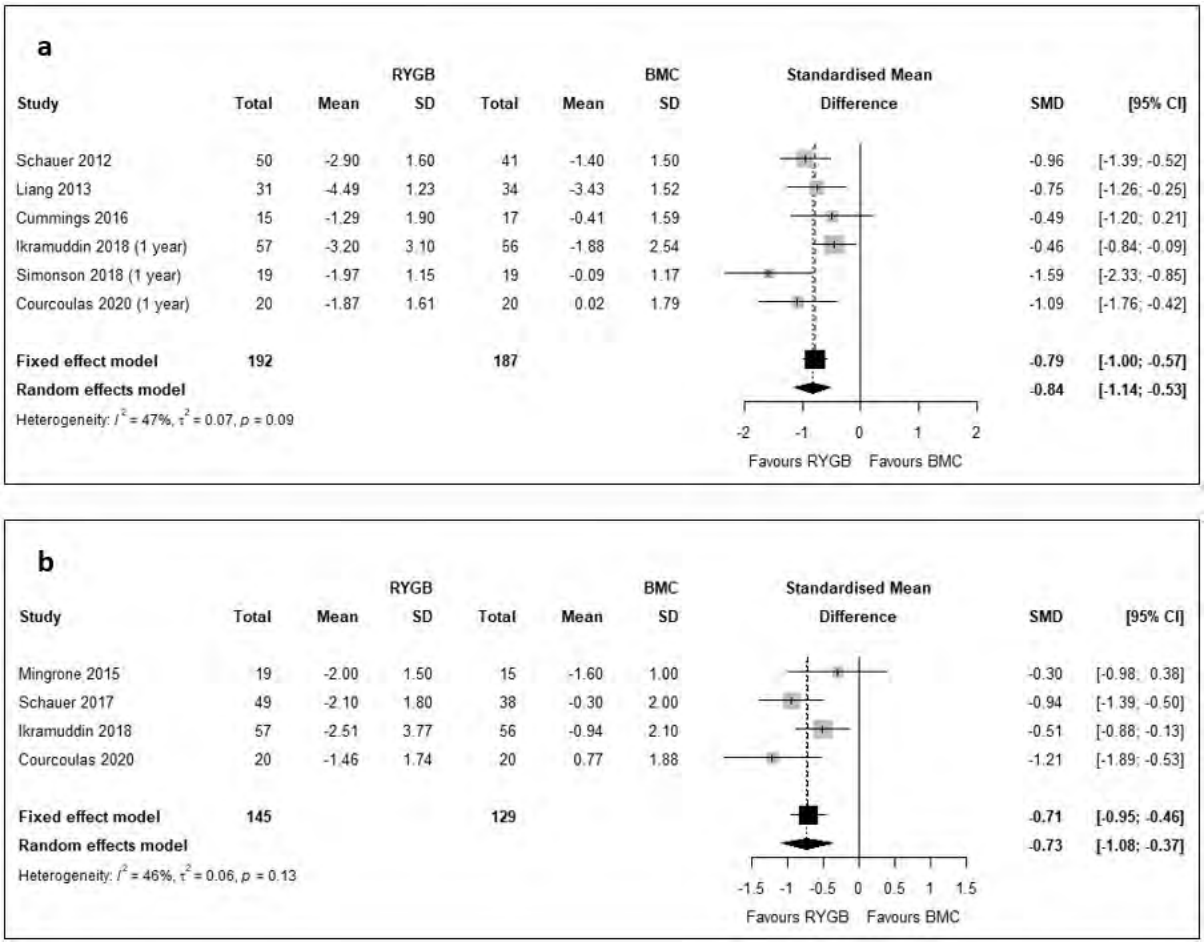
HbA1c was significantly reduced compared with best medical care for all other procedures at all time points, with the exception of LAGB at one year and BPD at five years' follow-up, respectively (Supplementary Appendix A3.5).[260]

Metabolic surgery compared with other metabolic surgeries

Random effects meta-analysis demonstrated no difference between RYGB and SG at one year follow-up (SMD=0.01; 95% CI: -0.22 to 0.24, I^2=0.0%; Figure 4.5).[271, 275, 277, 284] Insufficient data were available for pooling at subsequent time points. At subsequent time points (two, three and five years' follow-up), the difference between groups was not statistically significant (Supplementary Appendix A3.5).[259, 266, 268, 271, 275, 277, 284, 291]

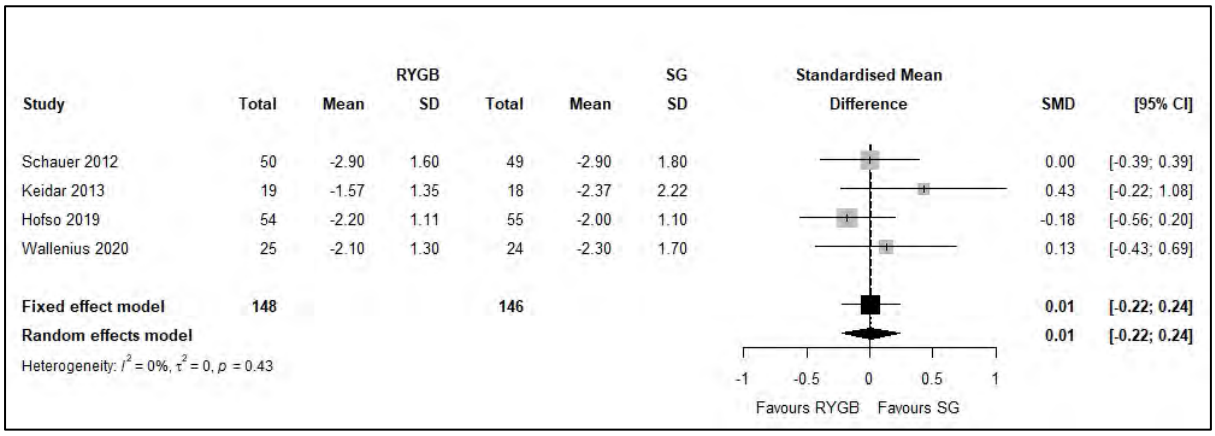
For most comparisons and time points, there was no evidence of significant differences between surgeries. Where statistically significant differences were reported, differences were generally not sustained at subsequent time points. Based on follow-up data from one RCT, there was a significant reduction in HbA1c in the RYGB group relative to the LAGB group at one year follow-up (SMD=-0.66; 95% CI: -1.29 to -0.03), but differences were not sustained at two (SMD=0.02; 95% CI: -0.59 to 0.63) and five years' follow-up (SMD=-0.49; 95% CI: -1.12 to 0.13).[260, 279, 287] LOAGB was associated with a significant decrease in HbA1c relative to LSG at one year (SMD=-0.70; 95% CI: -1.22 to -0.18), but not at five years' follow-up (SMD=-0.49; 95% CI: -1.01 to 0.02).[269, 285] Similarly, BPD was associated with a significant reduction in HbA1c compared with RYGB at two years (SMD=-1.07; 95% CI: -1.76 to -0.39), but the difference was not statistically significant at five (SMD=-0.30; 95% CI: -0.94 to 0.34) or at ten years (SMD=-0.31; 95% CI: -0.93 to 0.32) post-randomisation.[249, 283, 290]

Figure 4.4 Standardised mean difference in change from baseline in HbA1c for RYGB compared with best medical care at (a) 1 and (b) 5 years' follow-up†



Key: BMC – best medical care; Roux-en-y gastric bypass; SD – standard deviation; SMD – standardised mean difference.
† Where imputed data for earlier time points were reported in subsequent publications, imputed results are presented.

Figure 4.5 Standardised mean difference in change from baseline in HbA1c for RYGB compared with SG at one year follow-up



Key: Roux-en-y gastric bypass; SG – sleeve gastrectomy; SMD – standardised mean difference.

4.3.2.3 BMI

Twenty-two RCTs reported on change in BMI from baseline.[168, 169, 262, 265-268, 270-277, 279-285]

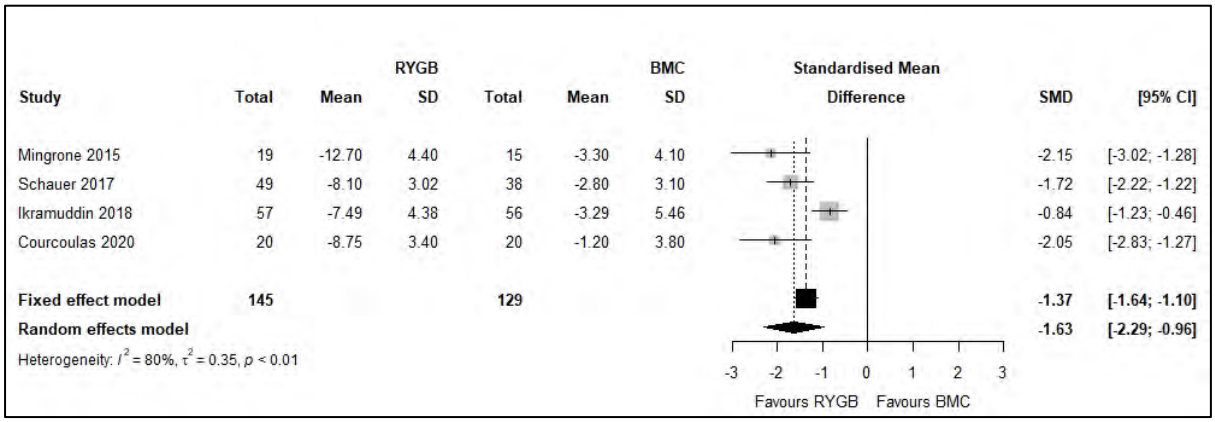
Metabolic surgery compared with best medical care

RYGB was consistently associated with a reduction in BMI compared with best medical care based on pooled random effect estimates at all available time points including five years' (SMD=-1.63; 95% CI: -2.29 to -0.96, I^2=80.1%; Figure 4.6)[259, 260, 278, 290] and ten years post-randomisation (SMD=-2.28; 95% CI -3.15 to -1.40).[249] While there was evidence of considerable statistical heterogeneity at five years' follow-up, the direction of effect was consistent.

Insufficient data were available for pooling for the comparison LSG versus best medical care. At five years' follow-up, reductions in BMI were significantly greater after LSG than for participants randomised to best medical care (SMD=-1.26; 95% CI: -1.73 to -0.79),[259, 260, 278, 290] consistent with earlier time points.[273, 284, 291]

For all other metabolic surgeries, across all lengths of follow-up, metabolic surgery was associated with a statistically significant reduction in BMI relative to best medical care (Supplementary Appendix A3.6).

Figure 4.6 Standardised mean difference in change from baseline in BMI for RYGB compared with best medical care at 5 years' follow-up



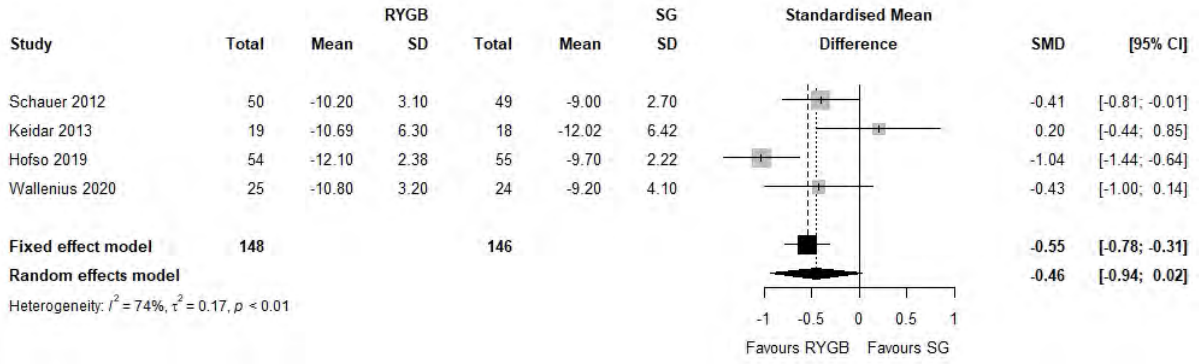
Key: BMC – best medical care; RYGB - Roux-en-Y gastric bypass; SD – standard deviation; SMD – standardised mean difference.

Metabolic surgery compared with other metabolic surgery procedures

At one year follow-up, pooled random effects meta-analysis demonstrated no significant difference in BMI change from baseline between RYGB and SG groups (SMD=-0.46; 95% CI: -0.94 to 0.02; I^2=74.0%, Figure 4.7).[271, 275, 277, 284] There was evidence of considerable statistical heterogeneity, reflecting uncertainty in both the magnitude and direction of effect. At three years' follow-up, RYGB was associated with a significant reduction in BMI relative to SG in two RCTs.[268, 291] Based on data from one RCT, RYGB was associated with a reduction in BMI relative to SG at five years' follow-up, however this was not statistically significant (SMD=-0.37; 95% CI: -0.78 to 0.03).[259]

RYGB consistently resulted in a significantly greater reduction in BMI across time points ranging from one to five years when compared to LAGB.[260, 279, 287] Variations of RYGB including addition of a gastric band,[292] and a longer biliopancreatic limb length[270, 286] were associated with a significantly greater reduction in BMI relative to procedures with a primarily restrictive component, including LSG and GCP or a less restrictive RYGB variation (Supplementary Appendix A3.6).

Figure 4.7 Standardised mean difference in change from baseline in BMI for RYGB compared with SG at one year follow-up



Key: RYGB - Roux-en-Y gastric bypass; SG – sleeve gastrectomy; SMD - standardised mean difference.

4.3.2.4 Systolic blood pressure

Seventeen RCTs reported on systolic blood pressure.[167-169, 261, 262, 271-273, 276, 277, 279-285]

Metabolic surgery versus best medical care

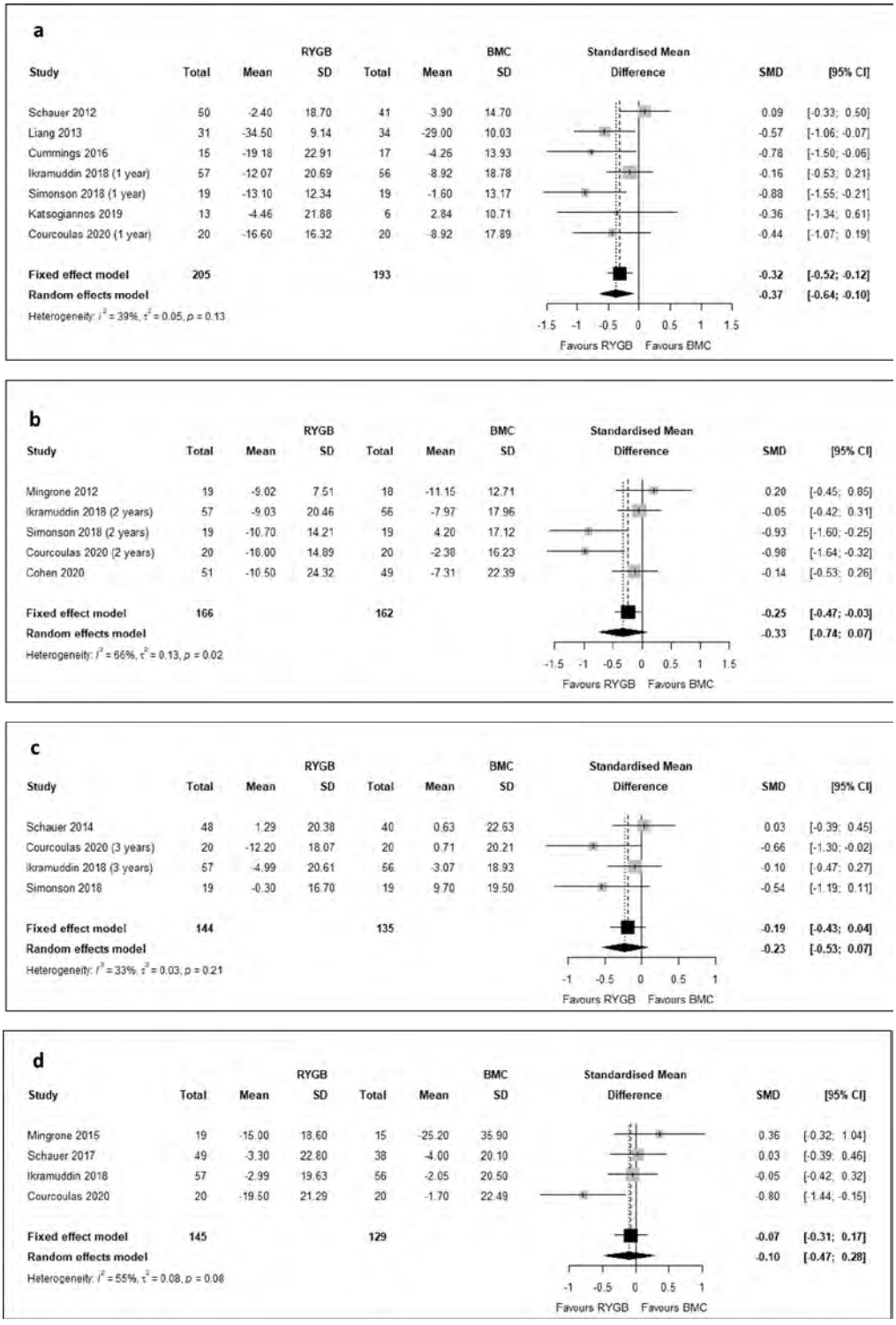
Random effect meta-analysis showed that RYGB was associated with a statistically significant reduction in systolic blood pressure compared with best medical care at one year follow-up (SMD=-0.37; 95% CI: -0.64 to -0.10, I^2=38.8%)(Figure 4.8a).[168, 169, 259-261, 263, 272, 278, 279, 281-284, 287-291] However, there was evidence of moderate statistical heterogeneity. At two (SMD=-0.33; 95% CI: -0.74 to 0.07, I^2=66.4%), three (SMD=-0.23; 95% CI: -0.53 to 0.07, I^2=33.4%), five (SMD=-0.10; 95% CI: -0.47 to 0.28, I^2=54.7%) (Figure 4.8, b to d) and ten (SMD=0.21; 95% CI: -0.46 to 0.88) years' follow-up there was no significant difference between groups.[249, 259, 260, 278, 290] In the pooled analyses, statistical heterogeneity reflected uncertainty in both the magnitude and direction of effect.

There was no significant difference in systolic blood pressure between best medical care and surgical groups for any other procedures (that is, SG, LAGB and BPDat any of the available time points up to five to ten years' follow-up (Supplementary Appendix A3.7).[167, 249, 259, 260, 264]

Metabolic surgery versus other metabolic surgeries

RYGB significantly decreased systolic blood pressure relative to LAGB at two, three and five years' (SMD=-0.93; 95% CI: -1.58 to -0.29) follow-up.[260] There was no significant difference in systolic blood pressure between groups for any of the following comparisons: RYGB versus SG (up to five years' follow-up),[259] BPD versus RYGB (up to ten years' follow-up),[249] LOAGB versus LSG (up to 5 years' follow-up)[269] and LSR-RYGB versus LSG (one year follow-up).[276] Of note, only one study was available for all comparisons at a given time point, with the exception of RYGB versus SG at one year post-surgery.

Figure 4.8 Standardised mean difference in change from baseline in systolic blood pressure for RYGB compared with best medical care at (a) 1, (b) 2, (c) 3 and (d) 5 years' follow-up†



Key: BMC – best medical care; RYGB – Roux-en-Y gastric bypass; SD – standard deviation; SMD – standardised mean difference.
† Where imputed data for earlier time points were reported in subsequent publications, imputed results are presented.

4.3.2.5 Diastolic blood pressure

Fifteen RCTs reported on diastolic blood pressure.[167, 168, 262, 271-273, 276, 277, 279-285]

Metabolic surgery versus best medical care

According to random effects meta-analysis at one year follow-up, there was no significant difference in diastolic blood pressure between RYGB and best medical care groups (SMD=-0.20; 95% CI: -0.43 to 0.03, I^2=0.0%, Figure 4.9a).[272, 279, 281, 282, 284] At two years' follow-up, RYGB was associated with a significant reduction in diastolic blood pressure relative to best medical care (SMD=-0.33; 95% CI: -0.55 to -0.11, I^2=0.0%).[168, 260, 263, 283, 288] However, the random effects pooled estimate demonstrated no significant difference at three or five years follow-up (Figure 4.9, c to d).[259, 260, 263, 278, 287, 289-291]

The difference between SG and best medical care groups was not statistically significant at any time point up to five years post-randomisation (SMD=-0.29; 95% CI: -0.72 to 0.14).[259]

Fixed effects meta-analysis indicated that LAGB was not associated with a significant reduction in diastolic blood pressure at any of the available time points up to five years' follow-up.[167, 260, 264] BPD was not associated with a reduction in diastolic blood pressure at two, five or ten years' follow-up (Supplementary Appendix A3.7).[249, 283, 290]

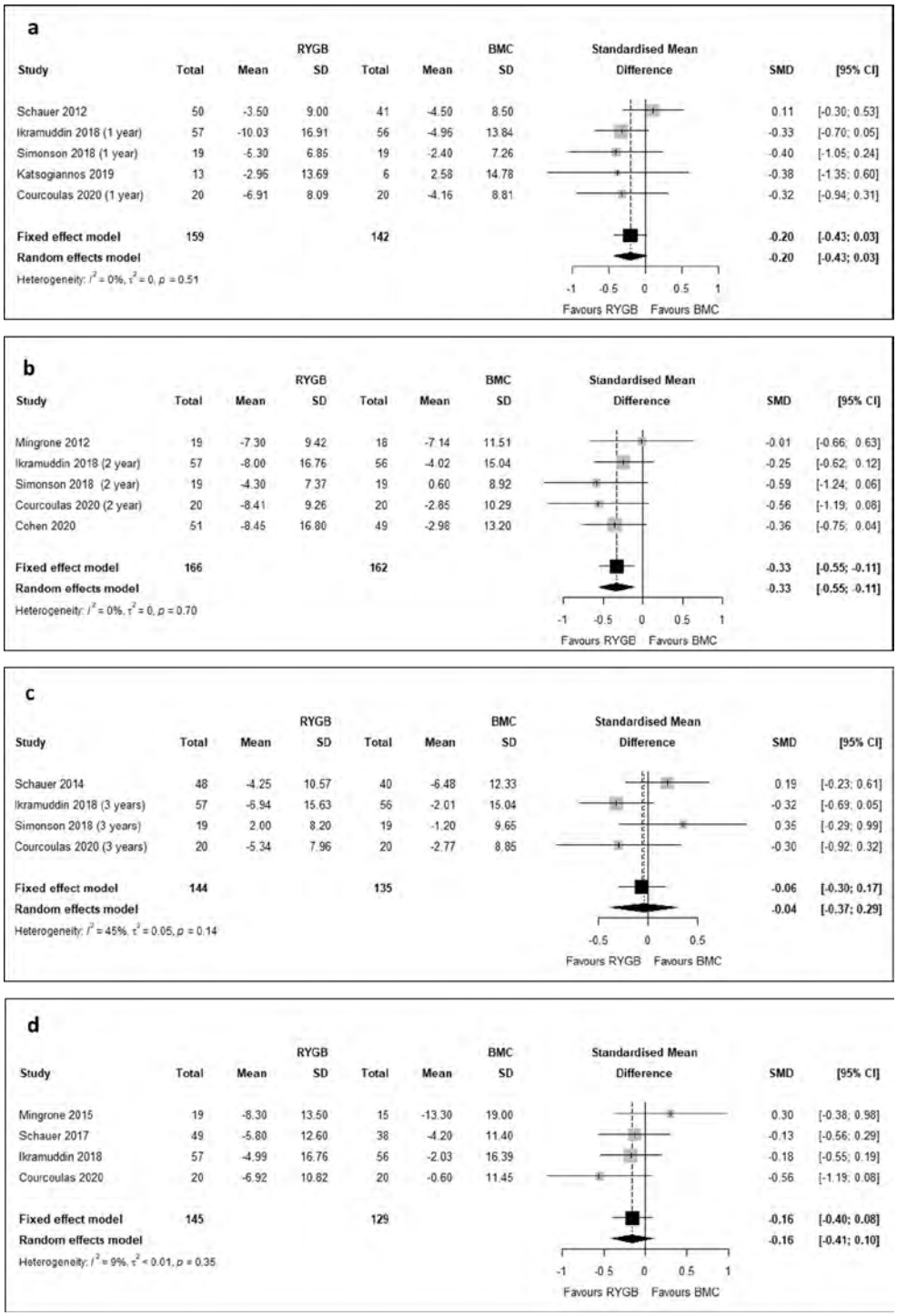
Metabolic surgery versus other metabolic surgeries

There was no significant reduction in diastolic blood pressure associated with RYGB relative to SG at one year follow-up (SMD=-0.24; 95% CI:-0.49 to -0.01, I^2=65.5%, Figure 4.10).[271, 277, 284] At two years' RYGB was associated with a significant reduction in diastolic blood pressure in one RCT (SMD=-0.84; 95% CI: -1.44 to -0.24).[277] However, at three (SMD=0.17; 95% CI: -0.23 to 0.57) and five (SMD=0.17; 95% CI -0.23 to 0.57) years' follow-up, there was no significant difference between groups based on one RCT.[259, 291]

There was no significant difference in diastolic blood pressure between RYGB and LAGB groups at one year follow-up,[279] however the difference was significant at subsequent time points up to five years' post-surgery in one RCT.[260, 287] The difference in the decrease in diastolic blood pressure from baseline between LOAGB and LSG was not significant at one year follow-up (SMD=-0.14; 95% CI: -0.36 to 0.65),[285] but reached statistical significance at five years (SMD=-0.79; 95% CI: -1.31 to -0.26).[269] There was no significant difference in change in diastolic blood

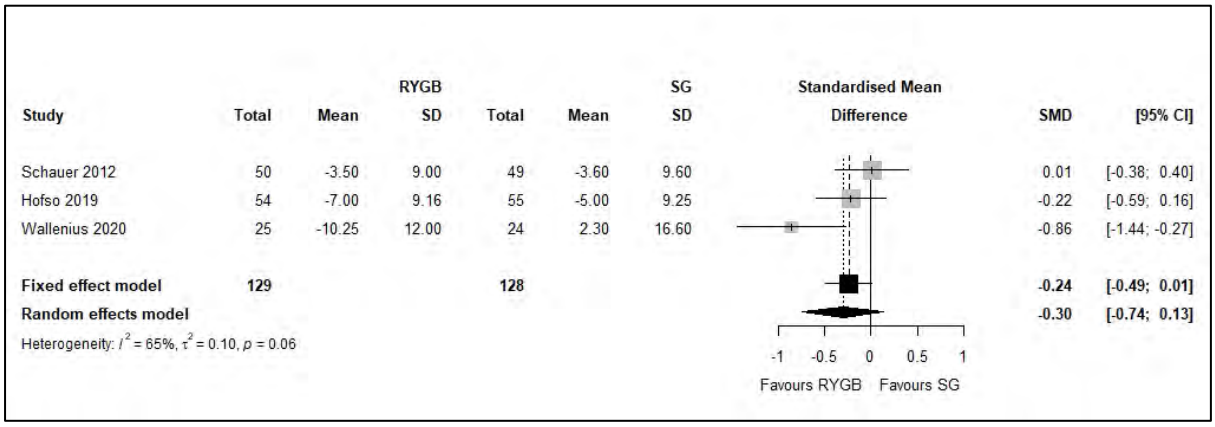
pressure from baseline between LSR-RYGB and LSG at one year follow-up (SMD=-0.08; 95% CI: -0.46 to 0.29)[276] or BPD and RYGB at any time point up to ten years' post-surgery (Supplementary Appendix A3.7).[249, 283, 290]

Figure 4.9 Standardised mean difference (SMD) in change from baseline in diastolic blood pressure for RYGB compared with best medical care at (a) 1, (b) 2, (c) 3 and (d) 5 years' follow-up†



Key: BMC – best medical care; RYGB - Roux-en-Y gastric bypass; SD – standard deviation; SMD – standardised mean difference.
† Where imputed data for earlier time points were reported in subsequent publications, imputed results are presented.

Figure 4.10 Standardised mean difference (SMD) in change from baseline in diastolic blood pressure for RYGB compared with SG at one year follow-up



Key: RYGB - Roux-en-Y gastric bypass; SG – sleeve gastrectomy; SD – standard deviation; SMD - standardised mean difference.

4.3.2.6 Total cholesterol

Eighteen RCTs reported on change from baseline in total cholesterol.[167-169, 266, 268, 271-274, 277, 279-285, 293]

Metabolic surgery versus best medical care

There was no significant difference in total cholesterol between RYGB and best medical care at any time point up to five years' follow-up (Figure 4.11, a to d). In the pooled analyses, moderate to substantial statistical heterogeneity reflected variability in both the magnitude and direction of effect. At ten years post-surgery, results favoured best medical care in one RCT (SMD=1.14; 95% CI: 0.41 to 1.87).[249]

At one year follow-up two RCTS reported no significant difference in total cholesterol between SG and best medical care (Supplementary Appendix A3.8).[273, 284] Data from subsequent time points were not available.

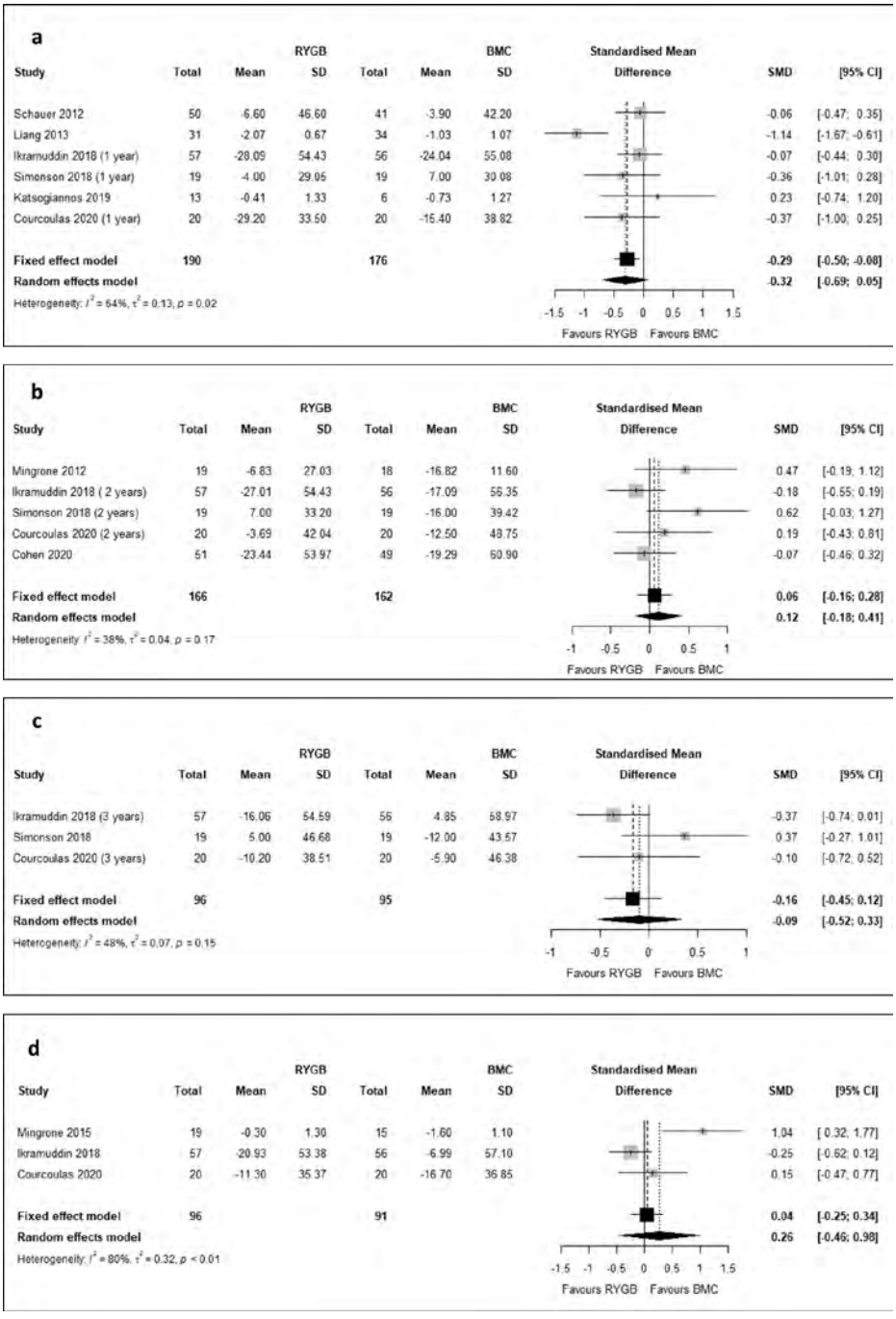
Fixed effect meta-analysis indicated no significant difference between LAGB and best medical care at any timepoint up to five years' follow-up (Supplementary Appendix A3.8). BPD was associated with a significant reduction in total cholesterol at two and five years, but not ten years' follow-up (Supplementary Appendix A3.8).

Metabolic surgery versus other metabolic surgeries

Fixed effects meta-analysis demonstrated no statistically significant difference in total cholesterol associated with RYGB relative to SG at one year (SMD=0.27; 95% CI: -0.02 to 0.52; I^2=89.2%; Figure 4.12), two (SMD=-0.34; 95% CI: -0.70 to 0.03, I^2=31.7%) or three (SMD=0.22; 95% CI: -0.31 to 0.75) years follow-up (Supplementary Appendix A3.8).[266, 268, 277]

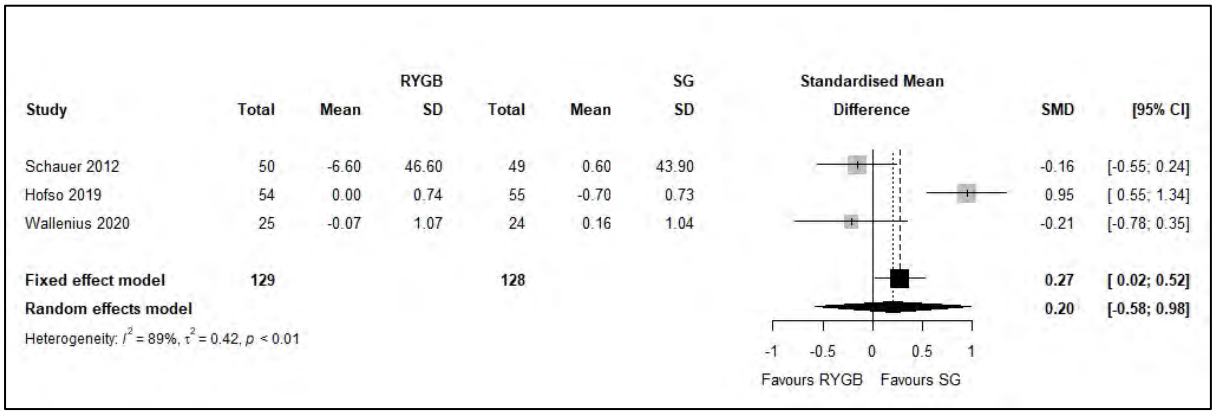
Total cholesterol levels were significantly lower at one year follow-up in participants randomised to LSR-RYGB than LSG in one RCT (SMD=-0.67; 95% CI: -1.06 to -0.29).[276] BPD was associated with a significant reduction in total cholesterol relative to RYGB at two, five and ten years' follow-up in one RCT (Supplementary Appendix A3.8).[249, 283, 290] There was no significant difference in total cholesterol levels for the following comparisons at up to five years' follow-up: RYGB versus LAGB and LOAGB versus LSG.[260, 269, 285]

Figure 4.11 Standardised mean difference in change from baseline in total cholesterol for RYGB compared with best medical care† at (a) 1, (b) 2, (c) 3 and (d) 5 years' follow-up†



Key: BMC – best medical care; RYGB - Roux-en-Y gastric bypass; SD –standard deviation; SMD – standardised mean difference.
† Where imputed data for earlier time points were reported in subsequent publications, imputed results are presented.

Figure 4.12 Standardised mean difference (SMD) in change from baseline in total cholesterol for RYGB compared with SG at one year follow-up



Key: RYGB - Roux-en-Y gastric bypass; SG – sleeve gastrectomy; SD – standard deviation; SMD - standardised mean difference.

4.3.2.7 LDL-cholesterol

Nineteen RCTs reported on change in low-density lipoprotein (LDL) cholesterol from baseline.[168, 169, 249, 259, 260, 262-264, 266-269, 272-274, 276-278, 294]

Metabolic surgery versus best medical care

There was no difference between groups at one to five years' follow-up based on the random effects pooled estimate (Figure 4.13, a to d). Statistical heterogeneity was substantial (≥70%). In one RCT, results favoured best medical care at ten years' follow-up (SMD=0.98; 95% CI: 0.26 to 1.69).[249]

There was no difference between LSG and best medical care groups at any time point up to five years post-randomisation (Supplementary Appendix A3.8).[259, 273, 284, 291]

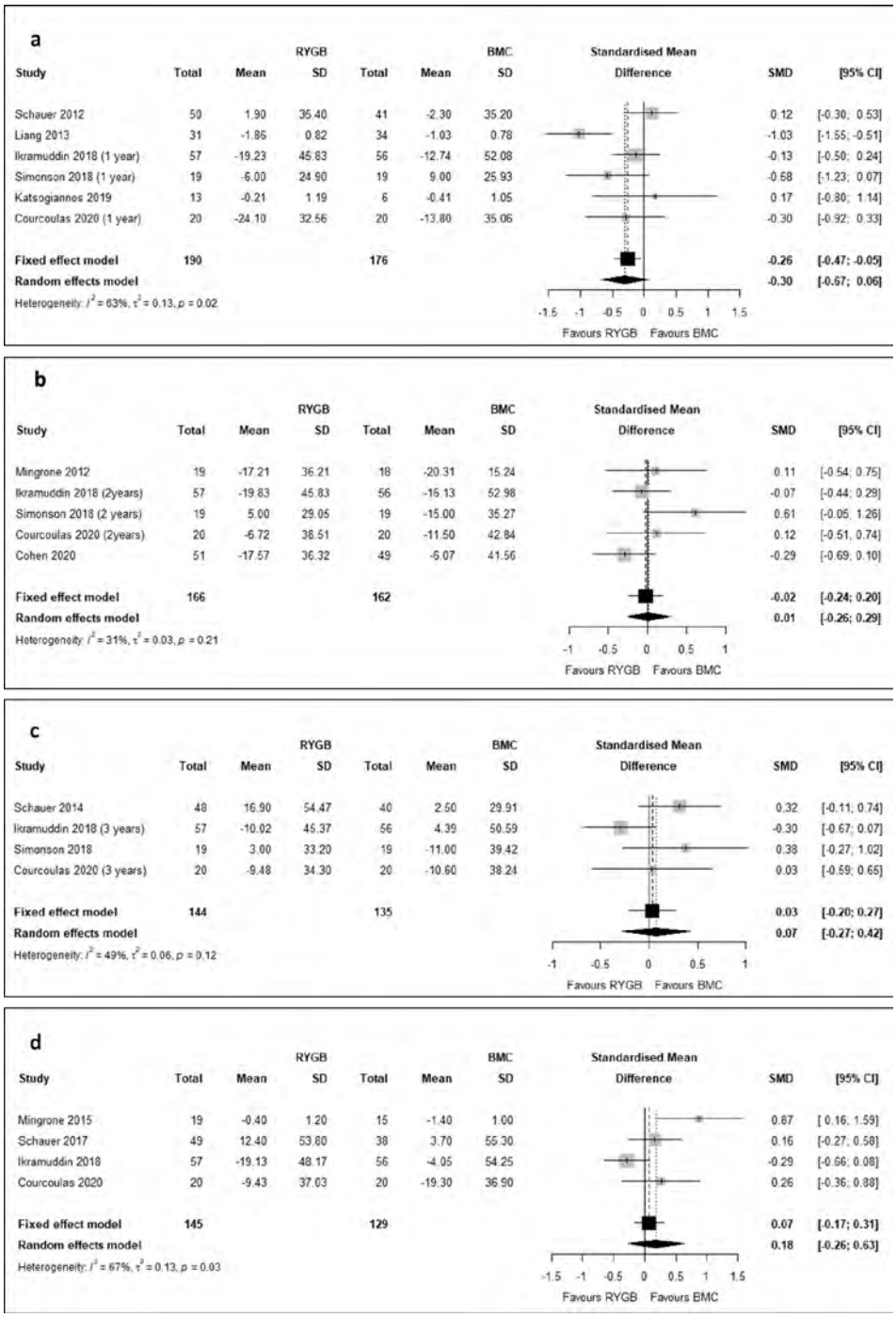
Results for LAGB versus best medical care were inconsistent at one year follow-up.[260, 264] There was no significant difference between groups at two to five years (Supplementary Appendix A3.8).[260, 264] BPD was associated with a significant reduction in LDL-C at two and five years,[283, 290] but not at ten years.[249] There was no significant difference in LDL-C between LSG-TB and best medical care groups at two years follow-up.[274]

Metabolic surgery versus other metabolic surgeries

Fixed effects meta-analysis demonstrated a statistically significant reduction in LDL-C in participants randomised to LRYGB versus LSG at one year follow-up, with evidence of substantial statistical heterogeneity (SMD=-0.41; 95% CI: -0.662 to -0.16, I^2=72.7%, Figure 4.14)).[271, 277, 284] There was no significant difference between groups at two to five years' follow-up (Supplementary Appendix A3.8).[259, 266, 268, 277, 291]

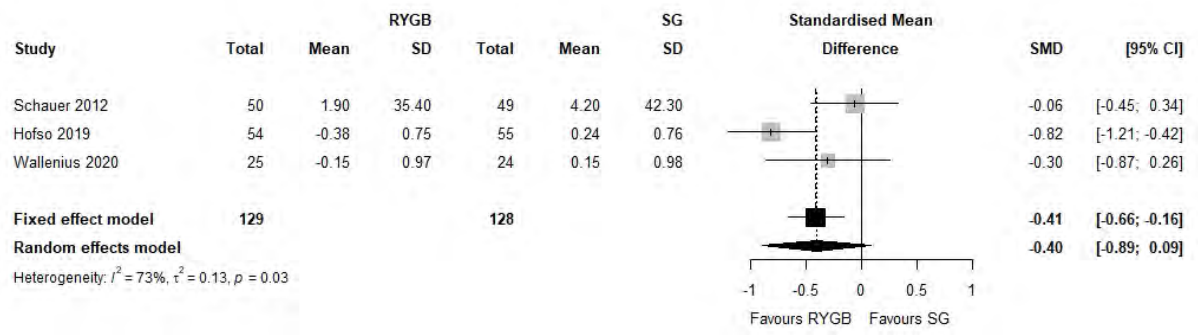
There was no significant difference between RYGB and LAGB groups at any time point up to five years in one RCT.[260] Relative to RYGB, BPD was associated with a significant reduction in LDL-C at two, five and ten years.[249, 283, 290] LOAGB was associated with a significant reduction in LDL-C compared with LSG at one, but not at five years (Supplementary Appendix 8). At one-year follow-up, LSR-RYGB was associated with a significant reduction in LDL-C relative to LSG (Supplementary Appendix A3.8).

Figure 4.13 Standardised mean difference in change from baseline in low-density lipoprotein cholesterol for RYGB compared with best medical management at (a) 1, (b) 2, (c) 3 and (d) 5 years' follow-up



Key: BMC – best medical care; RYGB - Roux-en-Y gastric bypass; SMD – standardised mean difference; SD – standard deviation.
† Where imputed data for earlier time points were reported in subsequent publications, imputed results are presented.

Figure 4.14 Standardised mean difference in change from baseline in low-density lipoprotein cholesterol for RYGB compared with SG at one year follow-up



Key: RYGB - Roux-en-Y gastric bypass; SG – sleeve gastrectomy; SMD - standardised mean difference; SD – standard deviation.

4.3.2.8 HDL-cholesterol

Twenty-one RCTs reported on changes in the level of high density lipoprotein (HDL) cholesterol from baseline.[167-169, 249, 259-262, 266-269, 272-274, 277, 278, 280, 281, 292, 294]

Metabolic surgery versus best medical care

Random effects meta-analysis demonstrated a statistically significant improvement in HDL-C levels in the RYGB group compared with best medical care at one to five years' follow-up (Figure 4.15, a to d). There was evidence of moderate to substantial heterogeneity at medium- to long-term follow-up ($I^2 \geq 45$). Based on the results of one RCT, the difference between groups was not statistically significant at ten years' follow-up (SMD=0.37; 95% CI: -0.30 to 1.05).[249]

SG was associated with a statistically significant increase in HDL-C relative to best medical care at one to five years' follow-up (Supplementary Appendix A3.8).[259, 273, 284, 291]

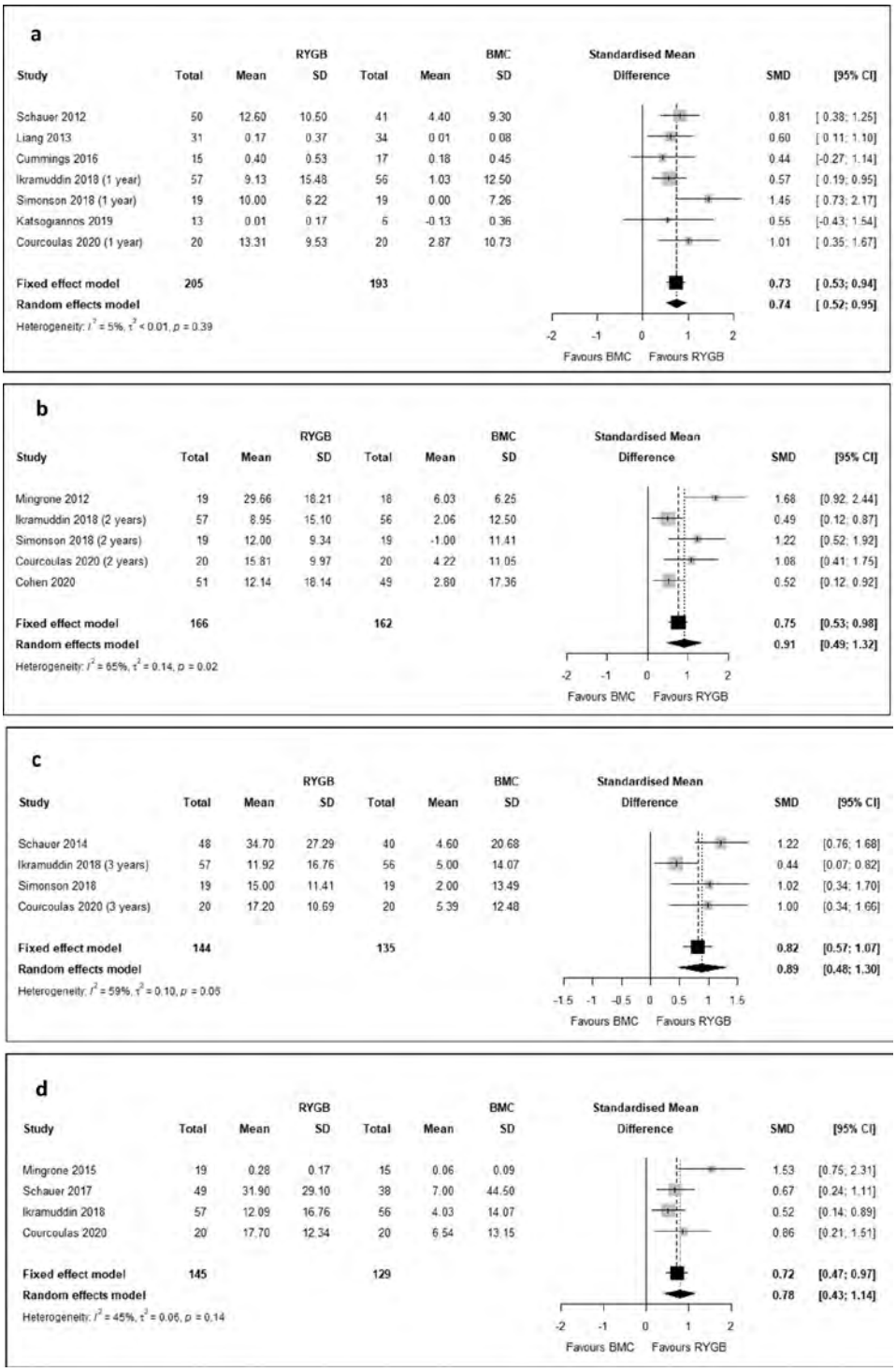
LAGB was associated with an increase in HDL-C relative to best medical care, although this was not statistically significant at all time points (Supplementary Appendix A3.8).[167, 260, 264] There was no significant difference between BPD and best medical care groups at two, five or ten years' follow-up.[249, 283, 290]

Metabolic surgery versus other metabolic surgeries

There was no evidence of a statistically significant difference between LRYGB and LSG at any of the one, two, three and five years' follow-up (Figure 4.16 and Supplementary Appendix A3.8).

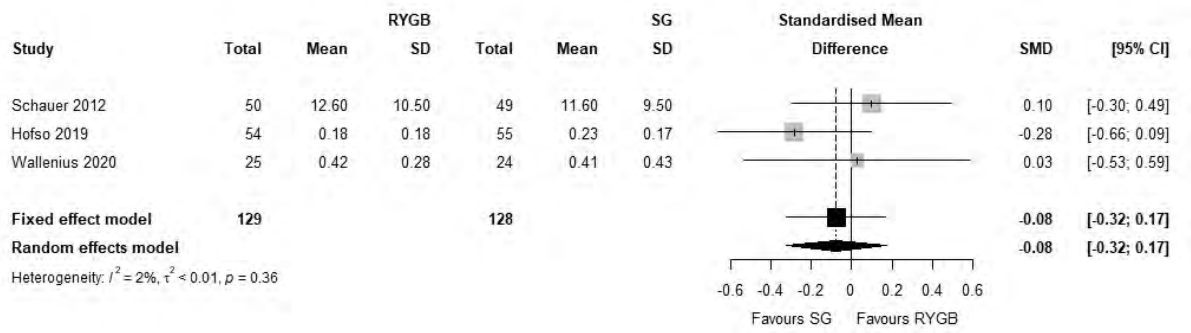
Based on the results of one RCT, RYGB was associated with a significant increase in HDL-C when compared with LAGB at one year follow-up (SMD=0.69; 95% CI: 0.05 to 1.32), but this was not evident at subsequent time points up to five years' post-randomisation.[260] RYGB was associated with a significant increase in HDL-C when compared with BPD participants at two and five years' follow-up, but there was no significant difference at ten years' follow-up.[249, 283, 290] There was no significant difference between LOAGB and LSG groups at one year follow-up, however at five years' follow-up LSG was associated with a significant increase in HDL-C relative to LOAGB (SMD=-0.56; 95% CI: -1.08 to -0.05).[269, 285]

Figure 4.15 Standardised mean difference in change from baseline in high density lipoprotein cholesterol for RYGB versus best medical management at (a) 1, (b) 2, (c) 3 and (d) 5 years' follow-up



Key: BMC – best medical care; RYGB - Roux-en-Y gastric bypass; SMD – standardised mean difference; SD – standard deviation.

Figure 4.16 Standardised mean difference in change from baseline in high density lipoprotein cholesterol for RYGB versus SG at one year follow-up



Key: RYGB - Roux-en-Y gastric bypass; SG – sleeve gastrectomy; SMD - standardised mean difference; SD – standard deviation.

4.3.2.9 Triglycerides

Twenty-one RCTs reported on change from baseline in triglycerides.[167-169, 249, 259-264, 266-269, 271-274, 276-278]

Metabolic surgery versus best medical care

RYGB was associated with a significant reduction in triglycerides at one (SMD=-0.65; 95% CI: -1.00 to -0.31; I^2=60.4%), two (SMD=-0.48; 95% CI: -0.78 to -0.17; I^2=0.0%) and three (SMD=-0.52; 95% CI: -0.76 to -0.28; I^2=0.0%) years' follow-up relative to best medical care (Figure 4.17, a to c). There was no significant difference between groups at five (SMD=-0.34; 95% CI: -0.81 to 0.13; I^2=69.7%) and ten years (SMD=0.44; 95% CI: -0.23 to 1.12).

Triglycerides levels were lower in the LSG group than the best medical group at one (SMD=-0.37; 95% CI: -0.73 to -0.02, I^2=0.0%) and five years' (SMD=-0.49; 95% CI: -0.93 to -0.06) follow-up, but not three years (SMD=-0.34; 95% CI:-0.76 to 0.09).

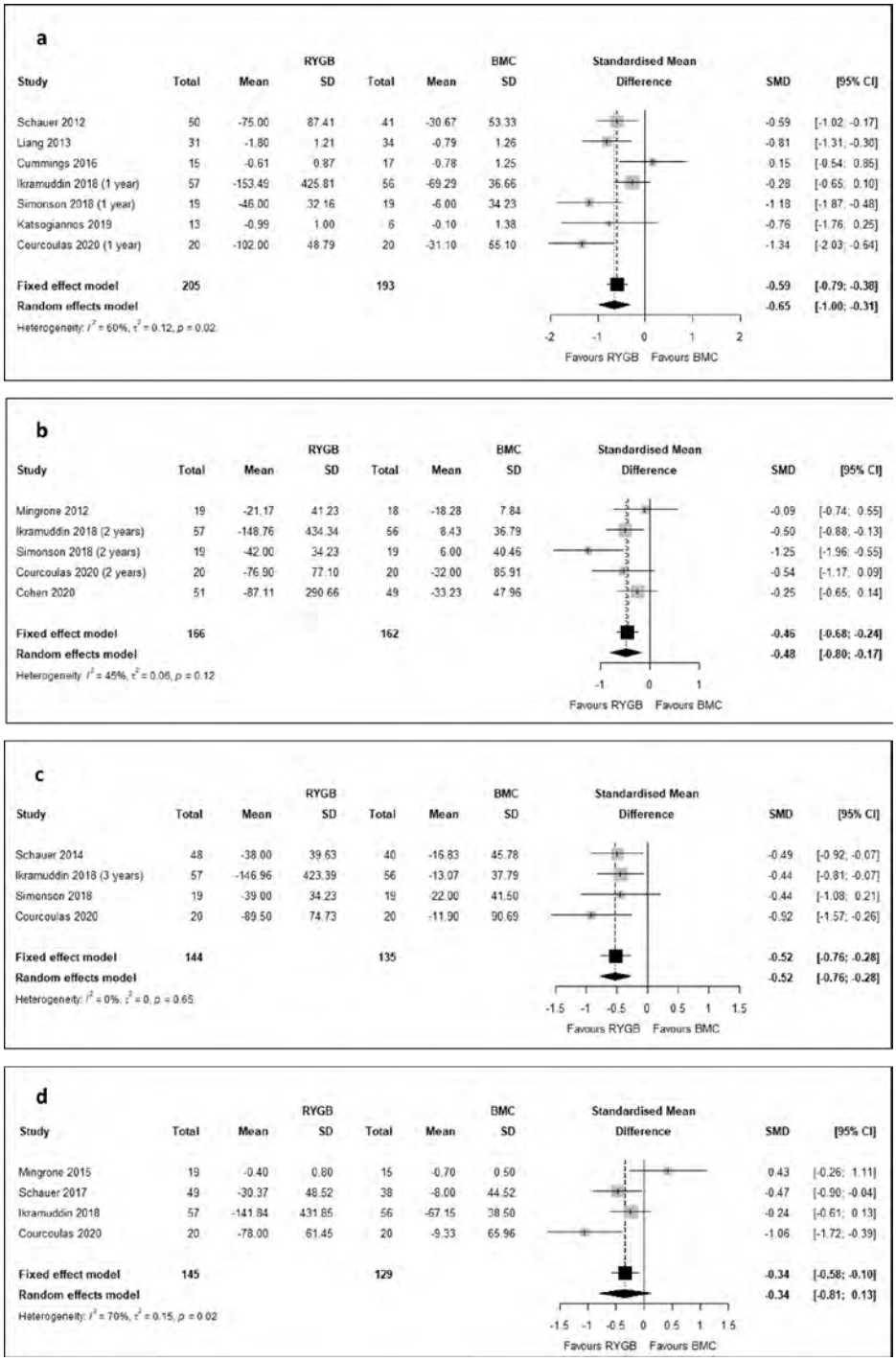
LAGB was associated with a significant reduction in triglycerides at two years' follow-up (SMD=-0.40; 95% CI: -0.73 to -0.06, I^2=0.0%), but not three (SMD=-0.30; 95% CI: -0.74 to 0.14, I^2=0%) or five years (SMD=-0.54; 95% CI: -1.17 to 0.08). BPD was associated with a significant reduction in triglycerides at two years (SMD=-2.86; 95% CI:-3.81 to -1.92), but not five (SMD=-0.65; 95% CI: -1.53 to 0.05) or ten years' (SMD=-0.62; 95% CI: -1.31 to 0.07) follow-up (Supplementary Appendix A3.8).[167, 249, 260, 264, 283, 290] There was no significant difference between the sleeve gastrectomy with transit bipartition (SG-TB) and best medical care groups at two years.[274]

Metabolic surgery versus other metabolic surgeries

Fixed effects meta-analysis indicated that LRYGB was not associated with a significant reduction in triglycerides at one year follow-up relative to LSG (SMD=-0.12; 95% CI: -0.36 to 0.13, I^2=5.5%, Figure 4.18). There was no significant differences between groups at subsequent follow-up up to five years (Supplementary Appendix A3.8).

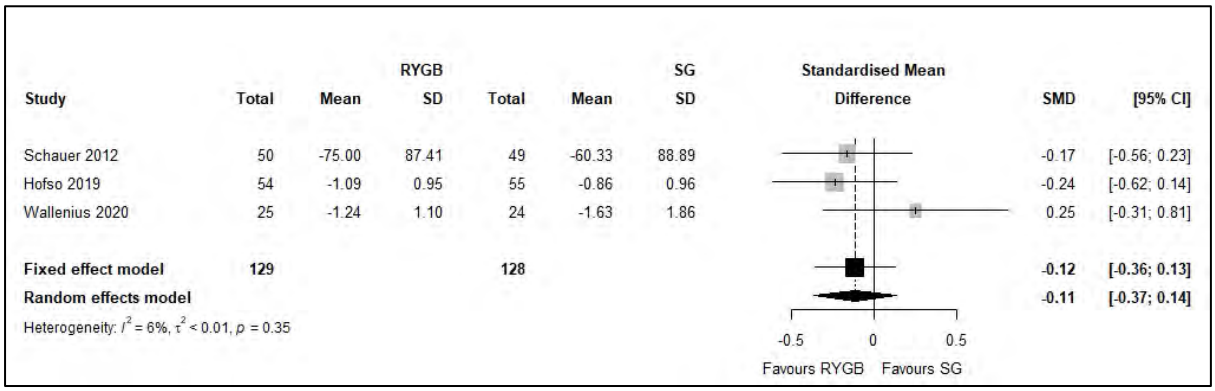
There was no significant difference between groups in reduction in triglycerides for any of the following comparisons: RYGB versus LAGB, laparoscopic one anastomosis gastric bypass (LOAGB) versus LSG and LSR-RYGB versus LSG (Supplementary Appendix A3.8). BPD was associated with a significant reduction in triglycerides at two (SMD=-1.11; 95% CI: -1.8 to -0.42), five (SMD=-0.92; 95% CI: -1.59 to -0.25) and ten years' follow-up (SMD=-0.97; 95% CI: -1.63 to -0.31) relative to LRYGB. [249, 283, 290]

Figure 4.17 Standardised mean difference in change from baseline in triglycerides for RYGB versus best medical management at (a) 1, (b) 2, (c) 3 and (d) 5 years follow-up



Key: BMC – best medical care; RYGB - Roux-en-Y gastric bypass; SMD – standardised mean difference.

Figure 4.18 Standardised mean difference (SMD) in change from baseline in triglycerides for RYGB versus SG at one year follow-up



Key: RYGB - Roux-en-Y gastric bypass; SG – sleeve gastrectomy; SMD - standardised mean difference.

4.3.2.10 Cardiovascular medication use

Fifteen RCTs reported on cardiovascular medication use.[167, 168, 261, 268, 274, 276, 277, 279-281, 283-286, 294] Synthesis of results was challenging due to variation in outcome reporting. As exemplars, data from RCTs reporting on the use of lipid-lowering medications, anti-hypertensive medications or changes in the mean number of cardiovascular medications were analysed.

Lipid-lowering medication

Based on the results of one RCT, participants that underwent RYGB had a statistically significant greater reduction in the mean number of lipid-lowering medications used compared with best medical care over a three year period (Figure 4.19).[263, 281]

Anti-hypertensive medication

Both LRYGB (MD= -2.50; 95% CI: -4.1 to -0.90) and BPD (MD= -3.40; 95% CI: -4.71 to -2.09) resulted in a statistically significant reduction in the mean number of anti-hypertensive medications used at ten years' follow-up relative to best medical care in one RCT (Figure 4.20).[249] Comparisons between LSG versus LRYGB (MD=-0.11; 95% CI: -0.88 to 0.66) and BPD versus LRYGB (MD= -0.90; 95% CI: -2.58 to 0.78) did not show a statistically significant difference at two or ten years post-surgery, respectively (Figure 4.21).[249, 277]

Cardiovascular medications

Two RCTs (reporting at different time points) reported that LRYGB was associated with a statistically significant reduction in cardiovascular medication use at three (MD=-1.73; 95% CI: -2.49 to -0.97), five (MD= -0.88; 95% CI: -1.66 to -0.10)[259] and ten years' (-4.40; 95% CI: -6.04 to -2.76)[249] follow-up when compared with best medical care (Figure 4.22). LSG was associated with a significant reduction in the mean number of cardiovascular medications at three years' follow-up (MD -0.82; 95% CI: -1.58 to -0.06)[291] but not at five years (MD -0.08; 95% CI: -0.84 to -0.68) compared with best medical care.[259]

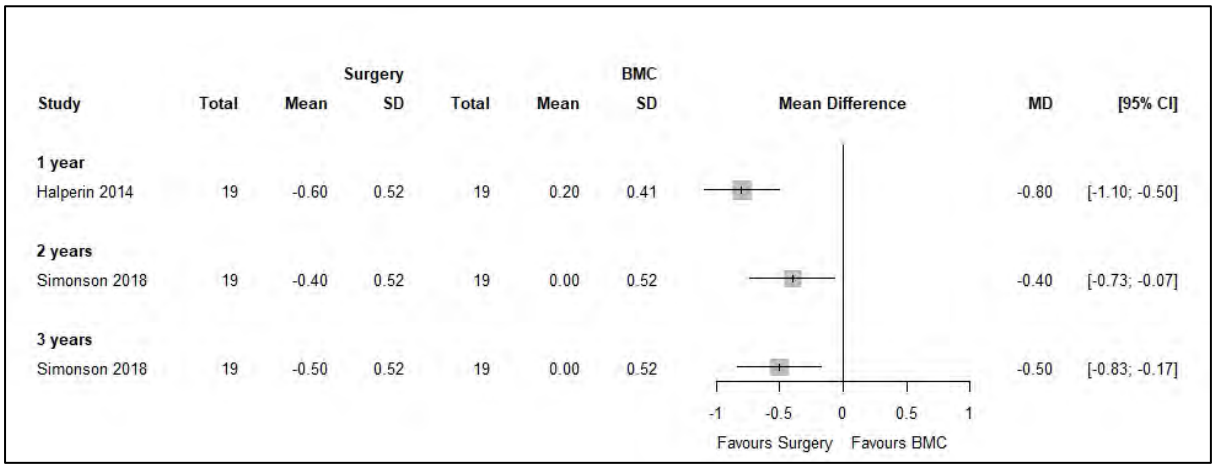
A statistically significant reduction in the mean number of cardiovascular medications was reported for LRYGB versus LSG at five years' follow-up in one study (MD -0.80; 95% CI: -1.51 to -0.09, Figure 4.23).[259] At ten years' follow-up, comparison of BPD and LRYGB showed no statistically significant difference between surgeries (MD -1.00; 95% CI: -2.72 to 0.72).[249]

Risk difference in the use of lipid-lowering or anti-hypertensive agents between metabolic surgery and best medical care

For studies that did not report the change from baseline in the use of cardiovascular medications, including lipid-lowering and anti-hypertensive agents, changes in the use of cardiovascular medications were determined for selected procedures based on the data provided at baseline and follow-up, where possible.

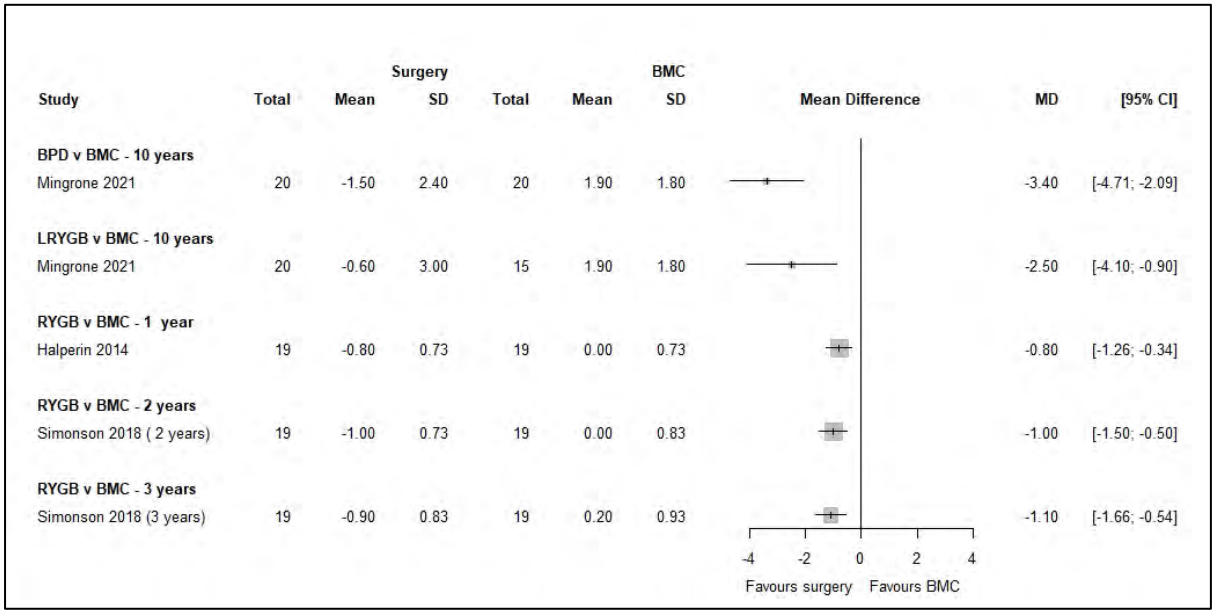
For RYGB compared with best medical care, there was a significant reduction in the use of lipid-lowering (RD =-0.38; 95% CI: -0.49 to 0.26) and anti-hypertensive agents (RD=-0.44; 95% CI: -0.63 to -0.26) at one to two years follow-up (Supplementary Appendix A3.8). A similar magnitude of reduction in the use of lipid-lowering (RD=-0.53; 95% CI -0.70 to -0.38) and anti-hypertensive agents (RD=-0.50; 95% CI -0.68 to -0.32) was observed for the comparison SG versus best medical care. Of note, the risk of lipid-lowering agent use was significantly higher in the RYGB group relative to best medical care at baseline. For SG versus best medical care, there was a trend towards a decreasing risk difference over time in the use of lipid-lowering agents. There was no evidence of a difference between RYGB and SG with regard to use of lipid-lowering or anti-hypertensive agents at follow-up. LAGB was associated with a statistically significant reduction in the use of antihypertensive medication (RD=-0.37; 95% CI: -0.61 to -0.13) but not lipid-lowering agents (RD=-0.13; 95% CI: -0.34 to 0.08).

Figure 4.19 Effect of metabolic surgeries versus best medical care on lipid-lowering medication use



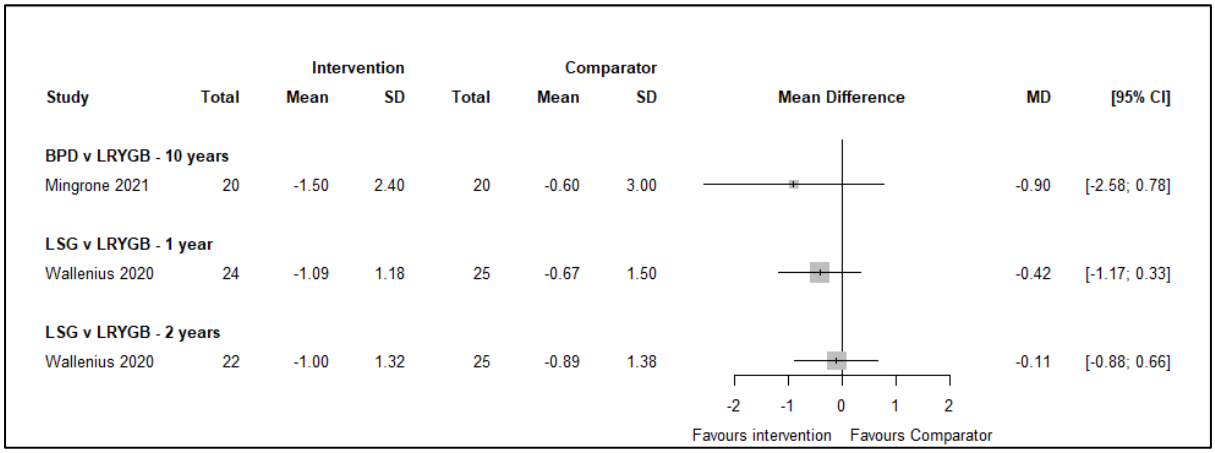
Key: BMC – best medical care; MD –mean difference; RYGB - Roux-en-Y gastric bypass; SD – standard deviation.

Figure 4.20 Effect of metabolic surgeries versus best medical care on anti-hypertensive medication use



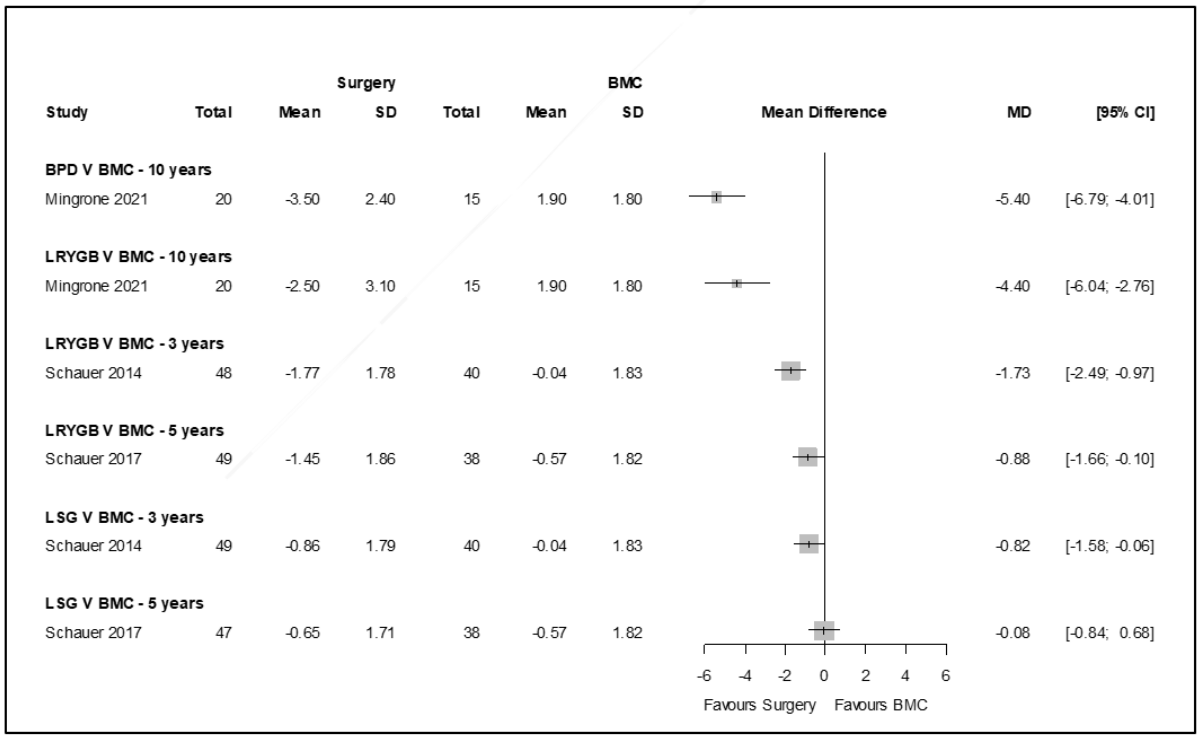
Key: BMC – best medical care; BPD – biliopancreatic diversion; MD –mean difference; LRYGB – Laparoscopic Roux-en-Y gastric bypass; SD – standard deviation.

Figure 4.21 Effect of metabolic surgeries versus other metabolic surgeries on anti-hypertensive medication use



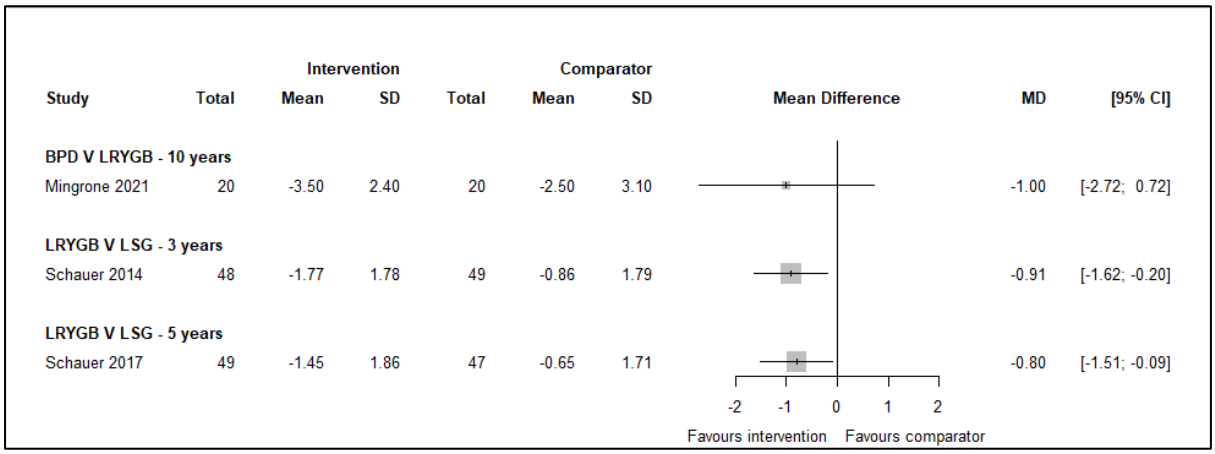
Key: BMC – best medical care; BPD – biliopancreatic diversion; MD –mean difference; LRYGB – Laparoscopic Roux-en-Y gastric bypass; LSG – laparoscopic sleeve gastrectomy; SD – standard deviation.

Figure 4.22 Effect of metabolic surgeries versus best medical care on cardiovascular medication use



Key: BMC – best medical care; BPD – biliopancreatic diversion; MD –mean difference; LRYGB – Laparoscopic Roux-en-Y gastric bypass; LSG – laparoscopic sleeve gastrectomy; SD – standard deviation.

Figure 4.23 Effect of metabolic surgeries versus other metabolic surgeries on cardiovascular medication use



Key: BMC – best medical care; BPD – biliopancreatic diversion; MD –mean difference; LRYGB – Laparoscopic Roux-en-Y gastric bypass; LSG – laparoscopic sleeve gastrectomy; SD – standard deviation.

4.3.2.11 Health-related quality of life

Six RCTs (of which two had three trial arms) reported on health-related quality of life (QoL). Of these, four RCTs measured quality of life using the 36-item short form health survey (SF-36),[168, 276, 284, 290] one used the EuroQol five-dimensions (EQ-5D),[261] and two RCTs used multiple tools.[263, 264] Six RCTs compared RYGB or LAGB with best medical care.[240, 249, 259, 261, 263, 264, 280, 281, 290, 291] In general, metabolic surgery was associated with improvements in quality of life relative to best medical care, which appears to be primarily mediated through changes in physical rather than mental health domains. There was no evidence of a difference between types of surgery.

At two years' follow-up, Cohen et al. reported a statistically significant improvement associated with RYGB relative to best medical care in seven out of eight domains of the SF-36 (scores for pain and social functioning differed between groups at baseline, with higher scores (indicative of better QoL) reported in the RYGB group).[168] There was no significant difference in the mental health score between groups at two years, although scores in both groups improved relative to baseline.[168] Schauer et al. reported a statistically significant improvement from baseline in five of eight domains in the RYGB group relative to best medical care at three years' follow-up.[291] The difference between groups was not statistically significant for social functioning and role limitations due to physical or emotional health. At five years' follow-up results favoured the RYGB group compared with best medical care across all eight domains, however the between-group difference was only statistically significant for general health and bodily pain.[259] Mingrone et al. reported that participants in the RYGB group scored significantly better for all subdomains of the SF-36 relative to the best medical care group at five and ten years' follow-up, however baseline scores were not reported.[249, 290] One RCT reported no significant difference between RYGB and best medical care groups at one year post-surgery, measured using the EQ5D.[261] One RCT used generic (SF-36) and disease-specific instruments including the Impact of Weight on Quality of Life (IWQOL)-Lite and Problem Areas in Diabetes Survey (PAID) to measure changes in QoL.[263] Significant improvements in the RYGB group relative to best medical care were only detected using the IWQOL suggesting that weight reduction has greater impact on improvement in perceived QoL than other measures.[263]

No significant difference between LAGB and best medical care groups was detected using generic (SF-36 and EQ5D) or disease-specific (PAID, IWQOL or barriers to being active) measures of QoL at three years' follow-up in one RCT.[264]

At five years' follow-up, SG was associated with a greater improvement in QoL across all eight domains relative to best medical care, however improvements were only statistically significant in two of eight domains (bodily pain and general health).[259]

In one RCT, the BPD group scored significantly better relative to best medical care at five and ten years' follow-up across all eight sub-domains, however baseline scores were not reported.[249, 290]

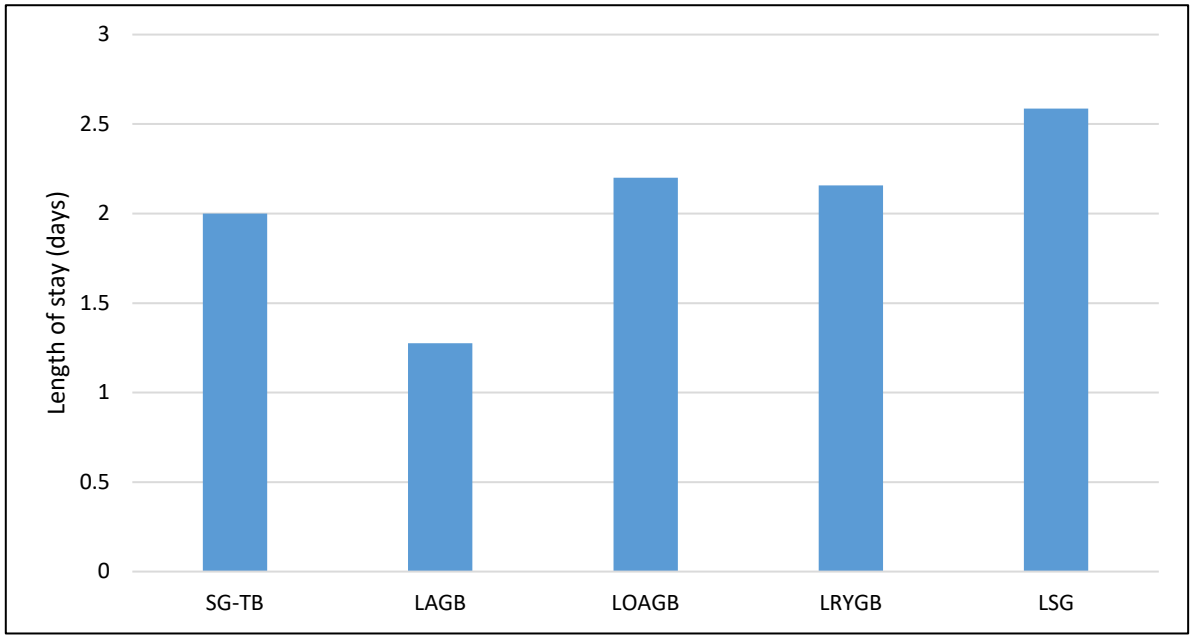
Three RCTs compared surgical procedures head-to-head.[249, 259, 276, 290, 291] Murphy et al., reported no significant difference in change in SF-36 subdomain scores at one-year follow-up between SR-LRYGB and LSG groups.[276] At three years' follow-up, Schauer et al. reported no significant difference between RYGB and SG groups for seven out of eight SF-36 subdomains; outcomes for emotional well-being favoured RYGB.[291] However, there was no significant difference between groups at five years.[259] In one RCT, at ten years' follow-up, participants in the RYGB group had significantly higher scores for vitality, physical role and mental health subdomains relative to BPD, however it is unclear if any difference existed at baseline.[249]

4.3.2.12 Resource use

Hospital length of stay

Seven RCTs reported on the mean length of stay (LOS) for metabolic surgery participants.[167, 267, 268, 271, 274, 277, 285] Mean LOS was approximately two days for LRYGB, LSG and LOAGB (Figure 4.24). LOS for LAGB was relatively shorter based on one RCT.[167] Two RCTs reporting mean post-operative LOS greater than five days were considered outliers and were excluded from the analysis.[267, 268] Both studies were conducted in China, thus reasons for these differences may be context-dependent.

Figure 4.24 Average length of hospital stay for metabolic surgery procedures†



Key: LAGB – laparoscopic adjustable gastric banding; LOAGB; Laparoscopic one-anastomosis gastric bypass; LRYGB – Laparoscopic Roux-en-Y gastric bypass; LSG – laparoscopic sleeve gastrectomy; SG-TB – sleeve gastrectomy with transit bipartition.
† For LRYGB[271, 277] and LSG[271, 277, 285] a weighted average is presented based on the sample size of trial arms. In one RCT, the median (IQR) was converted to the mean (SD) to facilitate comparison.[271]

Outpatient care

One RCT reported on outpatient visits.[295] The mean number of outpatient visits was significantly higher in the RYGB compared with the best medical care group in the first post-operative year (MD=7.00; 95% CI: 5.21 to 8.79).[295] However, mean outpatient visits were comparable in year two (MD=1.00; 95% CI: -1.48 to 3.48).[295]

Hospital re-admissions or emergency department visits

Hospital re-admissions were only extracted where clearly reported. Re-operations are described in section 4.3.3.3.

In the CROSSROADS trial, one (7%) inpatient hospitalisation was reported in the RYGB group during the first post-operative year relative to none in the best medical care group.[295] No inpatient hospitalisation events were reported in the second year in either group.[295] The early complication (<6 weeks after surgery) readmission rate was reported to be 9% and 13% in the SG and RYGB groups, respectively, in one RCT.[271] Serious adverse events requiring hospitalisation were reported in 22%, 8% and 9% of RYGB, SG and best medical care participants, respectively, during the first year follow-up in the STAMPEDE trial.[284] Parikh et al. reported a 10% readmission rate in the surgery group during six months' follow-up.[262]

Two RCTs reported on emergency department visits during the post-operative period.[280, 295] There was no significant difference in emergency room visits between RYGB and best medical care groups during the first or second post-operative years in one RCT.[295] Eight emergency department (44%) visits relating to post-operative complications were reported among five participants in the LAGB group relative to none in the best medical care group in another RCT.[264]

4.3.2.13 T2D-related complications

Microvascular events

Nephropathy

Three RCTs reported on renal outcomes.[168, 249, 259]

Two-year follow-up data from the MOMS trial suggest that those undergoing RYGB are 1.5 times more likely to achieve remission of microalbuminuria (that is, uACR levels <30mg/g) relative to best medical care (RR=1.51; 95% CI: 1.13 to 2.00) (Supplementary Appendix A3.10).[168] In addition, remission of early-stage chronic kidney disease (that is, urinary albumin to creatinine ratio less than 30mg/g of creatinine and eGFR greater than 60 mL/min/1.73m^2) was significantly higher among participants after RYGB than best medical care (RR=1.70; 95% CI: 1.24 to 2.33).[168] In the STAMPEDE trial, there was no significant difference between groups in albuminuria resolution at three or five years follow-up, however only 21% of participants had evidence of microalbuminuria at baseline.[259, 284, 291]

In the STAMPEDE trial, the albumin/creatinine ratio was significantly decreased (indicative of improved renal function) in the RYGB and SG groups relative to best

medical care at three and five years' follow-up (Supplementary Appendix A3.10).[259, 291] There was no significant difference between groups in other measures of renal function at three years' follow-up (Supplementary Appendix A3.10).[259, 291] At five years post-randomisation, serum creatinine was increased in all three groups (indicative of a decrease in renal function), with a significant increase in the surgery groups relative to best medical care, however this difference may not be clinically significant. Similarly, the glomerular filtration rate declined (indicative of a decrease in renal function) in all three groups over the five years' follow-up, with a significant reduction in those undergoing RYGB when compared with best medical care.[259] Mingrone et al. reported that over the ten years' follow-up the estimated GFR had declined in both the best medical care and surgical groups, however, RYGB participants had significantly better estimated GFR when compared with best medical care (MD=14.40; 95% CI: 2.86 to 25.94).[249] There was no significant difference in estimated GFR between BPD and best medical care groups (MD=-2.10; 95% CI: -12.62 to 8.42). There was no significant difference between groups in terms of albuminuria or proteinuria at five or ten years' follow-up.[249, 290]

Retinopathy

Three RCTs reported on ophthalmologic outcomes and found no significant difference in the development or progression of retinopathy between surgical and best medical care groups at time points ranging from two to ten years post-randomisation (Supplementary Appendix A3.10).[168, 259, 291]

Neuropathy

Two RCTS reporting on neuropathy found no significant difference in the number of participants with neuropathy between the RYGB and best medical care group at two to ten years' follow-up (Supplementary Appendix A3.10).[168, 249, 259, 290]

Macrovascular events

The relatively small sample sizes, limited number of events and short duration of follow-up precludes assessment of the impact of metabolic surgery relative to best medical care on the incidence of macrovascular complications in included RCTs. Cardiovascular events reported as adverse events are reported in Supplementary Appendix A3.10.

4.3.3 Adverse events

Twenty of 24 RCTs provided data on post-surgical adverse events.[167-169, 261, 262, 266, 268, 271, 274-277, 279-286]

4.3.3.1 Early and late mortality

Nineteen of 24 RCTs reported on early and late mortality.[169, 240, 249, 259-262, 266, 268-271, 274-291] There were no deaths in either trial arm up to 30 days post-surgery. There were five late deaths (>30 days) unrelated to metabolic surgery including three fatal cardiovascular events and one death from pancreatic cancer in participants managed with best medical care in four RCTs,[249, 259, 263, 278] and one fatal myocardial infarction in a participant who underwent laparoscopic one anastomosis gastric bypass (LOAGB) (Supplementary Appendix A3.11).[269] No significant difference in the risk of late mortality was detected for any comparison (Supplementary Appendix 10).

4.3.3.2 Hypoglycaemia

There was no statistically significant increase in the risk of severe or any hypoglycaemia for metabolic surgery relative to best medical care or other metabolic surgeries (Supplementary Appendix A3.11).[168, 249, 259, 261, 271, 281, 282] However, during the first year follow-up in one RCT, hypoglycaemia was more common after LRYGB than LSG among patients not taking insulin or sulfonylureas.[271]

4.3.3.3 Adverse events, reoperation or reintervention

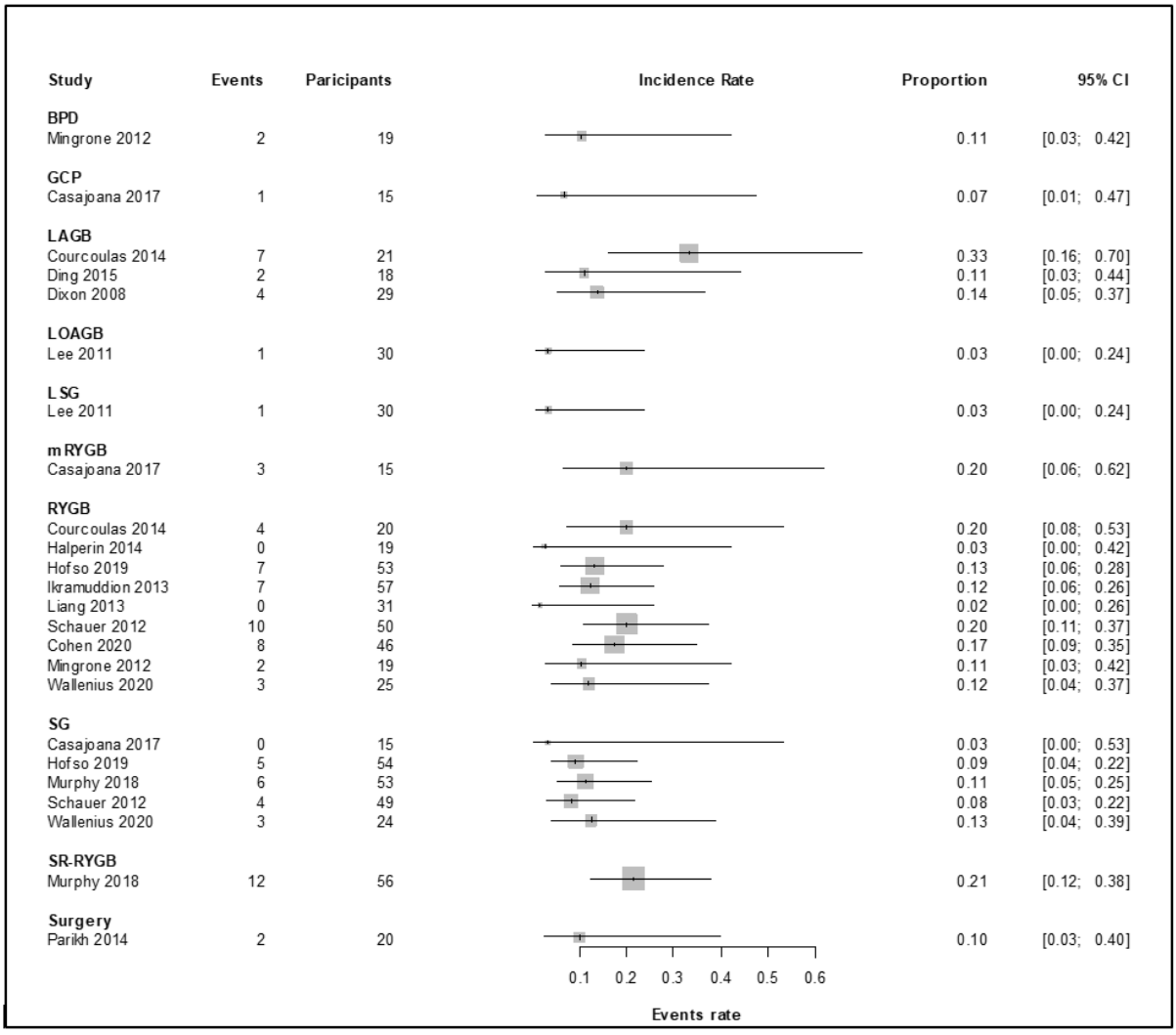
Surgery-related adverse events

Fifteen studies reported on post-operative surgery-related adverse events.[167-169, 262, 271, 276, 277, 279-286] Of these, three RCTs described early and late post-operative complications,[271, 283, 286] and three RCTs described post-operative complications according to their severity either through classification as major or minor adverse events or grading using validated scales.[168, 271, 286] In the remaining RCTs the timing or severity of post-operative complications was unclear, therefore categorisation of adverse events according to the timing of occurrence (for example, ≤30 days, >30 days post-surgery) or severity was not possible.

Banding procedures including LAGB and LSR-RYGB were generally associated with higher rates of technical complications, ranging from an event rate of 0.11 (95% 0.03 to 0.44) to 0.33 (95% CI: 0.16 to 0.70). There was no evidence of statistically significant difference between procedures (p=0.2720), however the included RCTs were not powered to detect differences in the risk of surgical complications. Variation in the rate of surgery-related adverse events between studies may be

related to factors such as the clinical characteristics of patients, the experience of the MDT, the quality of reporting and small sample sizes.

Figure 4.25 Proportion of technical complications at one to two years post-surgery†



Key: BPD – biliopancreatic diversion; GCP – greater curvature plication; LAGB – laparoscopic adjustable gastric banding; LOAGB; Laparoscopic one-anastomosis gastric bypass; mRYGB - metabolic Roux-en-Y gastric bypass; (SR)RYGB – (Silastic ring) Roux-en-Y gastric bypass; SG - sleeve gastrectomy; SG-TB – sleeve gastrectomy with transit bipartition.
† For studies reporting at two years follow-up, it was assumed that surgical complications occurred during the first year post-operatively.[167, 168, 277, 283]

Reoperation/re-intervention

Re-operations or re-interventions for conversion surgery or as a result of post-operative complications were reported in 17 RCTs (Supplementary Appendix A3.11). LSR-RYGB, SG-TB, GCP and LAGB were associated with the highest re-intervention

rates of 893, 500, 286 and 276 per 10,000 person years, respectively. Re-operation/re-intervention rates were comparable for SG, RYGB and mRYGB (165, 120 and 143 per 10,000 person years, respectively). BPD and OAGB showed relatively lower re-operation rates (50 and 83 per 10,000 person years, respectively). These findings should be interpreted with caution due to the limited number of RCTs, small sample sizes and short duration of follow-up available for some procedures.

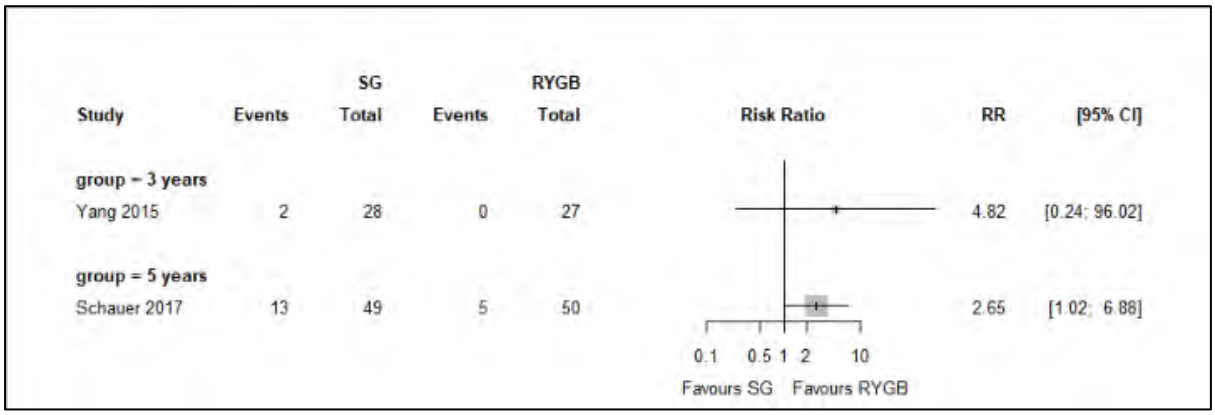
Of 44 re-operations, ten were conversion surgeries (n=9) or reversal to normal anatomy (n=1). Conversion surgery was most commonly reported after SG (six conversion surgeries of which four were carried out in one RCT) as a result of treatment targets not being met or post-operative complications including reflux oesophagitis, sleeve stricture or recurrent gastric fistula.[259, 269, 276]

4.3.3.4 Medium- to long-term clinical complications

Gastroeosophageal reflux

Seven RCTs reported on post-surgical gastroesophageal reflux.[167, 240, 259, 268-270, 278] There was no significant difference in the number of cases of gastroesophageal reflux between metabolic surgery and best medical care for any of the available comparisons (Supplementary Appendix A3.11). The risk of gastroesophageal reflux was increased in the SG group relative to RYGB group at medium to long-term follow-up in two RCTs, however estimates were statistically significant in one RCT only (Figure 4.26).[259]

Figure 4.26 Risk of post-surgical gastroeosophageal reflux for SG versus RYGB



Key: RYGB – Roux-en-Y gastric bypass; SG – sleeve gastrectomy.

Dumping syndrome

Three RCTs reported on dumping syndrome post-surgery;[168, 259, 271] of these, two RCTs provided data on the risk of dumping syndrome relative to best medical care.[168, 259] RYGB was associated with a statistically significant increases in the number of cases of dumping syndrome relative to the best medical care group at two years follow-up (RR=19.00; 95% CI: 1.14 to 317.06).[168] At five years follow-up in another RCT, the risk of dumping syndrome was increased in the RYGB (RR= 7.75; 95% CI: 0.43 to 139.99) and SG (RR=2.64; 95% CI: 0.11 to 63.06) groups compared with best medical care. However, this did not reach statistical significance.[259]

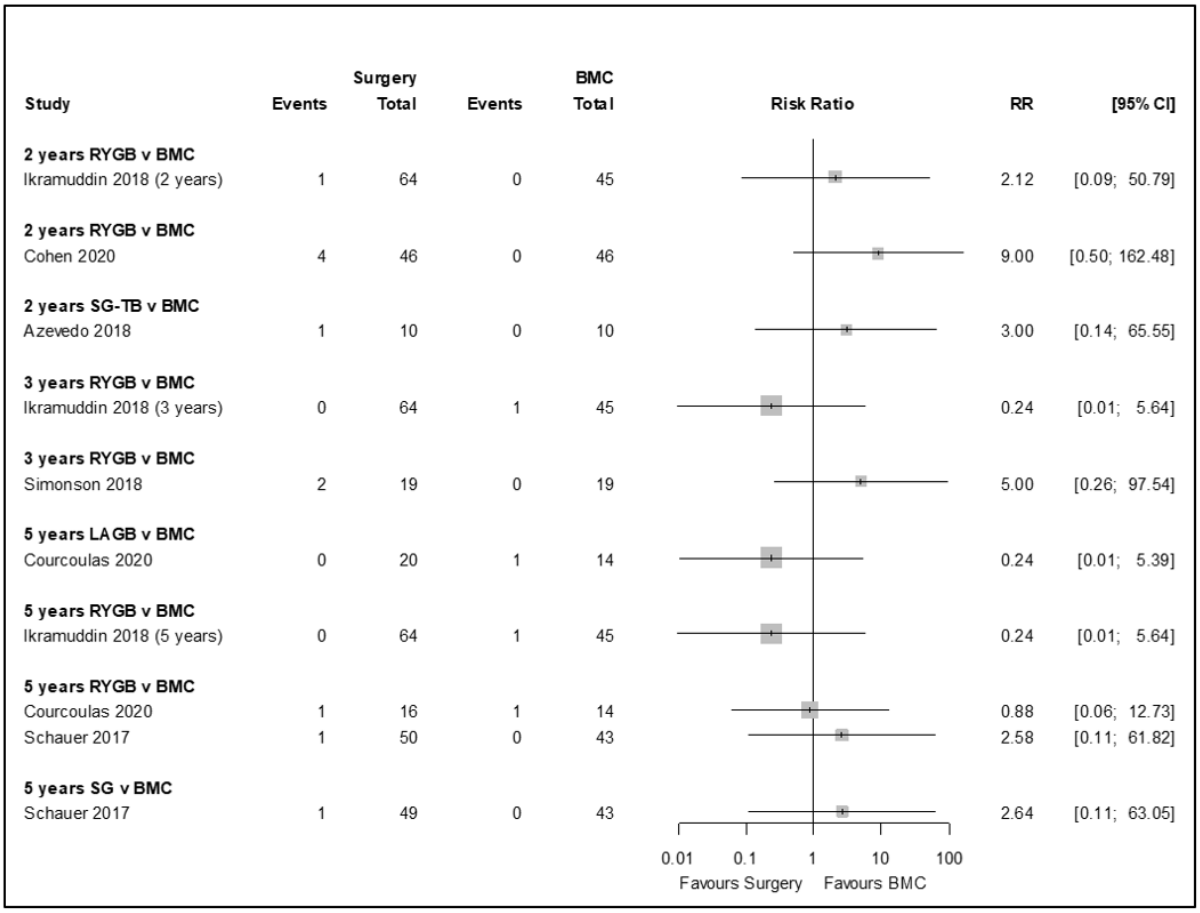
Two RCTs provided data for head-to-head comparison of surgeries.[259, 271] RYGB was associated with an increased risk of dumping syndrome post-surgery compared with SG, however this finding was not statistically significant (RR=3.92; 95% CI: 0.45 to 33.84).[259] Hofso et al. reported that the median Arts' early dumping

syndrome score was higher in the RYGB group than the SG group at one-year follow-up (2 (range 0 to 7) versus 0 (range 0 to 8)), although the score was low in both groups (maximum score 24).[271, 296] The late dumping syndrome score did not differ between groups (0 (range 0 to 4) versus 2 (range 0 to 4)).[271]

Gallstones

Seven RCTs reported post-surgical cholecystitis with or without cholecystectomy.[259, 260, 263, 271, 274, 278, 297] There was no significant difference in the number of cases of gallstones between groups for any of the available comparisons (Supplementary Appendix A3.11). Based on the available evidence, metabolic surgery may be associated with a non-significant increased risk of gallstones up to two years post-surgery relative to best medical care (Figure 4.27).

Figure 4.27 Risk of post-surgical gallstones for metabolic surgery versus BMC



Key: BMC – best medical care; LAGB – laparoscopic adjustable gastric band; RYGB – Roux-en-Y gastric bypass ; SG – sleeve gastrectomy.

Gout

No cases of gout were reported during the post-operative period in any of the included RCTs.

Nutritional deficiencies

Five RCTs reported on cases of anaemia post-surgery.[240, 259, 260, 268, 274] SG-TB[274] and RYGB[168, 259, 260, 284, 291] were associated with an increased risk of anaemia relative to best medical care, however this was not statistically significant at any time point up to five years (Supplementary Appendix A3.11). In one RCT, SG was associated with an increasing risk of anaemia over time relative to best medical care, which reached statistical significance at five years follow-up (RR=3.01; 95% CI: 1.44 to 6.28).[259]

RYGB was associated with an increased risk of anaemia relative to LAGB at five years, however this was not statistically significant (RR=3.71; 95% CI: 0.15 to 85.29).[260] In one RCT, SG was associated with a statistically significant increased risk of anaemia relative to RYGB at five years (RR=1.75; 95% CI: 1.03 to 2.97), but not at one or three years.[259] In another RCT, the difference between SG and RYGB at three years' follow-up was not statistically significant (RR=3.11; 95% CI: 0.13 to 73.10).[268]

Two RCTs reported on iron-deficiency anaemia.[282] At medium to long-term follow-up in one RCT, RYGB and BPD were associated with an increased risk of iron-deficiency anaemia relative to best medical care, however this was not statistically significant (Supplementary Appendix A3.11).[249, 290] The difference between BPD and RYGB for was not statistically significant at two (RR=1.00; 95% CI: 0.16 to 6.39), five (RR=1.67; 95% CI: 0.46 to 6.01) or ten (RR= 1.50; 95% CI: 0.28 to 8.04) years.[249]

Five RCTs reported on vitamin deficiencies during follow-up.[168, 271, 276, 282, 284, 290] In two RCTs, the number cases of vitamin B deficiency was significantly increased in the RYGB group relative to best medical care at one (RR= 5.50; 95% CI: 1.28 to 23.71) and two years' follow-up (RR=8.00; 95% CI: 1.04 to 61.42).[168, 282] Based on a limited number of RCTs, metabolic surgery was not associated with a statistically significant increase in the risk of vitamin D or potassium deficiency (Supplementary Appendix A3.11).[168, 282, 284] Mingrone et al. reported a non-significant increase in symptomatic vitamin A deficiency (night blindness) associated with BPD relative to best medical care throughout the ten year follow-up.[249] Two RCTs comparing metabolic surgeries head-to-head reported no statistically significant differences in nutritional and vitamin levels between surgery groups at one[271] and five years.[270]

One case of hypoproteinemia was reported in a participant that underwent mRYGB requiring conversion to normal anatomy.[270]

Information on nutrient supplementation was provided in one RCT.[271] Adherence was reported to be good where supplements were prescribed.

Bone health and fracture risk

Eight RCTs reported on bone-related adverse events including osteopenia, osteoporosis and fracture.[168, 249, 259, 260, 270, 271, 276, 278, 279, 282-284, 286-291, 294, 298] Fractures during the post-operative period were reported in four RCTs (Supplementary Appendix A3.11). [259, 260, 271, 278, 279, 282, 284, 287-289, 291, 294] However, the number of events was too small to make inferences.

Three RCTs reported cases of osteopenia and osteoporosis post-surgery.[168, 249, 298] Metabolic surgery was associated with more cases of osteopenia and osteoporosis when compared with best medical care in two RCTs.[168, 249] In two RCTs, cases of osteopenia and osteoporosis increased with increasingly malabsorptive procedures.[249, 298] A fourth RCT reported on surrogate markers of bone health only (percentage change in areal bone mineral density (aBMD) and absolute change in serum markers of bone turnover).[294] RYGB was associated with a greater reduction in aBMD and a greater increase in bone turnover markers relative to SG. However, the clinical significance of this is unclear.

4.3.4 Quality appraisal

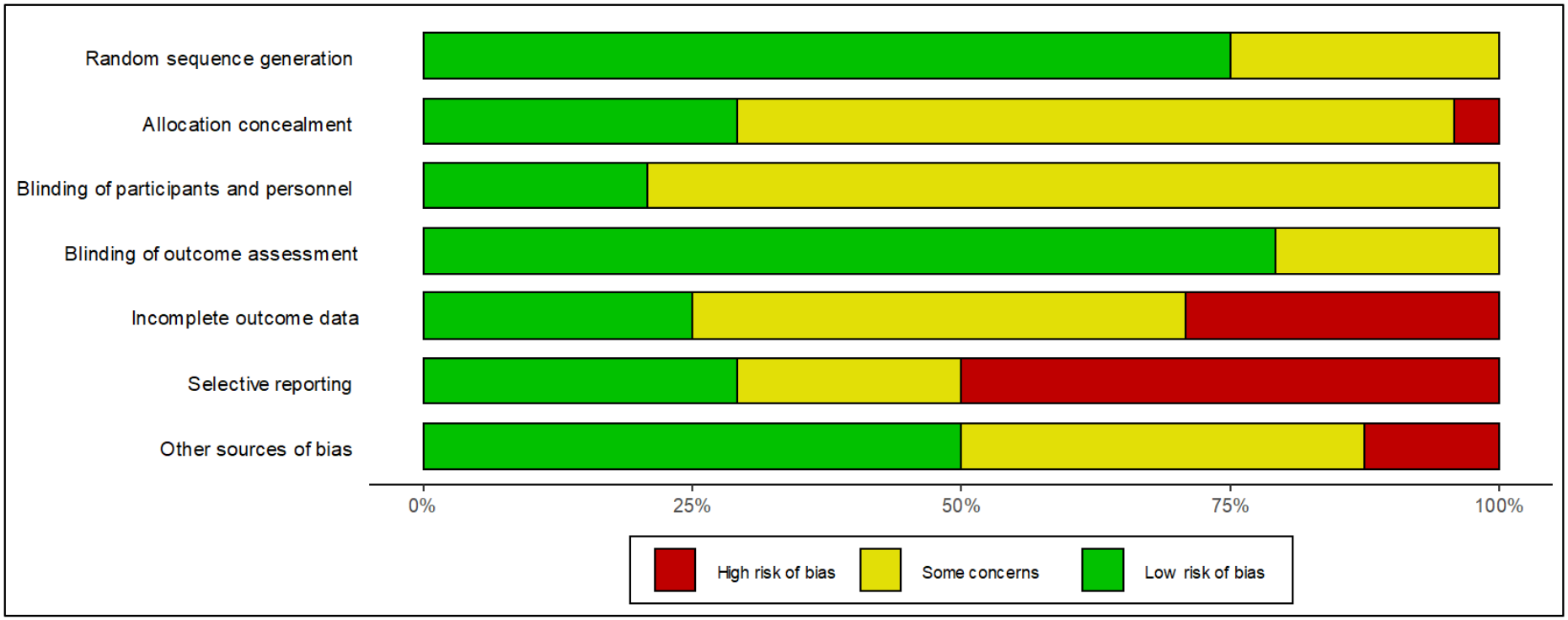
The main issues of concern identified during risk of bias assessment relates to blinding, incomplete outcome data and selective outcome reporting (Figure 4.28). In seven RCTs lack of blinding was linked to differential attrition whereby some participants refusing to undergo the allocated intervention post-randomisation, typically in the best medical care group.[168, 261, 262, 277, 279, 280, 284] In five RCTs of head-to-head surgical comparisons, where blinding is likely to be possible, information on blinding was not reported.[265-268] Although lack of blinding may be unlikely to impact assessment of objective outcomes, it has the potential to influence assessment of subjective outcomes such as QoL.[168, 249, 259, 261, 263, 264]

In four RCTs with five year follow-up data, loss to follow-up was imbalanced with higher loss to follow-up in the best medical treatment groups when compared with the surgery groups.[249, 259, 260, 278] Six RCTs were considered at high risk of bias relating to incomplete outcome data for the following reasons: considerable loss to follow-up with no imputation of results,[261, 262, 273, 277] and failure to report the CONSORT flow diagram including reasons for loss to follow-up.[272, 293]

Seven RCTs were considered at high risk of bias due to the potential for selective outcome reporting. In five RCTs there were no details of trial pre-registration or a protocol.[265-268, 273] In six RCTs discrepancies were identified between the trial registration and the published RCT without justification of protocol deviations.[169, 269, 272, 275-277]

Eights RCTs received industry funding which may represent a potential risk of bias due to the potential for the methods and results of the RCT to support the interests of the funding organisation.[167, 168, 259, 263, 264, 275, 276, 278]

Figure 4.28 Risk of bias assessment



4.4 Discussion

Treatment of comorbid T2D and obesity is aimed at reducing micro- and macrovascular complications. To this end, the American Diabetes Association (ADA) recommends treatment to correct hyperglycaemia, hypertension, and dyslipidaemia in patients with T2D.[233] The aim of this systematic review was to evaluate the impact of metabolic surgery on all aspects of T2D management including glycaemic and cardiovascular control, in addition to an evaluation of metabolic surgery-related adverse events to facilitate interpretation of the risk-benefit balance. The results of this systematic review demonstrate that metabolic surgery was more effective than best medical care in achieving improvements in glycaemic control. The probability of achieving long-term T2D remission post-surgery decreases with increasing duration of T2D, suggesting that optimal outcomes may be achieved with earlier intervention. T2D remission occurs alongside reductions in BMI and HbA1c levels. Over time, a considerable proportion of patients who initially achieved T2D remission secondary to metabolic surgery experienced relapse. However, glycaemic control was significantly better in participants randomised to metabolic surgery than those managed with best medical care. Overall, metabolic surgery was considered safe with no surgery-related mortality and a surgery-related adverse event rate of three to 20% depending on the procedure, in line with the expected rate.[299]

To date, interest in metabolic surgery for the treatment of T2D has largely focused on the glycaemic benefits of surgery, but management of diabetes also requires consideration of cardiovascular risk factors. Metabolic surgery, in particular RYGB and SG, was associated with improvements in triglycerides and HDL-C when compared with best medical care although the effect diminished over time. The effect of surgery on LDL-C, total cholesterol and blood pressure was subject to considerable uncertainty. Where comorbidities were reported (see characteristics of included studies, table 4.2) the proportion of participants with dyslipidemia or hypertension at baseline varied considerably between studies. It is likely that this clinical heterogeneity contributed to uncertainty in the treatment effect. Furthermore, anti-hyperglycaemic agents are now available with cardiovascular benefits independent of their glucose-lowering effects.[74, 300] Use of such agents in the best medical care group or in those who did not achieve T2D remission post-surgery may have contributed to the observed statistical heterogeneity. RCTs targeted at participants with comorbid dyslipidemia or hypertension would be necessary to determine to impact of surgery on cardiovascular risk factors, particularly in the context of the newer glucose-lowering drugs with additional cardiovascular benefits. Where reported, metabolic surgery was associated with a reduction in cardiovascular medication use relative to best medical care.

Putting these estimates in context, at five years follow-up, RYGB may be associated with an excess BMI reduction of between -6 to -10 units, depending on the baseline BMI of the population.[259, 260, 290] Although post-surgical improvements in glucose metabolism can occur through weight-independent mechanisms including changes in gut hormone signalling,[301] at two years post-surgery reductions of -1 to -9 and -10 to -14 BMI units have been associated with T2D remission rates of 48 to 70% and 77 to 97%, respectively, suggesting that the BMI reduction observed is likely to be clinically significant in a population with T2D.[302] An absolute difference in HbA1c of 1% has been shown to be associated with a lower risk of developing T2D-related complications, including a 14% lower odds of myocardial infarction and 37% lower odds of developing microvascular complications.[303] Thus, the excess reduction in HbA1c observed at five year follow-up in included RCTs comparing RYGB and SG with best medical care of approximately -1 to -2% are likely to result in clinically meaningful improvements in glycaemic control for patients, and in turn a reduction in health service utilisation associated with the management of T2D-related complications.

In general, there was no evidence of significant differences between RYGB and SG for any of the metabolic or cardiovascular end-points considered. However, it is possible that RCTs were underpowered to detect potentially small differences in secondary endpoints, which may not be clinically significant. Consistent with our findings, a systematic review comparing RYGB and SG noted that remission rates did not differ between RYGB and SG at two to five years' follow-up.[246] RYGB demonstrated superior efficacy relative to LAGB in terms of BMI reduction, consistent with a previous network meta-analysis of bariatric surgery.[304] Insufficient evidence was available for other head-to-head comparisons to draw definitive conclusions.

Although resolution of T2D may not last indefinitely following metabolic surgery, results of the UK Prospective Diabetes Study (UKPDS) and Steno-2 Study indicate that the health benefits of a period in T2D remission or improved glycaemic control may persist in the long-term.[305, 306] The magnitude and duration of improvements in glycaemic control and cardiovascular risk factors necessary to yield a clinically significant decrease in diabetes-related morbidity and mortality is currently unclear. Evidence from this systematic review suggests that metabolic surgery may be associated with a reduced risk of nephropathy in participants with albuminuria at baseline compared with best medical care.[168] In long-term observational studies of bariatric surgery with subgroups of participants with T2D, bariatric surgery has been associated with a reduced incidence of microvascular and macrovascular

complications relative to usual care in long-term observational studies.[307-309] While promising, data regarding the protective effects of surgery on microvascular complications of T2D should be interpreted in the context of the low prevalence of microvascular disease at baseline in two of three RCTs reporting on microvascular outcomes,[249, 259] small sample sizes, and the consequent low absolute number of diabetes-related complications. Further carefully designed controlled studies will be necessary to confirm whether changes in cardiovascular risk factors translate into improvements in diabetes-related morbidity and mortality, and the optimal timing of intervention to slow or arrest disease progression.

Consideration of potential surgery-related adverse events is necessary in the selection of the most appropriate surgery for an individual patient. Where surgery-related adverse events occurred, these were typically resolved with re-operation and no long-term morbidity, with the exception of one case of sepsis with systemic consequences.[282] Evidence for medium- to long-term clinical complications was limited, however there was a trend towards increased risk of gastroesophageal reflux post-surgery with SG relative to RYGB, consistent with clinical practice guidelines recommending the selection of RYGB rather than SG in patients with severe gastroesophageal reflux disease and/or severe esophagitis at baseline.[8] Although not significant, the risk of gallstones was more pronounced in patients who underwent metabolic surgery than those randomised to best medical care up to two years post-surgery, at which point weight loss is likely to have plateaued. Our findings are consistent with observational evidence from the Swedish Obese Subjects Study.[310]

Although there was some evidence that the risk of nutritional deficiencies was increased in metabolic surgery patients relative to usual care, these differences were largely not statistically significant. Nutrient deficiencies were generally not reported in the context of clinical manifestations, with the exception of non-significant increases in the risk of night blindness after BPD in one RCT, and anaemia requiring transfusion following RYGB in one RCT.[260] Thus, the clinical significance of reported nutritional deficiencies is largely unclear. Furthermore, without information on the prescribing of, and adherence to micronutrient supplementation, interpretation of the evidence is challenging. Long-term adherence to micronutrient supplementation after bariatric surgery is often suboptimal.[311] Healthcare system and patient-derived factors including inadequate biochemical monitoring during the post-operative period and poor adherence to prescribed supplementation, respectively, may contribute to the development of nutritional deficiencies.[312, 313] Nevertheless, nutritional deficiencies are likely to be a greater challenge in general practice where adherence is likely to be lower when compared with RCTs. Future RCTs should report clinical manifestations of micronutrient deficiencies including associated healthcare

utilisation and adherence to recommended supplementation to facilitate interpretation of severity. Few studies reported on fracture risk post-surgery. Where reported, there is some evidence of increased bone loss post-surgery, however the small sample sizes and short duration of follow-up make it difficult to draw conclusions on the impact of metabolic surgery on the risk of fracture. Evidence from the Swedish Obesity Subjects study has shown that bariatric surgery, particularly malabsorptive procedures, may have a deleterious effect on bone metabolism in the long-term.[314] Therefore, calcium and vitamin D supplementation coupled with monitoring of bone mineral density in metabolic surgery patients may be necessary to minimise fracture risk.

Included RCTs investigated the clinical effectiveness and safety of metabolic surgery only. In clinical practice, skin-fold removal is recognised as an important part of the metabolic surgery pathway, which may impact outcomes such as quality-of-life.

Strengths and limitations

A robust approach to the review process was employed with the publication of a predefined protocol and adherence to guidelines to standardised reporting guidelines. However, the findings of this systematic review should be interpreted with consideration of limitations relating to both the underlying evidence and the systematic review process.

Numerous concerns exist regarding the design and conduct of included RCTs. Firstly, the short duration of follow-up, small sample sizes and consequent low absolute number of surgery-related adverse events and diabetes-related complications mean that data on long-term risk and benefits of metabolic surgery should be interpreted with caution. Secondly, differential attrition is a challenge in RCTs where metabolic surgery is compared with best medical care, with higher loss to follow-up typical in the standard care arm.[279] Only five RCTs attempted to impute missing data or conducted sensitivity analysis to determine the impact of missing data on the primary outcome which may impact the internal validity of findings.[167, 259, 260, 269, 278] However, where available, estimates were based on imputed results. Thirdly, although blinding is not possible in trials comparing metabolic surgery with best medical care, the lack of blinding represents a significant limitation, given that blinding is essential to prevent the introduction of bias related to participant (for example, dietary or behavioural changes) or healthcare provider behaviour (for example, clinician variation in medication withdrawal thresholds and assessment or classification of diabetes-related complications). Fourth, the majority of RCTs were conducted in a single centre. Only two RCTs were multicentre studies which may limit the generalisability of findings to other contexts.[277, 278] Larger trials of

metabolic surgery compared with best medical care are unlikely to be possible owing to numerous research challenges including challenging retention in the usual care arm, the need for targeted pre-operative screening and a multicentre consortium to ensure generalisability of results, and the associated prohibitive costs.[260] Although evidence is available from large observational studies, such observational evidence may be biased because the characteristics of populations who choose to undergo surgery may differ from those who do not.[261] Large multicentre carefully designed observational studies powered to examine the benefits of hard cardiovascular endpoints (for example, stroke) as well as to detect the deleterious effects of metabolic surgery will be necessary to address identified research gaps.

A number of limitations are associated with the reporting of outcomes in the underlying trials and thus this systematic review. Variation in reporting across RCTs presented challenges for direct comparison. Definitions of diabetes remission were heterogeneous, which was further compounded by the recent update to the American Diabetes Association's definition of T2D remission which occurred subsequent to the publication of the included RCTs.[62] Consequently, results for T2D remission were synthesised using several approaches to facilitate comparison across studies and investigate the impact the definition adopted had on the estimated remission rate. An important consideration is that HbA1c values recorded at a single time point may not reflect potential variability in HbA1c over the course of the follow-up period. Greater variability of HbA1c has been associated with a higher risk of cardiovascular events and all-cause mortality in T2D.[315] Variation in HbA1c, collected through more frequent monitoring of glycaemic control, may be more informative than isolated HbA1c monitoring in future studies attempting to elucidate the relationship between HbA1c and the risk of T2D-related complications in this population.

In general, the usefulness of post-operative complication data was limited by the lack of grading of severity, failure to outline requirements for hospital admission or prolonged hospitalisation and the reporting of adverse events unrelated to metabolic surgery. Therefore, in the absence of grading of severity or requirements for medical intervention, the frequency of technical complications reported in this systematic review should not be interpreted as the frequency of serious adverse events which can result in death or life-threatening, disabling or incapacitating conditions.[316] Nevertheless, the reporting of adverse events in this systematic review is in line with best practice recommendations and are likely reflective or the burden of complications requiring prolonged hospitalisation or re-admission. In future RCTs reporting of internationally-accepted definitions of T2D remission and pre-specified surgery-related adverse events (including the severity of the complication and

requirements for medical intervention) at clinically-relevant time points would greatly assist future reviews in this subject area, particularly to facilitate pooled analyses.

Patients seeking metabolic surgery are typically older, with a lower BMI, and increased prevalence of comorbidities including more severe T2D (that is, lower HbA1c levels and insulin use at baseline) when compared with patients who seek bariatric surgery specifically for weight loss. This makes it difficult to generalise findings from RCTs of bariatric surgery to population with comorbid T2D and obesity.[17] Thus, this systematic review was limited to RCTs specifically enrolling patients with comorbid T2D and obesity in order to inform clinical decision-making regarding the potential introduction of a metabolic surgery programme in Ireland. Inclusion of RCTs in bariatric surgery populations would have increased the size of the evidence base, but would likely have contributed to increased clinical heterogeneity.

Pooling of data was limited by the range of procedures and variable duration of follow-up across studies. Where pooled analyses were undertaken, in general, there was evidence of significant statistical heterogeneity. Possible explanations for substantial statistical heterogeneity could be variability in terms of nature of the comparator (for example, the availability of newer anti-hyperglycaemic agents in some best medical care groups) or study populations in terms of the duration of T2D, insulin-dependence or comorbidities which have the potential to affect outcomes. In meta-analyses with few studies, such as those undertaken in this systematic review, there is potential for statistical heterogeneity as measured with the I^2 statistic to be biased. Depending on the circumstances, the bias of I^2 can be small or large.[317]

When an outcome is measured using different scales or units it requires standardisation to be pooled in a meta-analysis. Expressing outcomes in terms of SMDs facilitates comparison across RCTs but presents challenges for clinical interpretation.[318] Transforming standardised mean differences to natural units did not consistently produce valid estimates for all RCTs given that outcomes were measured in different units. Thus, the clinical significance of the findings of this systematic review are described in the context of the larger RCTs with long-term follow-up or RCTs of relevance to a specific outcome.

It was originally planned that the methodological quality of included RCTs would be assessed with the updated Cochrane RoB 2.0 tool. However, the use of this tool in this systematic review with multiple outcomes presented many challenges. Application of RoB 2.0 requires appraisal of a specific outcome (for example, T2D remission) at a specific time point (for example, 5 years) for a specific comparison

(for example, RYGB versus best medical care). Appraisal of eighteen outcomes reported across an average of three time points for a minimum of eight comparisons (for example, RYGB versus best medical care, SG versus best medical care, LAGB versus best medical care, BPD versus best medical care, RYGB versus SG, LOAGB versus SG, RYGB versus LAGB and RYGB versus BPD) is estimated to take five to six weeks to complete per reviewer.[257] Limiting quality assessment to specific outcomes at a specific time point would have resulted in some included RCTs not being eligible for quality appraisal. While it is recognised that the risk of bias may differ between outcomes within a single RCT, a practical approach to applying the RoB 2.0 tool to large systematic reviews is needed that will not impede timely provision of evidence to support decision-making.

Based on evidence from this systematic review, metabolic surgery is a safe and effective treatment option for screened surgical candidates with comorbid T2D and obesity compared with best medical care. It is acknowledged, however, that lifestyle interventions can result in clinically significant long-term weight loss and improvements in cardiovascular risk factors for some patients with T2D and overweight or obesity, as demonstrated in the Look Ahead trial.[319] The optimal treatment approach for an individual patient will depend on the clinical context. It is likely that for some patients, multimodal treatment including surgical, pharmacological and behavioural interventions will be necessary to produce long-term benefits. Careful candidate selection would be necessary to replicate results of included RCTs.

Conclusions

Metabolic surgery was more effective than best medical care for the management of comorbid T2D and obesity at up to five year follow-up, however longer-term evidence is lacking. Importantly, improvements in glycaemic control and weight loss occur in the setting of lower medication burden, improved QoL and low surgical risk. Although those in T2D remission may relapse over time, improvements in HbA1c relative to best medical care are sustained and may have ongoing health benefits in terms of the development or progression of T2D-related complications. Trials did not report efficacy and safety by patient subgroups, so it was not possible to identify subgroups that may stand to benefit more from surgery.

While outcomes of metabolic surgery seem to be favourable, these findings should be interpreted with caution due to the inherent limitations of the evidence base, which is constrained by the small sample sizes of included RCTs and the limited head to head evidence between surgical procedures.

5 Systematic review of cost-effectiveness

Key points

- A systematic review was undertaken to assess the available international evidence on the cost-effectiveness of metabolic surgery compared with usual care in patients with comorbid type 2 diabetes (T2D) and obesity.
- Thirty studies were identified that evaluated the cost-effectiveness of metabolic surgery in comparison with usual care in patients with comorbid T2D and obesity. Of these, 16 studies were conducted specifically in a T2D population. Patients with T2D represented a subgroup of the population in 14 studies.
- Twenty-eight studies were model-based economic evaluations. Two evaluations were based on a single trial or observational study without extrapolation of data beyond the study period. Of model-based economic evaluations, 20 studies used a Markov model to estimate the costs and benefits of surgery compared with usual care. Three studies used a hybrid decision-tree and Markov model and two evaluations used a microsimulation model. The model structure was unclear in three studies.
- Cost-effectiveness was determined using an Irish willingness-to-pay (WTP) threshold of €20,000/quality-adjusted life year (QALY) gained or €45,000/QALY using 2020 consumer price indices. Of studies carried out specifically in a T2D population, metabolic surgery was reported to be cost-effective in 10 studies, with incremental cost-effectiveness ratios (ICERs) ranging from €360 to €17,029/QALY. Surgery was reported to be cost-saving in eight analyses (from six studies). In one study, the ICER exceeded the WTP threshold of €20,000/QALY but would still be considered cost-effective at a WTP threshold of €45,000/QALY.
- Of studies in which T2D patients were considered in subgroup analysis, metabolic surgery was cost-saving in 10 studies. Metabolic surgery was cost-effective in three studies, with ICERs ranging from €2,462 to €10,651/QALY. In one study the outcome varied depending on the procedure and BMI category.
- Of two economic evaluations based on a single study, metabolic surgery was considered cost-effective at a threshold of €45,000/QALY.
- Where undertaken, the results remained robust in sensitivity and scenario analyses within the plausible ranges.

- The quality of included studies was variable, mainly due to insufficient reporting of input parameters and structural shortcomings. Studies were categorized as high (n =15), moderate (n = 5) or low (n = 10) quality using the Consensus Health Economics Criteria (CHEC)-list quality appraisal instrument.
- None of the studies were considered directly applicable to the Irish context. Seventeen studies were said to be partially applicable. The transferability of identified economic evaluations was limited by the health states and time horizon considered, the sources and applicability of clinical effectiveness estimates, and differences in health systems.
- Overall, twenty-six studies adopted a conservative approach whereby the impact of surgery on T2D status was modelled based on the proportion of patients who achieved complete remission only. As a consequence, the proportion of patients who experience improvements in glycaemic control but do not enterT2D remission were not considered. Even when studies adopted a conservative approach, surgery was still cost-effective or cost-saving.

5.1 Introduction

The aim of this chapter was to summarise the available international evidence on the cost-effectiveness of metabolic surgery in comparison with usual care in patients with comorbid type 2 diabetes (T2D) and obesity, and to assess the applicability of the evidence to inform an assessment of its cost-effectiveness in Ireland.

5.1.1 Review protocol

This systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria and registered on PROSPERO (PROSPERO ID: CRD42021234932) prior to the conduct of the review.[320, 321]

5.2 Methodology

Two systematic reviews of the cost-effectiveness of bariatric surgery compared with standard care have been conducted in recent years.[12, 322] However, these reviews were not conducted specifically in a population with comorbid T2D and obesity, therefore an update of an existing review was not considered appropriate in the context of this assessment. A de novo systematic review was undertaken in order to answer the specific research question for this HTA.

5.2.1 Review question

The specific question for this systematic review was developed to reflect the outcomes and costs associated with the management of comorbid T2D and obesity, and the potential impact of metabolic surgery on the underlying disease process. The PICO (Population, Intervention, Comparator, Outcomes) framework used to formulate the research question is presented in Table 5.1. Studies were considered for inclusion in accordance with the following hierarchy of evidence:

1. cost-effectiveness analyses of metabolic surgery in patients with comorbid T2D and obesity

2. cost-effectiveness analyses of bariatric surgery in patients with obesity, where sub-group analysis is carried out for patients with comorbid T2D and obesity.

Table 5.1 Inclusion criteria set out in the PICO framework

Population	Adults ≥ 18 years of age with comorbid type 2 diabetes and obesity* 1. Patients with comorbid T2D and obesity 2. Patients with obesity, where a subgroup of patients have T2D
Intervention	Bariatric/metabolic surgery procedures in current use, performed either as open or laparoscopic procedures
Comparator	Non-surgical management (usual care†)
Outcomes	ICER or NMB
Study Designs	CUA, CEA

Key: BMI – Body mass index; CEA – cost-effectiveness analysis; CUA – cost-utility analysis; ICER – incremental cost-effectiveness ratio; LYG – life years gained; NMB – net monetary benefit; QALYs – quality-adjusted life years; T2D – Type 2 Diabetes.
* BMI thresholds were not pre-specified as thresholds associated with obesity and obesity-related disease may vary dependent on the target population.
† Usual care can include descriptions such as conservative treatment, conventional or intensive medical management.

Economic evaluations can be considered partial (that is, costing studies in which only the cost of healthcare interventions are analysed) or full (that is, studies in which both costs and effects of two or more alternative interventions are compared).[323, 324] Partial economic evaluations do not involve a comparison between alternative interventions and do not relate costs to benefits.[325] Full economic evaluations can be considered under two major categories: cost-effectiveness analysis and cost-benefit analysis. Cost-benefit analyses present both costs and benefits in monetary terms and

are rarely used in healthcare due to the difficulties of expressing health benefits directly in monetary terms.[326] Only cost-effectiveness analyses were included in this systematic review.

The following exclusion criteria were applied:

- cost-consequence analysis, cost-benefit analysis, other types of cost analyses and comparative resource use studies
- commentaries, letters, conference papers and abstracts where a detailed description of the methods was not available
- economic evaluations of metabolic surgery for the prevention of T2D
- studies that did not predominantly comprise the target population of interest (that is, adults with comorbid T2D and obesity), or did not report results for a study subgroup that matched the target population
- studies which were not available in English.

5.2.2 Search strategy

The search string was developed in consultation with a librarian from the Royal College of Surgeons in Ireland (RCSI) and is presented in Appendix A4.1. A validated economic search filter developed by the Scottish Intercollegiate Guidelines Network (SIGN) was applied in addition to the clinical terms.[327]

Electronic searches were conducted in Medline (via Ovid) and Embase. The Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE), the HTA Database and the National Health Service Economic Evaluation Database (NHS EED) were included within these databases. Searches of electronic databases were carried out on 20 January 2021 and were supplemented by a search of grey literature including Google Scholar, national and HTA electronic sources (Supplementary Appendix A4.1). No date limits were applied to the search. Reference lists of included studies were searched for potentially relevant citations.

5.2.3 Selection of studies

Two reviewers independently screened titles and available abstracts in Covidence®. The full text of potentially eligible studies were retrieved and independently assessed for eligibility by two reviewers according to the criteria outlined in Table 5.1, with any disagreements resolved through discussion, or if necessary, a third reviewer. The study selection process is presented on a PRISMA flow diagram (Figure 5.1).

A list of excluded studies is presented in Appendix A4.2. Studies were often excluded for more than one reason, but the first reason identified is reported.

5.2.4 Data extraction and management

Data extraction was conducted independently by two reviewers using a standardised, pre-piloted electronic data extraction form. Disagreements were resolved through discussion. The cost per quality-adjusted life year gained (QALY) gained was the preferred outcome for this systematic review due to its ability to summarise the number and quality of additional life years attributable to an intervention. Other outcomes (for example, cost per life years gained (LYG)) were extracted where QALYs were not used as the measure of effect.

5.2.5 Assessment of study quality and applicability

Assessment of the methodological quality of economic evaluations was carried out using the Consensus on Health Economics Criteria (CHEC)-list.[328] The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) questionnaire was used to assess the transferability of model-based economic evaluations to the Irish setting.[329] Evaluation of methodological quality and applicability was carried out by two reviewers independently with any disagreements resolved through discussion, or if necessary, a third reviewer. Study quality was based on the judgement of the assessor (that is, numerical grading of studies was not carried out), in line with best practice.[330, 331]

5.2.6 Data synthesis

In line with best practice recommendations, the results of model-based (that is, data were synthesised from a number of sources) and empirical study-based (that is, economic evaluations based on a single trial or observational study) economic evaluations were synthesised separately.[324] Due to various potential sources of heterogeneity (for example, methodology, population or healthcare system characteristics), pooling of outcomes was not carried out. The results were synthesised narratively. Where different versions of a study were retrieved, only the results of the most recent update are presented.

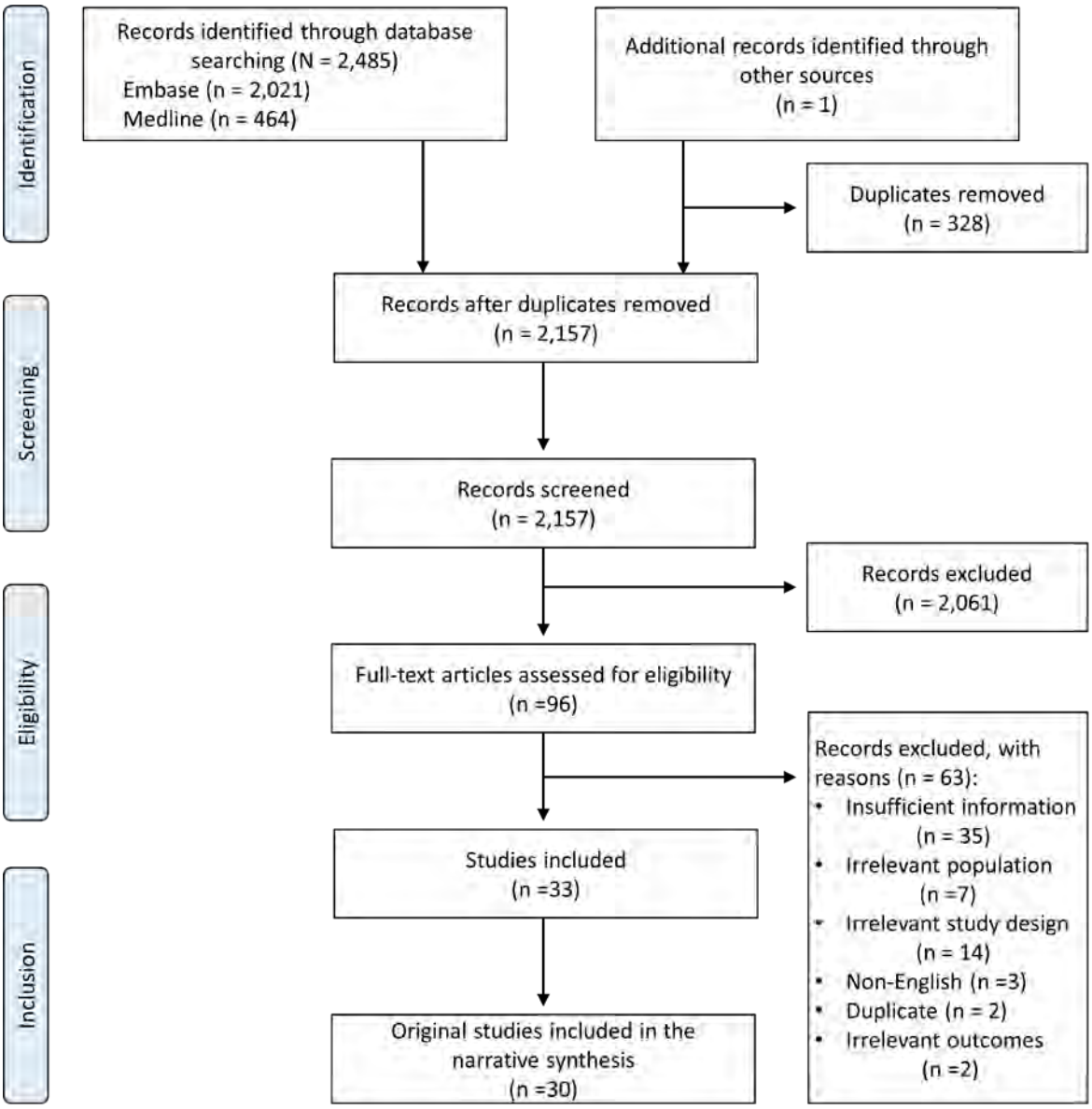
Willingness to pay (WTP) thresholds of €20,000 and €45,000 per QALY gained are typically used in Ireland as reference points for decision-making regarding the reimbursement of medicines.[326] To facilitate comparability of the results across countries and years, where appropriate, costs were inflated and adjusted to Irish euro using 2020 prices in accordance with national HTA guidelines.[326] Where the cost year was not reported, the average interval between the cost and publication

year in other included studies (3 years) was assumed unless other appropriate rationale was identified.

5.3 Results

Thirty original articles from 33 publications met the criteria for inclusion. Of these, 16 reported on the cost-effectiveness of metabolic surgery specifically in a population with comorbid T2D and obesity.[332-347] Of 17 studies that reported on the cost-effectiveness of bariatric surgery in a population with obesity in which a sub-group had comorbid T2D[348-363] three studies were excluded from data extraction and quality appraisal as the analyses were subsequently updated[353, 361] or reported in more than one study,[356] leaving 14 studies eligible for inclusion.[348-352, 354, 355, 357-360, 362-364] An overview of the study selection process is provided in Figure 5.1.

Figure 5.1 PRISMA flow diagram of search and selection process



5.3.1 Characteristics of included studies

Twenty-eight economic evaluations were model-based analyses. Two studies, specifically carried out in a T2D population, were based on a single trial[339] or observational study (that is, were empirical study-based analyses).[345]

5.3.1.1 Studies based on models

Fifteen studies were conducted in European countries including the six in the UK,[332, 341, 342, 349, 357, 362] three in Italy,[333, 343, 360] two each in Germany[332, 352] and Spain,[333,

[363] and one in each of Belgium,[350] France,[332] Austria,[333] Portugal,[355] Denmark[351] and Sweden.[348] Four studies were carried out in the United States,[336, 337, 340, 364] three in South America,[334, 335, 354] three in Asia,[344, 346, 347] two in Australia,[338, 358] and one in Canada.[359] In two studies, the cost-effectiveness of metabolic surgery in more than one country was evaluated.[332, 333]

Of 14 model-based studies conducted specifically in a T2D population, the target population had a BMI ≥35 kg/m^2 in six studies.[332-337] Three studies conducted in Asian countries used different BMI thresholds than typically adopted in Western countries.[344, 346, 347] Two studies were based on an RCT which included patients with class I (BMI 30 to 34.9 kg/m^2) and II (35 to 39.9 kg/m^2) obesity.[338, 342] One study did not report BMI criteria, however the mean baseline BMI of the modelled cohort was 47.2 kg/m^2 (SD 7.3).[341] The other two studies evaluated the cost-effectiveness of surgery across a range of BMI categories.[340, 343] In addition to analyses according to BMI criteria, two studies investigated the cost-effectiveness of metabolic surgery across subgroups defined by clinical or demographic characteristics including duration of T2D,[336] age[336] and sex.[340] No studies investigated the cost-effectiveness of surgery according to the presence, absence or severity of T2D-related complications at baseline.

Of the 14 studies in which a sub-population had T2D, one study included patients with a BMI ≥40 kg/m^2,[357] four studies modelled populations with a BMI ≥35 kg/m^2,[354, 358, 359, 364] eight studies carried out the analyses across all classes of obesity[348-352, 355, 360, 363] and one study modelled participants with class I or II obesity and recent onset T2D based on the population enrolled in an RCT.[362] Eight studies carried out further sub-group analysis according to age[358] or sex.[348-352, 360, 363]

Economic evaluations considered a single bariatric procedure,[334, 337, 338, 342, 345-347, 354, 362, 364] or a range of procedures reflective of the distribution of procedures in clinical practice in the country of interest.[332, 333, 335, 336, 340, 341, 343, 344, 348-352, 355, 357-360, 363] Eleven model-based studies conducted in a T2D population considered Roux-en-Y gastric bypass (RYGB) either as a single procedure or among a range of procedures.[332-337, 340, 341, 344, 346, 347] Sleeve gastrectomy was included in four analyses.[335, 341, 343, 344] Seven model-based evaluations considered adjustable gastric banding (AGB).[332, 333, 336, 338, 340, 342, 343] Of 14 model-based studies in which T2D patients represented a subgroup of the population, 11 evaluations considered more than one procedure.[348-352, 355, 357-360, 363] The other three evaluations considered RYGB[354, 364] or LAGB only.[362] In some studies, the surgical approach (that is, laparoscopic or open) was not specified.

In general, usual care was poorly described. Of 14 model-based studies conducted specifically in a T2D population, only four studies reported the T2D medications included as part of standard T2D management in the usual care group and for patients with persistent T2D post-surgery.[341, 344, 346, 347] Of those, one study included insulin-dependent patients at baseline and newer anti-diabetic medications such as, glucagon-like peptide 1 receptor agonists (GLP-1 RA) and sodium glucose transport protein 2 (SGLT2) inhibitors as part of escalation of care in subsequent years.[341] Among studies in which a subgroup of the population had T2D, usual care typically comprised diet, physical activity and treatment of T2D. In addition, three studies included pharmacological treatment of obesity (orlistat) as part of conventional medical management.[335, 358, 362] Of note, many of the analyses were undertaken prior to the adoption of newer anti-diabetic agents, and country-specific clinical practice guidelines for the pharmacological management of T2D may differ.[365] Inter-study variation in the T2D treatment approach, in particular the number of patients requiring insulin, may have implications of the cost of T2D treatment.

5.3.1.1.1 Input parameters

Estimates of clinical effectiveness and safety

In general, the effect of metabolic surgery was modelled through measures of T2D status (for example, T2D remission, relapse, persistent T2D) and BMI changes (Table 5.2). In some analyses, model predictions also depended on factors such as systolic blood pressure and lipid parameters to determine changes in the relative risk of T2D-related events (for example, stroke, myocardial infarction).[336, 337, 341-343, 348-352, 360, 363] Nine studies used long-term data from the Swedish Obesity Study (SOS) either as the single source of the estimated T2D remission rate or to extrapolate data beyond RCT time horizons.[334, 338, 348, 349, 351, 352, 354, 360, 363] Four studies applied a T2D remission rate to the metabolic surgery group based on evidence from RCTs,[342, 344, 350, 362] which was extrapolated to 20 years in one study[362] or a lifetime time horizon in four studies.[336, 338, 342, 350] Other sources of clinical effectiveness estimates were literature reviews,[332, 333, 335] systematic reviews or meta-analyses,[336, 343, 359] cohort studies[337, 346, 347] or national datasets.[340, 341, 350, 357] In three studies T2D remission rates was not reported.[355, 358, 364] The sources of the T2D remission rate used in identified economic evaluations are detailed in Appendix A4.3.

Remission rates in the usual care group differed between studies, depending on the source of the clinical effectiveness estimates. While some models assumed that patients in the usual care group would achieve minimal to no improvement in

glycaemic control,[332, 333, 341, 346, 347] others assumed low levels of remission that declined with increasing time horizons.[334, 338, 348-352, 354, 359, 360, 363] In a number of models, assumptions regarding the probability of T2D remission with non-surgical management were not clearly stated.[335-337, 340, 344, 355, 358, 364]

Post-surgical complications were generally limited to technical complications (for example, bleeding, leakage, gastric band erosion, revision surgery) or acute clinical complications (for example, hypoglycaemic events) occurring up to two years post-surgery.[334, 335, 337, 341, 343, 348-352, 359, 360] Medium- to long-term clinical complications (for example, clinical manifestations of micronutrient deficiencies or gastrointestinal disturbances such as dumping syndrome, gastro-esophageal reflux disease (GERD), or esophagitis) were infrequently reported. One study included micronutrient deficiencies, namely vitamin B12 and iron deficiency, however this was only considered over a five-year time horizon.[335] Exclusion of clinical complications that do not require surgical intervention may not have significant cost implications, but may overestimate utility gains in the short-term for patients with surgically-induced gastrointestinal disturbances. As described below, some studies employed methods to account for this. Of note, long-term evidence from RCTs is lacking, and studies with small sample sizes may not be powered to detect low-probability adverse events.

Utility values

In general, the value and source of utility values was incomplete or not clearly reported. Utility decrements associated with post-surgical complications (for example, wound infection, gastric band erosion) were reported in five studies and were applied up to two years post-surgery.[335, 337, 341, 343, 354] In addition to complications requiring re-intervention, two studies applied a disutility in the immediate-term post-surgery to all patients to take into account the potential for reduced quality of life during the recovery period.[341, 359] One study incorporated declining utility gains over time.[357] In the remaining studies, the incidence of surgical complications was only captured as an additional cost in the surgical group in the base case analysis.

In four studies, utility weights reflected the presence or absence of T2D alone and did not attempt to capture improvements in quality of life associated with weight loss.[334, 338, 346, 347] Seven studies applied utility increments per BMI unit lost or assigned utility weights per BMI category.[336, 337, 341, 342, 354, 357, 358] In thirteen studies, utility values were dependent on both BMI and T2D status, although the approach used to reflect reversion to normoglycaemia or improved glycaemic control was not clearly described in all studies.[332, 333, 335, 343, 348-352, 359, 360, 362, 363] In one

study, EQ-5D-derived utility values collected from bariatric surgery patients were extrapolated beyond the data collection period.[364] The utility values used were not reported in three studies.[340, 344, 355]

Additional considerations

In addition to anti-hyperglycaemic agents, a limited number of studies reported incorporating changes to the cost of medications used for cardiovascular risk reduction such as aspirin, lipid-lowering (for example, statins) and anti-hypertensive agents.[337, 338, 342, 359]

Skinfold removal following sustained weight loss was included in eight studies.[334, 336, 348, 349, 354, 359, 363, 364] Where reported, the modelled proportion of patients undergoing post-operative body contouring surgery varied considerably between studies, from 0.8% in two studies[348, 349] 29% in one study.[359]

Table 5.2 Characteristics of model-based studies

Author (year)	Target population	Measure of treatment effect	Intervention	Comparator
T2D population or sub-cohort				
Ackroyd (2006)	BMI ≥35kg/m^2 and T2D, after failure of at least 1 year of medical treatment	T2D-free years; BMI year (combines magnitude and duration of BMI variation)	AGB; GBP	Usual diabetes care
Anselmino (2009)	BMI ≥35 kg/m^2 after failure of at least 1 year of medical treatment	See Ackroyd (2006)	AGB; GBP	Usual diabetes care
Assumpção (2019)*	Severely obese individuals (BMI >35 kg/m^2) with and without T2D	T2D remission; Fatal and non-fatal MI	RYGB (open)	Usual diabetes care
Gil-Rojas (2019)*	1) BMI ≥40 kg/m^2 with or without comorbidities, 2) BMI 35 - 40 kg/m^2 with comorbidities (T2D, sleep apnoea, hypertension or dyslipidaemia)	Remission of T2D; weight reduction (Risk of stroke and AMI linked to BMI)	GBP; SG	Pharmacologic treatment (orlistat) and lifestyle changes (diet and exercise)
Hoerger (2010)	Severely obese (BMI ≥35 kg/m^2) adults with newly-diagnosed (<5 years) or established diabetes (>10 years)	T2D remission; SBP; total cholesterol; HDL; BMI	AGB; GBP	Usual diabetes care
Ikramuddin (2009)	BMI ≥35 kg/m^2 and T2D after failure of 1 year of medical treatment	SBP, BMI, HbA1C, lipid parameters (total cholesterol, LDL-cholesterol, HDL cholesterol, triglycerides)	RYGB	Usual diabetes care
Keating (2009b)	Recently diagnosed T2D in class I/II obesity	Number of years in T2D remission	LAGB	See Keating 2009a
Kim (2018)*	10 subgroups based on 5 levels of BMI (30–34.9; 35–39.9; 40–44.9; 45–49.9; >50) with or without T2D	BMI values and self-reported T2D status	LRYGB (base case); ORYGB; LAGB	Non-surgical intervention
McGlone (2020)	Insulin-dependent T2D	BMI; HbA1c; SBP and total cholesterol to HDL ratio	RYGB (reference procedure); SG	best medical treatment (including nutritional counselling) Year 1: Insulin + Metformin + DPP4 inhibitors Year 2: Insulin + Metformin + GLP-1 RA Year 3: Insulin + Metformin + SGLT2 inhibitor + GLP-1 RA Year 4: Insulin + Metformin + SGLT2 inhibitor + GLP-1 RA

				Year 5: Insulin + Metformin + SGLT2 inhibitor + GLP-1 RA
Pollock (2013)	Obese patients with T2D	BMI; HbA1c, SBP, lipid parameters (total cholesterol; triglycerides; HDL); minor and hypoglycaemic events	LAGB	Usual diabetes care
Rognoni (2020)*	1) BMI 40 kg/m^2 without complications + patients with BMI 35 kg/m^2 with complications; 2) BMI 35 kg/m^2 and T2D; 3) BMI 30 to 35 kg/ m^2 and T2D	SBP, lipids, T2D (dependent on BMI)	AGB (16.8%); GBP; (24.6%); SG (58.6%)	Usual diabetes care
Tang (2016)	1) Aged 16 to 65 years; 2) BMI ≥28 kg/m^2; 3) T2D (≤15 years duration)	partial remission; complete remission	LSG; LRYGB	Usual diabetes care (metformin, sulfonylurea, and insulin)
Viratanapanu (2019)	T2D with BMI >32.5 kg/m^2	BMI and HbA1c	RYGB (61.6%)	Usual diabetes care (Metformin, Sulfonylurea group, Thiazolidinedione group, Alpha-glucosidase inhibitors group, Insulin)
Wan (2019)	1) Aged 18 to 65 years with recently diagnosed T2D (within 2 years) 2) BMI >28kg/m^2 3) Fasting serum c-peptide in the lower 1/2 of the lower limits of normal	Remission of T2D	LRYGB	Usual diabetes care (metformin, sulfonylurea, and insulin)
Population subgroup with T2D				
Borisenko (2018)a	Subgroup analyses were performed for 8 diabetic cohorts, namely, males and females with: 1) moderate obesity (BMI 33kg/m^2), 2) severe obesity (BMI 37kg/m^2), 3) morbid obesity (BMI 42kg/m^2) 4) super obesity (BMI 52kg/m^2)	BMI, SBP and T2D. Risk of obesity-related CVD is dependent on patient characteristics: age, sex, SBP, BMI, T2D and smoking status.	GBP (56%); SG (22%); AGB (22%);	Standard care
Borisenko (2018)b	See Borisenko 2018a	See Borisenko 2018a	GBP (75%); SG (20%); AGB (5%)	Standard care
Borisenko (2017)a	See Borisenko 2018a	See Borisenko 2018a	GBP (68.8%); SG (31%); AGB (0.2%)	Standard care
Borisenko (2017)b	See Borisenko 2018a	See Borisenko 2018a	GBP (51%); SG (17%); AGB (33%)	Standard care

Borisenko (2015)	See Borisenko 2018a	See Borisenko 2018a	GBP (98 %); SG (1.6 %,); AGB (0.4 %)	Standard care
Cohen (2017)	1) BMI ≥40 kg/m^2 2) BMI ≥35 kg/m^2 with co-morbidities	BMI, T2D, SBP, and lipid profile	Open RYGB (90%)	Standard care
Faria (2013)	Patients with T2D and overweight (BMI 25-30 kg/m^2) or obesity (BMI ≥30 kg/m^2)	Weight loss	GB; GBP	Standard care
Gulliford (2017)	Morbid obesity (BMI ≥40 kg/m^2) and diabetes	Remission of T2D	AGB (33%); GBP (33%); SG (33%)	Standard care
James (2017)	Diabetes and obesity (BMI 35 kg/m^2)	BMI	AGB; RYGB; SG	Standard care (including orlistat)
Klarenbach (2010)	1) BMI of 40 kg/m^2 or more 2) BMI of 35 kg/m^2 or more with a major obesity-related comorbidity	BMI; prevalence of obesity-related comorbidities	RYGB (base case); LAGB; BPD	Standard care
Lucchese (2017)	Subgroup analyses were performed for 8 diabetic cohorts, namely, males and females with: 1) moderate obesity (BMI 33kg/m^2), 2) severe obesity (BMI 37kg/m^2), 3) morbid obesity (BMI 42kg/m^2) 4) super obesity (BMI 52kg/m^2)	BMI, SBP, and T2D	GBP; SG; AGB	Standard care (ranging from sophisticated lifestyle intervention and behaviour modification to no treatment)
McEwen (2010)	1) BMI 35 kg/m^2 with two life threatening comorbidities or 2) 40 kg/m^2	QoL	ORYGB (64%) LRYGB (33%)	Standard care
Picot (2012)	Class I and class II obesity (BMI ≥30 and <40), with T2D	BMI; prevalence of obesity-related comorbidities	LAGB	Standard care (including diet and pharmacotherapy)
Sanchez-Santos (2017)	Subgroup analyses were performed for 8 diabetic cohorts, namely, males and females with: 1) moderate obesity (BMI 33kg/m^2), 2) severe obesity (BMI 37kg/m^2), 3) morbid obesity (BMI 42kg/m^2) 4) super obesity (BMI 52kg/m^2)	BMI, SBP, and T2D	GBP (76%); SG (22%); AGB (2%)	Standard care

Key: AGB – adjustable gastric band; BMI – body mass index; BPD – biliopancreatic diversion; CVD – cardiovascular disease; GB- gastric band; GBP - gastric bypass (generally RYGB); HbA1c – Haemoglobin A1c; HDL – high-density lipoprotein; LAGB – laparoscopic adjustable gastric band; LDL – low-density lipoprotein; LRYGB – laparoscopic Roux-en-Y Gastric Bypass; LSG – laparoscopic sleeve gastrectomy; ORYGB – open Roux-en-Y Gastric Bypass; ; QoL – quality of life; RYGB - Roux-en-Y Gastric Bypass; SBP – systolic blood pressure; SG – sleeve gastrectomy.
*Indicates sub-cohort.

5.3.1.1.2 Modelling approach

Fourteen studies carried out specifically in a T2D population were CUAs.[332-338, 340-344, 346, 347] Of these, five studies presented results of both CUA and CEA (for example, cost per life-year gained).[332, 333, 337, 338, 342] Among studies in which a subgroup of the population had T2D, all analyses were CUAs,[348-352, 354, 355, 357-360, 362-364] and one study presented results of CUA and CEA.[354]

Models differed considerably in the range of diabetes-related health states considered (Table 5.3). Of model-based evaluations carried out specifically in a T2D population, 11 models assumed a binary presence or absence of T2D, or included an additional state to capture T2D improvement.[332-335, 337, 338, 340, 342, 343, 346, 347] In three models, metabolic surgery was associated with changes in HbA1c.[337, 341, 342] Seven studies modelled health states representing any diabetes-related complications, although the number of complications included varied between models.[334-337, 341-343]

Microvascular complications were poorly represented in the 14 model-based evaluations where T2D patients represented a subgroup of the overall population with obesity, with only one study including end-stage renal disease.[355] However, macrovascular outcomes were included in 11 of these models.[348-352, 354, 355, 357, 360, 362, 363] In three studies, how T2D patients were represented in the model was unclear as T2D-related health states were not reported[358, 364] or were poorly described.[355]

Analysis type and model structure

Of 14 model-based studies carried out specifically in a T2D population, ten studies were modelled CUAs.[332-336, 340, 342-344, 346] Four studies adopted a hybrid approach whereby patient data from a single study was used to extrapolate clinical and economic outcomes beyond the study period.[337, 338, 341, 347] For studies in which a T2D population was considered in subgroup analysis, 13 studies were modelled CUAs,[348-352, 354, 355, 357-360, 362, 363] and one study projected data from a managed care population.[364]

Of T2D-specific models, eight used a Markov model to estimate costs and health outcomes of metabolic surgery.[336-338, 340, 342-344, 347] Of these, three studies adopted existing validated models used extensively in T2D-related health economic research.[336, 337, 342] Three studies used a hybrid decision tree and Markov model[334, 335, 346] and one study used a microsimulation (patient-level) model.[341] In two studies, the modelling method was described as a deterministic linear algorithm, but details of the model structure were not provided (Table 5.4).[332, 333]

Of 14 model-based economic evaluations in which T2D patients represented a subgroup of an overall population with obesity, 12 were Markov models. Of these, seven studies replicated the same model structure and adopted input parameters specific to the context/jurisdiction.[348-352, 360, 363] One study used a microsimulation model[354] and in one study the model structure was not reported but was based on the extrapolation of observational data.[364]

Perspective

Of the 14 T2D-specific model-based analyses, six studies adopted a public payer perspective[332-335, 341, 342] and two studies adopted a third-party payer (for example insurance) perspective.[337, 347] One study reported a public and third-party payer perspective over different time horizons,[340] and one study reported results from both a societal and payer perspective.[343] The perspective was unclear or not reported in four studies (Table 5.4).[336, 338, 344, 346]

Of studies in which T2D represented a subgroup of the overall population, the analysis assumed a public payer perspective in nine studies.[348, 349, 352, 354, 357-359, 362, 363] Three studies adopted the third party payer perspective.[350, 351, 360] One study reported results from the societal perspective (although it is unclear whether indirect costs were included),[355] and in one study the perspective was not reported.[364]

Discount rate

Discount rates applied to costs and outcomes after the first year in T2D-specific model-based economic evaluations included 3%,[336-338, 340, 343, 346] 3.5%[332, 333, 341, 342] and 5%.[334, 335, 344]

Studies in which a subgroup of patients had T2D, applied discount rates of 3%[348, 351, 352, 355, 357, 360, 363, 364] 3.5%[349, 362] and 5%[354, 358, 359]. Differential discounting, whereby health effects were discounted at a lower rate than costs was applied in one study (costs 3%; outcomes 1.5%).[350]

Time horizon

For T2D-specific models, four models assumed a time horizon of five years or less.[332, 333, 335, 341] One study adopted a time horizon of ten years[334] and six studies adopted a lifetime time horizon.[336-338, 343, 346, 347] Two studies considered more than one time horizon to reflect different perspectives (public and third party payer),[340] or to reflect increasing uncertainty overtime due to the use of relatively short-term clinical data to make projections over a 40-year time horizon.[342] In one study, the time horizon was not reported.[344]

Of the models in which T2D patients represented a subgroup of the population, one study modelled costs and outcomes over 20 years[354] and four models adopted a lifetime time horizon.[348, 355, 357, 358] Given the dependence on assumptions to model over longer time horizons, nine studies considered more than one time horizon to account differences in data availability and quality at different time points.[349-352, 359, 360, 362-364]

Table 5.3 Diabetes-related and surgical complications included in model-based studies*

Author (year)	T2D status		Macrovascular complications						Microvascular complications			Foot ulcer or amputation	Acute glycaemic event	Surgical complications
	T2D remission	T2D improvement	Stroke	CHD	MI	Angina	HF	PAD	Nephropathy or ESRD	Neuropathy	Retinopathy or blindness			
T2D population or sub-cohort														
Ackroyd (2006)	X													
Anselmino (2009)	X													
Assumpção (2019)	X				X									X
Gil-Rojas (2019)	X		X		X									X
Hoerger (2010)	X	X	X	X					X	X	X			
Ikramuddin (2009)	X	X	X		X	X	X	X	X	X	X	X	X	X
Keating (2009b)	X													
Kim (2018)	X													
McGlone (2020)	X	X	X	X	X		X		X		X	X		X
Pollock (2013)	X	X	X		X	X	X	X	X	X	X	X	X	
Rognoni (2020)	X		X		X				X		X	X	X	X†
Tang (2016)	X													
Viratanapanu (2019)	X	X												
Wan (2019)	X													

Population subgroup with T2D														
Borisenko (2018)a	X		X		X	X	X	X						X†
Borisenko (2018)b	X		X		X	X	X	X						X†
Borisenko (2017)a	X		X		X	X	X	X						X†
Borisenko (2017)b	X		X		X	X	X	X						X†
Borisenko (2015)	X		X		X	X	X	X						X†
Cohen (2017)	X		X	X			X							X
Faria (2013)‡§			X	X	X	X	X		X					X†
Gulliford (2017)	X		X	X										X
James (2017)§														
Klarenbach (2010)	X													X
Lucchese (2017)	X		X		X	X	X	X						X†
McEwen (2010)§														
Picot (2012)	X		X	X										
Sanchez-Santos (2017)	X		X		X	X	X	X						X†

Key: CHD – chronic heart disease; ESRD – end-stage renal disease; HF – heart failure; MI – myocardial infraction; PAD – peripheral arterial disease; T2D – Type 2 diabetes .
* Economic evaluations based on a trial or observational study are synthesized separately.[339, 345] While some models incorporated other obesity-related health states (for example, sleep apnoea, cancer), only T2D-related health states are presented.
† No disutility assigned to surgical complications health state.
‡ Specific cardiovascular health states not reported. Inclusion of all relevant cardiovascular events is assumed.
§ Adaptation of the model structure to include T2D-related health states was not reported.

Table 5.4 Characteristics of model-based studies (setting, model structure and perspective)

Author (year)	Country	Type of analysis	Model type	Perspective	Time horizon	Discount rate (costs and outcomes)
T2D population or sub-cohort						
Ackroyd (2006)[332]	Germany, UK and France	CEA; CUA	Deterministic linear algorithm	Public payer	5 years	3.5%
Anselmino (2009)[333]	Austria, Italy and Spain	CEA; CUA	Deterministic linear algorithm	Public payer	5 years	3.5%
Assumpção (2019)[334]	Brazil	CUA	Hybrid decision tree and markov model	Public payer	10 years	5%
Gil-Rojas (2019)[335]	Columbia	CUA	Hybrid decision tree and 4 single-cohort markov models	Public payer	5 years	5%
Hoerger (2010)[336]	United States	CUA	Markov (CDC-RTI Diabetes Cost-Effectiveness Model)	Not reported	Lifetime	3%
Ikramuddin (2009)[337]	United States	CEA; CUA	Markov (CORE diabetes model)	Third party payer	Lifetime (35 years)	3%
Keating (2009b)[338]	Australia	CEA; CUA	Markov	"Health sector"*	Lifetime	3%
Kim (2018)[340]	United States	CUA	Cohort state transition model (Markov)	Private payer	5 year	3%
				Public payer (Medicare)	Lifetime	
McGlone (2020)[341]	United Kingdom	CUA	State-transition microsimulation model	Public payer	5 years	3.5%
Pollock (2013)[342]	United Kingdom	CEA; CUA	Markov (CORE diabetes model)	Public payer	10, 20, 30 and 40 years	3.5%
Rognoni (2020)[343]	Italy	CUA	Markov	Public payer and societal	Lifetime	3%
Tang (2016)[344]	China	CUA	Markov	Unclear†	Not reported	5%
Viratanapanu (2019)[346]	Thailand	CUA	Hybrid decision tree and markov model	Not reported	Lifetime	3%
Wan (2019)[347]	China	CUA	Markov	Third party payer (insurance)	Lifetime (40 years)	5%

Population subgroup with T2D						
Borisenko (2018)a[349]	England	CUA	Markov	Public payer	10 years; Lifetime	3.5%
Borisenko (2018)b[350]	Belgium	CUA	Markov	Third party payer	10 years; Lifetime	3% costs; 1.5% outcomes
Borisenko (2017)a[351]	Denmark	CUA	Markov	Third party payer	10 years; Lifetime	3%
Borisenko (2017)b[352]	Germany	CUA	Markov	Public payer (statutory health insurance)	10 years; Lifetime	3%
Borisenko (2015)[348]	Sweden	CUA	Markov	Public payer	Lifetime	3%
Cohen (2017)[354]	Brazil	CEA;CUA	Markov microsimulation model	Public payer	20 years	5%
Faria (2013)[355]	Portugal	CUA	Markov	Societal	Lifetime	3%
Gulliford (2017)¶[357]	UK	CUA	Markov	Public payer	Lifetime	3%
James (2017)[358]	Australia	CUA	Markov	Public payer	Lifetime	5%
Klarenbach (2010)[359]	Canada	CUA	Markov	Public payer	10 years; 20 years; Lifetime	5%
McEwen (2010)[364]	United States	CUA	Not reported	Not reported	2 years; lifetime	3%
Lucchese (2017)[360]	Italy	CUA	Markov	Third party payer	10 years; Lifetime	3%
Picot (2012)‡[362]	UK	CUA	Markov	Public payer	2, 5 and 20 years	3.5%
Sanchez-Santos (2017)[363]	Spain	CUA	Markov	Public payer	10 years; Lifetime	3%

* Health sector perspective comprised direct healthcare costs to government, private insurers, and patients.
† Costs including direct health expenditures, non-health expenditures and indirect expenses.
‡ Third update of a Health Technology Assessment funded by the National Institute of Health Research.[353, 361, 362] Only data from the most recent update (2012) is presented.
¶ Published as a HTA and academic publication.[356, 357]

5.3.1.2 Studies based on trials or observational studies

In two studies, input parameters were based on a single study (Table 5.5). An Australian within-trial cost-effectiveness analysis, with 2 years' follow-up,[339] compared laparoscopic AGB with conventional therapy for T2D management. Participants in the RCT had recent onset (<2 years) T2D and class I or II obesity. Cases of T2D remitted was used as the measures of cost-effectiveness.

A second Chinese CUA was carried out in parallel with a four-year observational study that compared LRYGB with usual T2D care.[345] The BMI threshold used to select surgical candidates was ≥27.5 kg/m^2. The baseline BMI and duration of T2D differed substantially between participants in the surgical (BMI kg/m^2 30.7 (SD 3); duration of T2D 8 (SD 4.8)) and usual care group (BMI kg/m^2 24.8(SD 3.8); duration of T2D 4.3 (SD 2.8)) which may have produced biased results. Utility values were assigned based on HbA1c values (per 1% change) in the surgical and non-surgical groups.[345]

In both studies, the perspective adopted was unclear (Table 5.6).[339, 345] Discounting was not applied in the two-year trial based economic evaluation.[339] In the second study, it was unclear if health effects and costs were discounted.[345]

Table 5.5 Characteristics of economic evaluations based on a trial or observational study

Author (year)	Study population	Measure of treatment effect	Intervention	Comparator
Keating (2009a)	Recently diagnosed T2D (<2 years) with class I/II obesity	Cases of T2D remitted	LAGB	Usual diabetes care
Tu (2019)	1. Poorly controlled T2D (duration ≤15 years) with adequate islet function 2. age 18–65 years; 3. BMI ≥27.5 kg/m^2; 4. >2 symptoms of the metabolic syndrome	HbA1c values	LRYGB	Usual diabetes care

Key: BMI – body mass index; LAGB – laparoscopic adjustable gastric banding; LRYGB – laparoscopic Roux-en-Y gastric bypass; T2D – type 2 diabetes.

Table 5.6 Characteristics of economic evaluations (setting, model structure, perspective)

Author (year)	Country	Type of analysis	Model type	Perspective	Time horizon	Discount rate (costs and outcomes)
Keating (2009a)	Australia	CEA	Trial-based economic evaluation	"Health sector"†	2 years	NA
Tu (2019)	China	CUA	Parallel economic evaluation of an observational study	Unclear	4 years	Not reported

Key: CEA – cost-effectiveness analysis; CUA – cost utility analysis; NA – not applicable.
† Health sector perspective comprised direct healthcare costs to government, private insurers, and patients.

5.3.2 Summary of findings

5.3.2.1 Studies based on models

T2D populations or sub-cohorts

At a WTP threshold of €20,000 per QALY gained, using T2D-specific model-based analyses, metabolic surgery was reported to be cost-effective in 14 comparisons (from nine studies)[332-336, 340, 342, 344, 346] Surgery was reported to be cost-saving in twelve analyses (from six studies).[332, 333, 339, 341, 343, 347] In one study, the ICER exceeded the WTP threshold of €20,000, but would still be considered cost-effective at a WTP threshold of €45,000 per QALY gained.[337] In general, the results of the economic models were sensitive to the modelled time horizon. Better outcomes were observed over longer time horizons.

In three studies, the intervention was a mix of surgeries based on usage patterns in the country of interest (Table 5.7).[335, 341, 343] In two studies, metabolic surgery was reported to dominate usual care (that is, more effective and cheaper).[341, 343] In the third study, the ICER was €4,531/QALY over a five year time horizon.[335]

Ten analyses (from six studies) compared gastric banding to usual care (Table 5.8).[332, 333, 336, 338, 340, 342] Metabolic surgery was reported to be cost-saving in five analyses (from three studies).[332, 333, 338] In the remaining five studies, metabolic surgery was reported to be cost-effective, with ICERs ranging from €2,104/QALY[333] to €17,029/QALY.[336]

Thirteen analyses (from 9 studies) compared gastric bypass to usual care (Table 5.9).[332-334, 336, 337, 340, 344, 346, 347] Metabolic surgery was reported to be dominant in five analyses (from 3 studies).[332, 333, 347] Surgery was cost-effective in seven studies, with ICERs ranging from €449/QALY[344] to €15,720/QALY.[336] The ICER exceeded the WTP threshold in one study carried out in the context of the US healthcare system, which may not be transferable to the Irish context.[337]

One study estimated the cost-effectiveness of sleeve gastrectomy compared with usual care, reporting an ICER of €360/QALY (Table 5.10).[344]

Table 5.7 Results of metabolic surgery versus usual care in T2D populations or sub-cohorts*†

Author	Country	Time horizon	Intervention	Adjusted ICER (€/QALY)
Gil-Rojas (2019)	Columbia	5 years	GBP/SG	4,531/QALY
McGlone (2020)	United Kingdom	5 years	RYGB/SG	Dominant
Rognoni* (2020)	Italy	Lifetime	AGB/GBP/SG	Dominant

Key: AGB – adjustable gastric band; GBP - gastric bypass (generally RYGB); QALY – quality-adjusted life year; RYGB - Roux-en-Y Gastric Bypass; SG – sleeve gastrectomy; T2D – type 2 diabetes.
* Results have been adjusted to 2020 Irish Euro using purchasing power parity and consumer price indices.
† Bariatric surgery comprises a mix of surgeries, typically based on the mix of surgeries in use in the index country.

Table 5.8 Results of gastric banding versus usual care in T2D populations or sub-cohorts*

Author	Country	Time horizon	Adjusted ICER (€/QALY)	
Ackroyd (2006)	Germany	5 years	Dominant	
	France	5 years	Dominant	
	UK	5 years	3,269/QALY	
Anselmino (2009)	Austria	5 years	Dominant	
	Italy	5 years	Dominant	
	Spain	5 years	2,104/QALY	
Hoerger (2010)†	United States	Lifetime	**Newly-diagnosed T2D:** 14,410/QALY	**Established T2D:** 17,029/QALY
Keating (2009b)	Australia	Lifetime	Dominant	
Kim (2018)‡§	United States	Lifetime	7,019/QALY	
Pollock (2013)	United Kingdom	40 years	5,275/QALY	

Key: QALY – quality-adjusted life year; T2D – type 2 diabetes.
* Results were adjusted to 2020 Irish Euro using purchasing power parity and consumer price indices.
† Results of sub-group analysis by age are presented in supplementary appendix A4.4.
‡ Overall ICER for laparoscopic AGB is shown. ICERs per BMI category and sex for the 5-year and lifetime time horizon are presented in supplementary appendix A4.4. Overall results were calculated based on the information provided in the study and may be subject to rounding error.
§ Cost year not reported. The cost year was assumed to be 2014 based on the information provided in the study.

Table 5.9 Results of gastric bypass versus usual care in T2D populations or sub-cohorts*

Author	Country	Time horizon	Adjusted ICER (€/QALY)	
Ackroyd (2006)	Germany	5 years	Dominant	
	France	5 years	Dominant	
	UK	5 years	2,571/QALY	
Anselmino (2009)	Austria	5 years	Dominant	
	Italy	5 years	Dominant	
	Spain	5 years	3,850/QALY	
Assumpção (2019)	Brazil	10 years	1,278/QALY	
Hoerger (2010)	United States	Lifetime	**Newly-diagnosed T2D:** 9,170/QALY	**Established T2D:** 15,720/QALY
Ikramuddin (2009)	United States	Lifetime	26,502/QALY	
Kim (2018) †‡	United States	Lifetime	6,884/QALY	
Tang (2016) ‡§¶	China	Not reported	116/QALY	
Viratanapanu (2019)	Thailand	Lifetime	1,863/QALY	
Wan (2019)§	China	40 years	Dominant	

Key: QALY – quality-adjusted life year; T2D – type 2 diabetes.
* Results were adjusted to 2020 Irish Euro using purchasing power parity and consumer price indices.
†Overall ICER for laparoscopic RYGB (base case) is shown. ICERs per BMI category and sex for the 5-year and lifetime time horizon and open RYGB are presented in supplementary appendix A4.4. Overall results were calculated based on the information provided in the study and may be subject to rounding error.
‡ Cost year not reported. The average interval between cost and publication year in other identified studies is assumed. For Kim et al., the cost year was assumed to be 2014 based on the information provided in the study.
§ ICERs were not presented in the original study. ICERs were calculated based on the incremental costs and QALYs provided.
¶ Results were presented in international dollars only. Consumer price index (CPI) and purchasing power parity (PPP) of the United States were used for cost adjustments.

Table 5.10 Results of sleeve gastrectomy versus usual care in a T2D population*

Author	Country	Time horizon	Adjusted ICER (€/QALY)
Tang (2016) †‡	China	Not reported	92/QALY

Key: QALY – quality-adjusted life year; T2D – type 2 diabetes.
* Results were adjusted to 2020 Irish Euro using purchasing power parity and consumer price indices.
† ICER was not presented in the original study and was calculated based on the incremental costs and QALYs provided.
‡ Results were presented in international dollars only. Consumer price index (CPI) and purchasing power parity (PPP) of the United States were used for cost adjustments.

T2D subgroups

At a WTP threshold of €20,000 per QALY gained, metabolic surgery was the dominant strategy (that is, it was more effective and less costly than the usual care comparator) in 11 comparisons (from 10 studies).[348-352, 354, 358-360, 363] Surgery was cost-effective in three studies, with adjusted ICERs ranging from €2,462 to €10,651 per QALY gained.[356, 362, 364] In one study, the outcome varied depending on the procedure and BMI category.[355] All analyses were undertaken over a minimum time horizon of 20 years.

Eight studies in which T2D patients represented a subgroup of an overall population with obesity included a mix of the most common procedures performed in the reference country (Table 5.11).[348-352, 355, 360, 363] Of these, ICERs were stratified according to BMI category in seven studies, all of which reported metabolic surgery to be cost-saving irrespective of BMI category over a lifetime time horizon.[348-352, 360, 363] In the remaining study, metabolic surgery was reported to be cost-effective (adjusted ICER €8,296/QALY).[357]

Three studies analysed the cost-effectiveness of gastric banding compared with usual care (Table 5.12).[355, 358, 362] In one study, surgery was cost-effective over a 20-year time horizon,[362] while the second study reported it to be cost-saving over a lifetime time horizon.[358] In the remaining study, surgery was reported to be cost-saving for class II and III obesity. At the lower end of the obesity scale (BMI of 30 to 35 kg/m^2), gastric banding was cost-effective at a WTP threshold of €45,000.[355] However, it was not cost-effective at the upper extreme of the obesity scale (BMI 50 to70 kg/m^2).[355]

Five studies estimated the cost-effectiveness of gastric bypass compared with usual care in a T2D subgroup (Table 5.13).[354, 355, 358, 359, 364] Gastric bypass was reported to be cost-saving in three studies,[354, 358, 359] and cost-effective in one study over a lifetime time horizon (adjusted ICER €10,651/QALY).[364] In the remaining study, gastric bypass was dominant for T2D patients with a BMI ≥35 kg/m^2, but marginally exceeded the WTP threshold of €20,000 in those with a BMI 30 to 34.9 kg/m^2 (adjusted ICER €20,547/QALY).[355]

Only one study examined the cost-effectiveness of sleeve gastrectomy compared with usual care in a T2D subgroup. Surgery was found to be the dominant strategy (Table 5.14).[358]

Table 5.11 Results of metabolic surgery versus usual care in T2D subgroups*†

Author	Country	Time horizon	Procedure mix†	Adjusted ICER (€/QALY)
Borisenko (2018)a‡	England	Lifetime	GBP/SG/AGB	Dominant
Borisenko (2018)b‡	Belgium	Lifetime	GBP/SG/AGB	Dominant
Borisenko (2017)a‡	Denmark	Lifetime	GBP/SG/AGB	Dominant
Borisenko (2017)b‡	Germany	Lifetime	GBP/SG/AGB	Dominant
Borisenko (2015)	Sweden	Lifetime	GBP/SG/AGB	Dominant
Gulliford (2017)	UK	Lifetime	GBP/SG/AGB	8,296/QALY
Lucchese(2017)	Italy	Lifetime	GBP/SG/AGB	Dominant
Sanchez-Santos (2017)‡	Spain	Lifetime	GBP/SG/AGB	Dominant

Key: AGB – adjustable gastric band; GBP - gastric bypass (generally RYGB); SG – sleeve gastrectomy; T2D – type 2 diabetes.
* Results were adjusted to 2020 Irish Euro using purchasing power parity and consumer price indices.
† Bariatric surgery comprises a mix of surgeries, typically based on the mix of surgeries in use in the index country.
‡ Results of analysis over a lifetime time horizon are shown. Results of analysis over other time horizons are presented in supplementary appendix A4.4.

Table 5.12 Results of gastric banding versus usual care in T2D subgroups*

Author	Country	Time horizon	Adjusted ICER (€/QALY)			
Faria (2013)†	Portugal	Lifetime	**BMI 30-35 kg/m²** 44,704/QALY	**BMI 35-40 kg/m²** Dominant/QALY	**BMI 40-50 kg/m²** Dominant/QALY	**BMI 50-70 kg/m²** 66,744/QALY
James (2017)‡	Australia	Lifetime	Dominant			
Picot (2012)§	UK	20 years	2,462/QALY			

Key: BMI – body mass index; QALY – quality-adjusted life year; T2D – type 2 diabetes.
* Results were adjusted to 2020 Irish Euro using purchasing power parity and consumer price indices.
† Cost year not reported. The average interval between cost and publication year in other identified studies is assumed.
‡ Results by age at baseline are presented in appendix 4.
§ Results of analysis over other time horizons are presented in supplementary appendix A4.4.

Table 5.13 Results of gastric bypass versus usual care in T2D subgroups*

Author (year)	Country	Time horizon	Adjusted ICER (€/QALY)	
Cohen (2017)†	Brazil	20 years	Dominant	
Faria (2013)†	Portugal	Lifetime	**BMI 30-34.9 kg/m²** 20,547/QALY	**BMI ≥35kg/m²** Dominant
James (2017)‡	Australia	Lifetime	Dominant	
Klarenbach (2010)§	Canada	Lifetime	Dominant	
McEwen (2010)†	United States	2007§	10,651/QALY	

Key: BMI – body mass index; QALY – quality-adjusted life year; T2D – type 2 diabetes.
* Results were adjusted to 2020 Irish Euro using purchasing power parity and consumer price indices.
† Cost year not reported. The average interval between cost and publication year in other identified studies is assumed.
‡ Results by age at baseline are presented in supplementary appendix A4.4.
§ Results of analysis over other time horizons are presented in appendix 4.

Table 5.14 Results of sleeve gastrectomy versus usual care in T2D subgroups*

Author (year)	Country	Time horizon	Adjusted ICER (€/QALY)
James (2017)†	Australia	Lifetime	Dominant

Key: QALY – quality-adjusted life year; T2D – type 2 diabetes.
* Results were adjusted to 2020 Irish Euro using purchasing power parity and consumer price indices.
† Results by age at baseline are presented in supplementary appendix A4.4.

Results for clinical subgroups

Some studies estimated the cost-effectiveness of surgery according to BMI category,[340, 343, 348-352, 355, 360, 363] sex,[340, 348-352, 360, 363] age[336, 358] and duration of T2D.[336] In one study ICERs for both gastric bypass and gastric banding were more favourable in younger patients (supplementary appendix A4.4).[336] In another study, surgery was the dominant approach irrespective of the age at baseline, but was reported to represent better value for money in older patients.[358] Additional information necessary to interpret these inconsistent findings (for example, the estimated T2D remission rate, duration and severity of T2D for each age band in the modelled population) was not reported. Sex had no to little effect on ICERs.[340, 348-352, 360, 363]

Eight studies reported that metabolic surgery was dominant compared to usual care irrespective of BMI category over a lifetime time horizon,[343, 348-352, 360] although in two studies the cost-effectiveness of surgery increased with increasing BMI.[340, 363] In one study, the ICER for gastric bypass marginally exceeded the WTP threshold in patients with class I obesity, and gastric banding was not cost-effective at the extremes of the obesity scale (BMI 30 to 35 and BMI 50 to 70 kg/m^2).[355]

Hoerger et al. conducted subgroup analysis according to duration of T2D, finding that metabolic surgery was more cost-effective in newly-diagnosed T2D (<5 years after diagnosis) than established T2D (≥10 years after diagnosis), regardless of surgical procedure or age group, which was said to be as a result of the higher T2D remission rate in those with a shorter duration of disease.[336]

Impact of delayed access to surgery

Two studies examined the impact of length of time on the waiting list prior to surgery on cost-effectiveness. In both analyses, delays in accessing surgery were associated with increasing costs and decreasing benefits.[348, 354]

Sensitivity analysis

For studies carried out specifically in a T2D population, where one-way sensitivity analysis was undertaken, the results were largely robust to variations of the tested input parameters. However, utility weights,[334, 336, 337, 341, 347] the probability of T2D remission,[346] the impact of surgery and treatment on HbA1c values (due to the effects on further diabetic complications)[341] and a number of cost parameters including the cost of treatment,[334, 336, 341, 344, 346, 347] surgery,[334, 336, 344, 347] diabetes-related complications (stroke)[335] and follow-up care[336] were identified as key drivers. For the remaining studies where T2D patients were a subgroup of an overall

population with obesity, deterministic sensitivity analysis was generally undertaken in the context of the overall population. Therefore, the applicability of the results to the sub-population with T2D is unclear. In some of these evaluations, the presence of T2D or T2D treatment costs were among the most influential parameters during one-way sensitivity analysis.[349, 350, 352, 360]

Overall, twenty-one studies investigated methodological or structural uncertainty through scenario analysis.[332, 333, 337, 338, 340-343, 348, 349, 351, 352, 354, 357-360, 362-364] Of these, eight studies were specifically in a T2D population.[332, 333, 337, 338, 340-343] In general, results remained robust after changes to model structure or inputs. In T2D populations, only three scenarios yielded an ICER that would exceed the WTP threshold (in the context of the original study), namely a "worst-case scenario", excluding the negative impact of increased BMI on quality-of-life, and decreasing the time horizon to 5 or 10 years.[337, 342] The results of scenario analysis are presented in supplementary appendix A4.4.

5.3.2.2 Studies based on trials or observational studies

T2D populations

In a trial-based CEA, LAGB was reported to be cost-effective in comparison with usual care in a population with recent-onset T2D (Table 5.15). In the second study in which RYGB was compared with usual care, surgery was not cost-effective at the €20,000/QALY threshold but would be considered cost-effective at a threshold of €45,000/QALY.[345] Of note, the time horizon of the analysis was four years, therefore the initial costs of surgery had not yet been offset by the long-term benefits.[345]

No sensitivity or scenario analysis was undertaken in these studies.[339, 345]

Table 5.15 Results of economic evaluations based on trial or observational evidence*

Author	Intervention	Comparator	Adjusted ICER (€/QALY or €/case of T2D remitted)
Keating (2009a)	LAGB	Usual care	16,554/case of T2D remitted
Tu (2019)	RYGB	Usual care	32,270/QALY

Key: ICER – Incremental cost-effectiveness ratio; LAGB – laparoscopic adjustable gastric band; QALY – quality-adjusted life year; RYGB – Roux-en-Y gastric bypass.
* Results were adjusted to 2020 Irish Euro using purchasing power parity and consumer price indices.

5.3.3 Quality appraisal

The methodological quality of included economic evaluations was variable. Studies were categorized as high (n=15)[336, 337, 341, 342, 348-352, 354, 357, 359, 360, 362, 363], moderate (n=5)[332, 335, 340, 343, 358] or low (n=10)[332, 334, 338, 339, 344-347, 355, 364] quality based on the information reported (Figure 5.2). The most common issues related to insufficient reporting of input parameters and the modelling approach. In a number of studies, aggregated costs were presented for the surgical and usual care groups, making it difficult to determine if all relevant costs had been considered in the summary estimate.[334, 340, 344-347, 355, 364] Where the study perspective was unclear,[338, 339, 344, 345, 355] or not reported,[336, 346, 364] it was not possible to determine if all costs relevant to the chosen perspective were considered. In six studies, the time horizon, discount rate, cost year or currency were not reported.[340, 344, 345, 354, 355, 364] A fully incremental analysis was not carried out in two studies; the average cost-effectiveness ratio (ACER) was presented for each intervention (that is, total costs were divided by total QALYs per intervention as opposed to incremental costs and effects).[344, 347] For CUAs (n=29), the methods used to generate utility weights and the weights assigned to health states were often poorly described, particularly in relation to the utility gain associated with T2D remission.[333-337, 340, 342, 344, 346, 348-352, 355, 360, 362, 363]

Of 16 studies carried out specifically in a T2D population, only five studies considered both microvascular and macrovascular outcomes.[336, 337, 341-343] Of studies in which T2D patients represented a subgroup of the overall population with obesity, one study included a microvascular outcome (end-stage renal disease).[355] Modelling a reduced amount of T2D-related health states may be a reasonable approach in models where the T2D population was only a subgroup of interest. However, the number of diabetes-related health states considered has implications for the face validity of the modelled outcomes.

The strength of an economic evaluation depends on the reliability of the underlying evidence. Data regarding the clinical effectiveness of metabolic surgery on T2D status were derived from a variety of sources and were rarely based on a systematic review of the evidence (supplementary appendix A4.3). Given uncertainty regarding the long-term effects of surgery due to limited high-quality evidence with long-term follow-up, estimation of cost-effectiveness over two or more time horizons, adopted in eleven models, was considered to be the most appropriate approach to dealing with uncertainty.[340, 342, 349-352, 359, 360, 362-364] Given the chronic nature of T2D, it is unlikely that the impact of surgery on diabetes-related morbidity and premature mortality and the potential for relapse of disease are fully captured by shorter time

horizons (up to 5 years), as well as the potential for long-term post-surgical complications.[332, 333, 335, 339, 341, 345]

The approaches to assessing methodological, structural or parameter uncertainty were considered inadequate in nine studies. In two studies based on a single empirical study, sensitivity or scenario analysis was not reported.[339, 345] In the context of a within-study analysis, evaluation of uncertainty related to model results may not be necessary where context-specific data inputs are available, however economic evaluations could explore the possibility that some of the model inputs are biased (for example, due to loss to follow-up) through sensitivity analysis. The remaining economic evaluations carried out only one of the following: scenario analysis, probabilistic or deterministic sensitivity analysis.[332, 333, 340, 344, 346, 355, 364] In these studies, where scenario analysis was undertaken the selection of model inputs was not clearly justified.

An actual or potential conflict of interest refers to circumstances in which financial or personal considerations may compromise, or have the appearance of compromising the integrity of the research data. Conflicts of interest are typically related to studies being sponsored by the manufacturers of surgical supplies for bariatric surgical procedures or undertaken by employees of the manufacturing companies.[332-334, 337-339, 341, 342, 348-352, 354, 360, 363]

Figure 5.2 Methodological quality assessment of economic evaluations using CHEC-list

Key: CHEC - Consensus Health Economic Criteria.

5.3.4 Applicability of the evidence

No studies were considered directly applicable to the Irish context. Seventeen studies were considered partially applicable.[335-337, 341-343, 348-352, 354, 357, 359, 360, 362, 363] The use of context-specific input parameters and structural shortcomings such as the time horizon and health states modelled limit the transferability of published economic models to the Irish setting (Figure 5.3). In eight studies, the context was not considered to be applicable due to the perspective,[355] population or healthcare system characteristics.[336, 337, 340, 346, 347, 358, 364]

Long-term diabetes-related complications account for the majority of the social and economic burden of T2D. Twelve economic evaluations did not include any T2D-related complications as health states,[332, 333, 338-340, 344-347, 358, 359, 364] and 12 studies included macrovascular outcomes only[334, 335, 348-352, 354, 357, 360, 362, 363] and therefore do not fully reflect the natural history of the disease. In general, the health states represented in models in which T2D patients only represented a sub-group of an overall obese population do not sufficiently reflect the natural history of T2D.

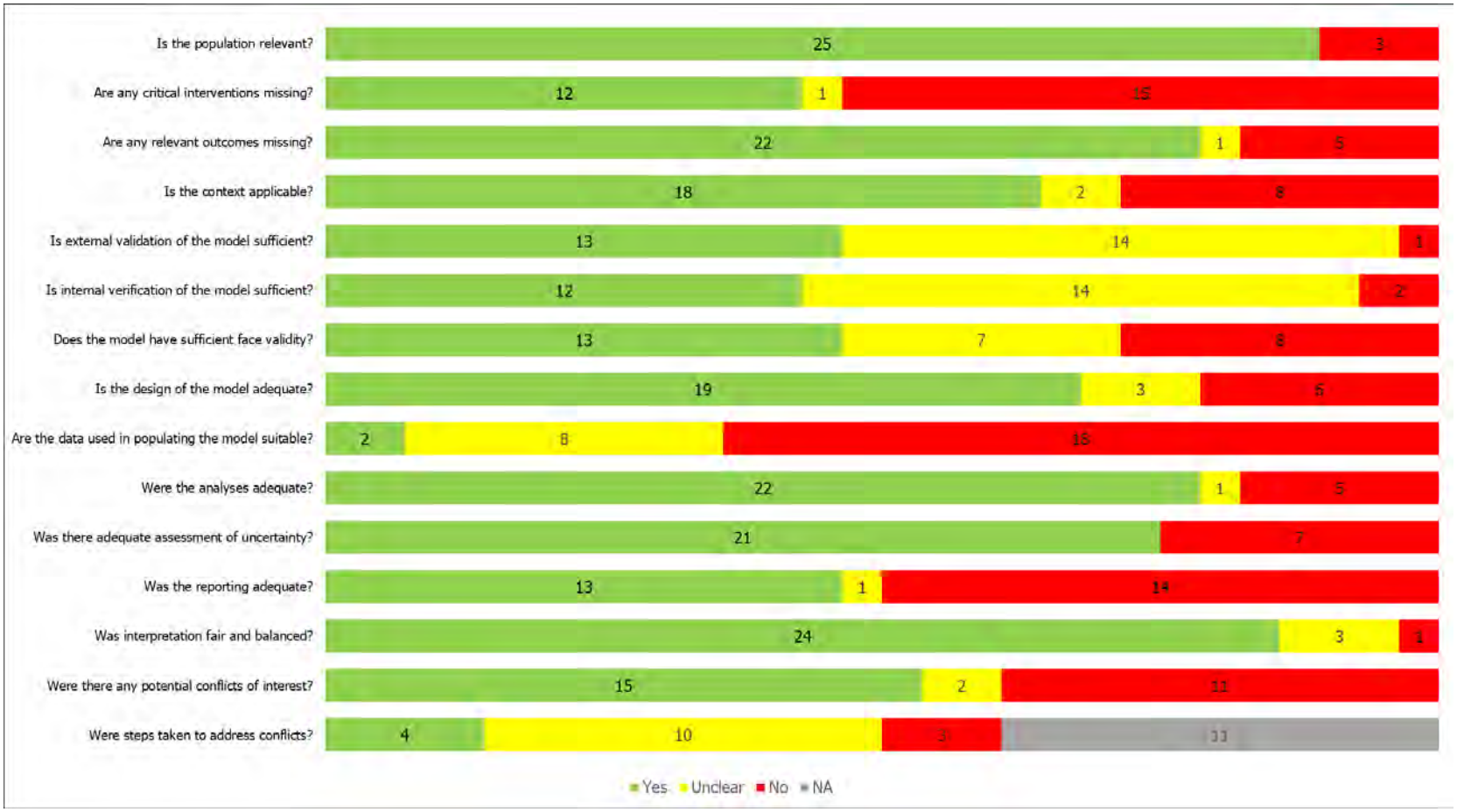
Clinical and safety outcomes vary depending on the surgical procedure, thus the resulting costs and clinical gains are dependent on the surgeries considered. Banding procedures have been associated with lower remission and higher rates of complications.[8] Current clinical practice in Ireland is predominantly characterised by sleeve gastrectomy and RYGB, thus efficacy and safety estimates derived from studies where the intervention of interest was gastric banding may underestimate the effectiveness of surgery, and overestimate requirements for surgical revision and therefore costs.[332, 333, 336, 338-340, 342, 355, 358, 362] Four analyses used efficacy data derived from an RCT in which surgical candidates had been diagnosed with T2D less than two years prior to entering the trial.[338, 339, 342, 362] Therefore, results may not apply to surgical candidates with a longer history of disease due to deterioration of β-cell function over time.

The length of follow-up of RCT evidence (up to five years) is a limitation across all modelled analyses. Some studies have attempted to overcome limitations in the evidence base by extrapolating data beyond the end of trial follow-up or through the use of observational evidence from the SOS. There is uncertainty regarding the applicability of the available long-term data from the SOS due to the use of discontinued procedures (for example, vertical banded gastroplasty) and advances in current clinical practice, including use of the laparoscopic approach, which may contribute to improved clinical and safety outcomes.

Seven studies assigned utility values based on BMI.[336, 337, 341, 342, 354, 357, 358] Use of weight-centric utility values may underestimate health gains for patients achieving T2D remission but lower levels of weight loss, particularly for patients with lower baseline BMI. However, irrespective of the method used, QALY gains were consistently greater in the surgical group.

Fifteen economic evaluations reported insufficient information on external model validation.[332-335, 338, 340, 343, 344, 346, 347, 355, 357, 358, 362, 364] Internal verification procedures were not reported or unclear in sixteen studies thus the reliability of modelled outcomes is uncertain.[332-335, 337-340, 342-344, 346, 347, 355, 358, 362, 364]

Figure 5.3 Transferability assessment of economic evaluations to the Irish context using the ISPOR questionnaire



Key: ISPOR - The Professional Society for Health Economics and Outcomes Research.

5.4 Discussion

A systematic review was conducted to synthesise the evidence on the cost-effectiveness of metabolic surgery for people with comorbid T2D and obesity, and to assess the applicability of the evidence to inform an assessment of its cost-effectiveness in Ireland. In the Irish context, metabolic surgery was reported to be cost-saving or cost-effective in the base case analysis at a WTP threshold of €20,000/QALY in 27 studies. In two studies, the ICER marginally exceeded a WTP threshold of €20,000/QALY, but would still be considered cost-effective at a WTP threshold of €45,000/QALY.[337, 345] In one study the outcome ranged from cost-saving to exceeding to WTP threshold depending on the procedure and BMI category.[355]

The population with T2D is likely to be heterogeneous in the response to surgery due to differences in clinical characteristics at baseline. The ability to distinguish between the different subgroups that may have better or worse outcomes from surgical intervention is important to inform the optimal selection of surgical candidates. In general, the results of sub-group analyses indicate that surgery is likely to be cost-effective irrespective of BMI category or sex. The finding of increasing cost-effectiveness or cost-savings with increasing BMI at baseline in some studies may be a function of the modelling approach, whereby greater utility gains are accrued with greater weight loss.[340, 363] This approach is reasonable where weight loss is the only outcome of interest, but may favour those with greater levels of obesity in the context of T2D management. In one study, running the analysis for a population with T2D and a BMI of 30 to 34 kg/m^2 approximately doubled the ICER, primarily due to the smaller change in BMI and the consequent smaller utility gains.[336] For patients with T2D and lower baseline BMI, gains in quality of life are relatively low using BMI-centric utility values and may therefore underestimate the clinical benefits of surgery for these patients. The relationship between BMI and quality of life is unlikely to be linear. In real-world settings, patients are likely to experience greater utility by reaching a desired clinical or functional "goal" (for example, attaining treatment targets, ability to perform activities of daily living). Other factors, including the duration or severity of T2D, may provide a better indicator of the likelihood of benefiting from surgery through slowing the progression or preventing long-term T2D complications. Only one study investigated the cost-effectiveness of surgery according to duration of T2D, reporting better value for money in those with shorter duration of disease.[336] In order to maximise the health and economic benefits of surgery, delays in accessing surgery should be minimised, as demonstrated by the increased cost-effectiveness of surgery in those with recent-

onset T2D and the negative impact of delays in surgery provision on outcomes of surgery.

Safety outcomes were typically limited to short- or medium-term surgery-related adverse events in the identified economic evaluations. While exclusion of long-term complications may be unlikely to significantly impact ICERs, it has the potential to underestimate the long-term risks associated with surgery and overestimate QALYs in the surgical group. Few models incorporated the cost of skinfold removal following sustained weight loss, which may be related to availability within the public healthcare system in the reference country. Inclusion of additional surgeries to remove excess skin in the surgery group, where indicated, would result in additional costs, but may contribute to improvements in quality of life.

While two previous systematic reviews have evaluated the cost-effectiveness of bariatric surgery for the treatment of obesity,[12, 322] neither review focused specifically on the costs and benefits of metabolic surgery in populations with T2DT2D, who differ substantially from the general population with obesity both in terms of the cost of usual care and the clinical benefits of surgery. The results of this systematic review are in agreement with those of previous systematic reviews; bariatric surgery is a cost-effective approach to treating obesity, particularly in populations with comorbid T2D. Since the publication of the previous systematic reviews, at least nine cost-effectiveness models have been published,[334, 335, 340, 341, 343, 345-347, 349] eight specifically in T2D populations,[334, 335, 340, 341, 343, 345-347] consistent with the shift in the clinical focus of bariatric surgery towards increased consideration of the potential for surgery to treat obesity-related comorbidities as opposed to weight loss alone.

Limitations and future perspectives

A major driver of diabetes-related treatment costs is the treatment of vascular complications which occur secondary to the metabolic and cardiovascular derangements observed in patients with comorbid T2D and obesity. In general, the majority of published economic evaluations did not model all relevant diabetes-related complications and therefore may not adequately reflect the natural history of disease. However, it is acknowledged that evidence regarding the impact of surgery on the incidence or progression of diabetes-related complications remains limited, particularly for microvascular complications.

High-quality evidence from long-term studies is limited. The majority of economic models based input parameters on extrapolation of data from available medium-term RCTs or observational evidence from the SOS.[308, 366] The surgical methods used in the SOS may not reflect current surgical practice which may produce biased

results, however this approach may be considered reasonable in the absence of long-term evidence. Modelling over longer time horizons requires increasing dependence on assumptions due to limitations in the evidence base, however, the shorter time horizons adopted in some studies may produce biased outcomes by failing to capture the costs and effects of long-term surgical or diabetes-related complications. RCT data with 10 years' follow-up is now available,[367] which can be used in future analyses to provide confidence in the robustness of modelled outcomes from economic evaluations published to date.

Estimates of gains in quality of life post-surgery were largely based on assumptions regarding the impact of weight loss on quality of life, which may not adequately reflect the potential benefits of surgery in terms of T2D management which may affect some aspects of daily living (for example, reductions in medication burden, daily planning of injection times for insulin-treated T2D). Future studies could investigate the impact of quality-of-life estimates derived from medium- or long-term RCTs in this patient population on modelled outcomes.[249, 259]

While not specifically investigated, a previous economic evaluation noted that GLP-1 RA and SGLT2 inhibitors may confer additional benefits for patients with T2D in terms of reduction of adverse cardiovascular and renal outcomes.[341, 368] Future analyses should consider the possibility of improved diabetes-related outcomes for those using newer medications in the usual care group.

Conclusion

Results from the identified economic evaluations show that metabolic surgery may be considered a cost-effective intervention for patients with comorbid T2D and obesity, or cost-saving if outcomes are modelled over a long-term horizon. Where undertaken, the findings were generally robust to a variety of sensitivity and scenario analyses.

Due to limitations of published economic evaluations in terms of the modelled health states, time horizons and procedures considered as well as the use of context-specific input parameters, a de novo economic model specific to the Irish context is needed to comprehensively assess the costs, resource utilisation and consequences of metabolic surgery.

6 Economic evaluation and budget impact analysis

Key points

- An economic model was developed to estimate the cost-effectiveness and budget impact of metabolic surgery with or without pharmacological management compared with pharmacological management only (that is, current best medical care) in patients with comorbid type 2 diabetes (T2D) and obesity in Ireland.
- A Markov model was used to estimate the costs and outcomes associated with changes in pharmacological management of T2D and the risk of cardiovascular events for patients with comorbid T2D and obesity following metabolic surgery compared with best medical care. A time horizon of ten years was used in the base case analysis.
- The estimated treatment effects were obtained from the systematic review of clinical effectiveness and safety and the published literature. Metabolic surgery was assumed to have diminishing benefits over time in terms of HbA1c and BMI based on extrapolation of RCT evidence.
- It was assumed that a metabolic surgery programme in Ireland would compromise a mix of Roux-en-Y gastric bypass and sleeve gastrectomy.
- Compared with best medical care, the incremental cost-effectiveness ratio (ICER) for a metabolic surgery programme was estimated at €4,079 (95% CI: €946 to €7,418) per quality-adjusted life year (QALY) gained. In the probabilistic sensitivity analysis, metabolic surgery was considered cost-effective at a willingness to pay (WTP) threshold of €20,000 per QALY gained in all simulations. Extension of the time horizon yielded more favourable ICERs.
- One-way sensitivity analysis demonstrated that the model was most sensitive to treatment-related costs and transition probabilities between health states. The results of the base case analysis were stable in multiple sensitivity and scenario analyses.
- The incremental budget impact over five years was estimated at €7.4 million (95% CI: €5.4 to €9.5), assuming an annual cohort size of 200 patients. The five-year budget impact was most sensitive to the cost of metabolic surgery. The additional costs associated with the provision of metabolic surgery are offset by savings associated with reductions in anti-hyperglycaemic medication use.

- The estimated incremental budget impact does not include capital investment costs or specialist training. Requirements for additional theatre space or specialist staff would be associated with additional costs. Patients not currently eligible to be managed as part of the Chronic Disease Management Programme would accrue to out-of-pocket expenses associated with GP visits during long-term follow-up.

6.1 Introduction

This chapter describes the cost-utility and budget impact analyses undertaken to estimate the costs and benefits associated with the introduction of metabolic surgery for the treatment of type 2 diabetes (T2D) and obesity in Ireland.

As outlined in chapter 5, published economic evaluations may not be directly applicable to the Irish context due to differences in population and healthcare system characteristics. Thus, a de novo economic model tailored to the Irish context was developed.

6.2 Methods

The analyses described in this chapter were conducted in line with national HTA guidelines,[369-371] reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement,[372] and undertaken in Excel 2013.

6.2.1 Study objective

The purpose of this health economic evaluation was to estimate the cost-effectiveness and budget impact of introducing a metabolic surgery programme for the treatment of comorbid T2D and obesity in Ireland.

The cost-utility analysis estimates the costs and outcomes of metabolic surgery compared with best medical care, while the budget impact analysis provides a means of predicting the potential financial impact of introducing metabolic surgery into the T2D clinical care pathway.

6.2.2 Target population

The proposed population for the model comprises screened surgical candidates with a diagnosis of comorbid T2D and obesity (Table 6.1). Data from RCTs was used to inform population baseline characteristics.

The epidemiology of T2D is described in Chapter 3. T2D onset typically occurs in

middle-age and the prevalence increases with age.[6, 147] At model entry, patients were assumed to be 47 years of age on average, based on the mean age of enrolled participants in relevant RCTs and the epidemiology of disease. In practice, the age of patients will follow a distribution influenced by the age of disease onset and the duration of time on waiting lists for both initial MDT assessment and surgery.

Table 6.1 Baseline characteristics of the modelled population

Parameter	Value	Source
Age (years)	47	(167-169, 260-264, 266, 267, 271-277, 282-286, 293)
Female	58%	(167-169, 261, 262, 265-268, 271, 272, 275-277, 279-286)
BMI (kg/m^2)	36	(272, 279, 281, 284)
Type 2 diabetes	100%	By definition
HbA1c (mmol/mol)	≥58	(168, 169, 261, 279, 281-284)

Key: BMI – body mass index.

6.2.3 Intervention

The model included the two most commonly performed types of bariatric/metabolic surgery in Ireland and internationally: laparoscopic Roux-en-Y gastric bypass (LRYGB) and laparoscopic sleeve gastrectomy (LSG). It was assumed that a metabolic surgery programme in Ireland would comprise an equal mix of these two procedures.

6.2.4 Comparator

The comparator was best medical care, that is current standard care for patients with comorbid T2D and obesity in Ireland, which can include treatment with a range a pharmacological agents including oral anti-hyperglycaemic agents and/or injectable agents such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and insulin.[74] In clinical practice, the choice of pharmacological agent(s) depends on the clinical context for an individual patient (for example, comorbidities, glycaemic control, risk of hypoglycaemia). Combination therapy during treatment intensification is common to ensure sustained glycaemic control.

In Ireland, under the long-term illness (LTI) scheme, patients with at least one of 16 chronic diseases, including diabetes mellitus, can obtain medication and medical

equipment directly related to that illness free of charge. Total expenditure and prescribing frequency related to anti-hyperglycaemic medications under the LTI scheme is recorded by the HSE Primary Care Reimbursement Service (PCRS). It is not possible to estimate the number of patients prescribed more than one anti-hyperglycaemic agent from the published PCRS data. For the purposes of this evaluation, the prescribing pattern for combination therapy was based on medication use data recorded in the UK Clinical Practice Research Datalink (CRPD) during 2017 to 2020 for a population with T2D who did not have established cardiovascular disease.[373] Anti-hyperglycaemic medications recorded in the CRPD database include:

- metformin
- sulfonylureas
- thiazolidiones
- dipeptidyl peptidase 4 (DPP-4) inhibitors
- sodium-glucose co-transporter 2 (SGLT-2) inhibitors
- glucagon-like peptide-1 receptor agonists (GLP-1 RAs)
- insulin.

Of note, overall usage of SGLT-2 inhibitors and GLP1-RAs was reported to be low in the UK for the period up to 2020.[373] Thus, the approach adopted can be considered conservative, given that newer classes of anti-hyperglycaemic agents such as DDP-4 inhibitors, GLP-1 RAs, and SGLT2 inhibitors have been associated with higher drug acquisition costs.[227]

6.2.5 Study design

A cost-utility analysis (CUA) was undertaken to estimate the incremental cost and health benefits associated with metabolic surgery relative to best medical care. Health benefits were expressed in terms of quality-adjusted life years (QALYs), which reflect the impact of the intervention on patients' quality and quantity of life. The analysis was undertaken within a decision-analytic framework, that simulated the long-term costs and patient outcomes associated with comorbid T2D and obesity.

The budget impact analysis estimates the incremental cost of implementing a metabolic surgery programme over a five-year time horizon.

6.2.6 Model structure

A closed-cohort Markov chain simulation model was developed to compare metabolic surgery with best medical care in terms of costs (in Irish Euro) and outcomes (QALYs). A schematic of the Markov model is presented in Figure 6.1.

After the initial treatment period, patients entered the Markov model in one of the four health states, indicative of increasing treatment intensity, corresponding to the type of anti-hyperglycaemic medication use one year after metabolic surgery or initiating best medical care:

- no anti-hyperglycaemic agents
- oral anti-hyperglycaemic agents only
- GLP-1 RAs with or without oral agents
- insulin with or without non-insulin medications.

Patients could progress from one medication-based health state to another, but could not revert back to a previous health state after the first cycle (year one). The four health states considered in the model were based on differences in treatment cost, risk of adverse events and disutility associated with the individual treatment strategies. Although SGLT2 inhibitors and GLP1 RAs can both be considered second-line therapy in patients with comorbid T2D and obesity,[54] the complexity associated with injectable therapy may lead some clinicians and patients to give preference to oral agents when intensifying treatment regimes, thus GLP-1 RAs were considered third-line for the purposes of this model.[374-376]

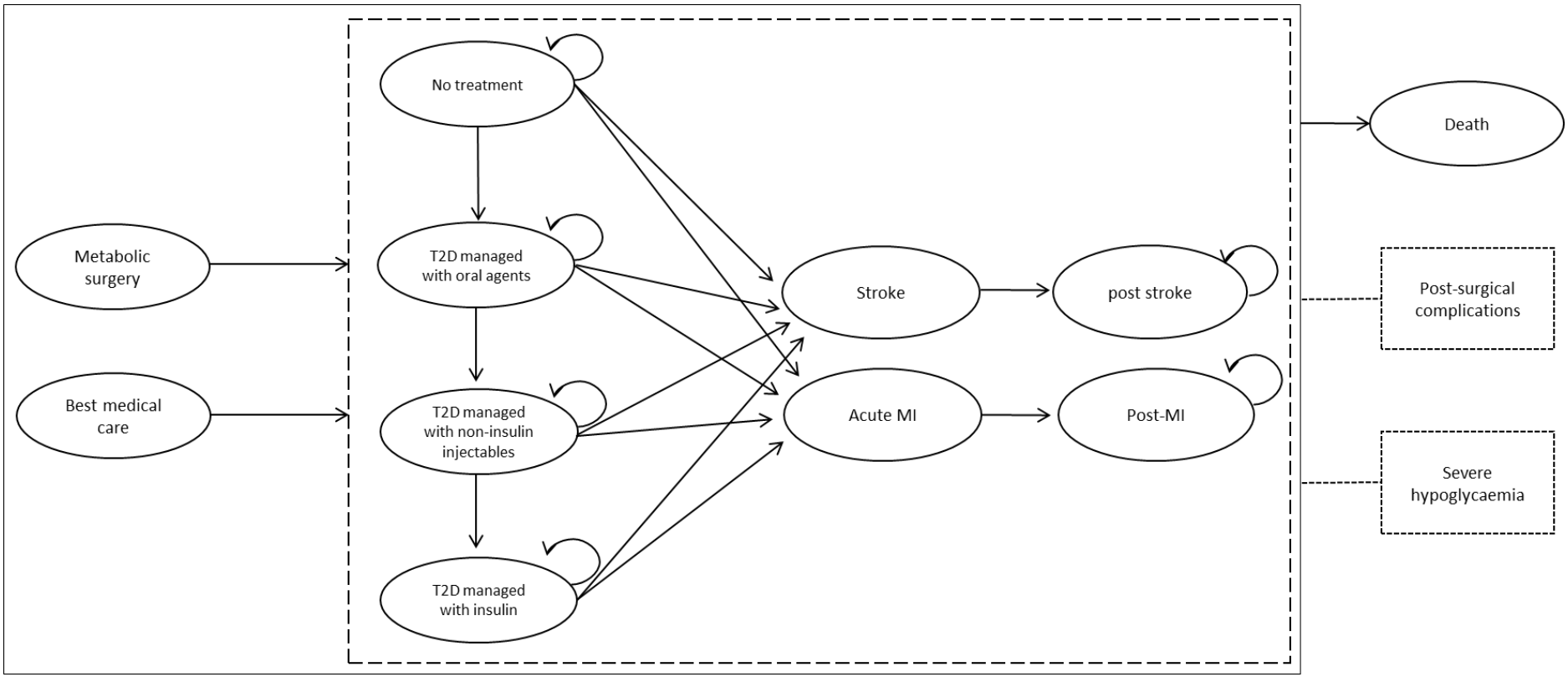
Additional T2D-related complications were selected for inclusion in the model based on a number of criteria:[377]

- there is either strong or moderate evidence that the epidemiology of the complication is influenced by changes in HbA1c
- the complication has a considerable impact on health-related quality of life (HRQoL) and/or life expectancy
- the complication has a considerable impact on healthcare resource use and costs.

Accordingly, patients were at risk of experiencing a stroke, myocardial infarction or hypoglycaemic event at any time. In the metabolic surgery cohort, patients could experience surgery-related complications and cholecystectomy for up to five years and 10 years, respectively, post-surgery.

The BIA was designed as an open-cohort model whereby new cohorts of patients underwent metabolic surgery each year for five years. The model also included costs related to follow-up care and surgery-related complications for patients in previous years. The net budget impact per annum and total budget impact over five years were estimated, defined as the difference in average annual costs between the metabolic surgery and best medical care cohorts.

Figure 6.1 Schematic representation of the model structure



Key: MI – myocardial infarction; T2D – type 2 diabetes.
Notes: Patients in the metabolic surgery and best medical care cohorts enter the Markov model one year after initiating treatment (that is, metabolic surgery or best medical care (non-surgical management)). Once in the Markov model, patients cannot return to a previous health state. Patients in both cohorts can experience stroke, myocardial infarction or severe hypoglycaemia. Only patients in the metabolic surgery cohort can experience post-surgical complications. Patients can enter the death state from any state in any model cycle.

6.2.7 Perspective, time horizon and discounting

The analysis adopted the perspective of the Irish publicly-funded health and social care system, namely the Health Service Executive (HSE). Only direct medical costs to the HSE were estimated. Indirect costs such as productivity losses associated with morbidity and mortality, and out-of-pocket expenses incurred by individuals attending healthcare services were not considered.

The base case analysis estimated the costs and benefits of surgery over a ten year time horizon. The time horizon for the analysis was chosen with consideration to the current absence of high-quality follow-up data beyond this period, and specifically in relation to uncertainty regarding the durability of reductions in HbA1c in the population with T2D and obesity.[249] Longer time horizons were also considered, however these were based on projections of RCT data and are associated with greater uncertainty.

In line with national HTA guidelines for the economic evaluation of health technologies, costs and benefits were discounted at a rate of 4%.[326] Discounting reflects a societal preference for benefits to be realised in the present and costs to be experienced in the future.

The BIA projected costs over a five-year time horizon, consistent with national guidelines.[378]

6.2.8 Model input parameters

Probabilities, costs, and utility values were estimated from a variety of published sources and national datasets for Ireland or other countries, where necessary (including the Central Statistics Office (CSO),[379] Hospital In-Patient Enquiry (HIPE) system, Health Service Executive-Primary Care Reimbursement Service (HSE-PCRS),[229] Scandinavian Obesity Surgery Registry (SOReg),[380] the UK National Bariatric Surgery Registry (NBSR)),[381] and supplemented by input from clinical experts, where necessary.

Model inputs were selected with consideration to the hierarchy of evidence, as well as generalisability to the Irish context.

Inputs for the BIA were consistent with those used in the CUA with the exception of the addition of VAT (where applicable); no discounting was applied, to reflect the actual cost accruing to the HSE in each year reported.

Assumptions underlying the model structure and input data are outlined in supplementary appendix A5.1.

6.2.9 Treatment effects

Treatment effects were informed by a systematic review of the clinical effectiveness and safety of metabolic surgery compared with best medical care or another metabolic surgery undertaken as part of this HTA (see Chapter 4). Briefly, the assessment of clinical effectiveness showed that the use of metabolic surgery leads to, on average, improved glycaemic control and reductions in BMI when compared with best medical care, although a gradual reduction in the treatment effect is observed over time.

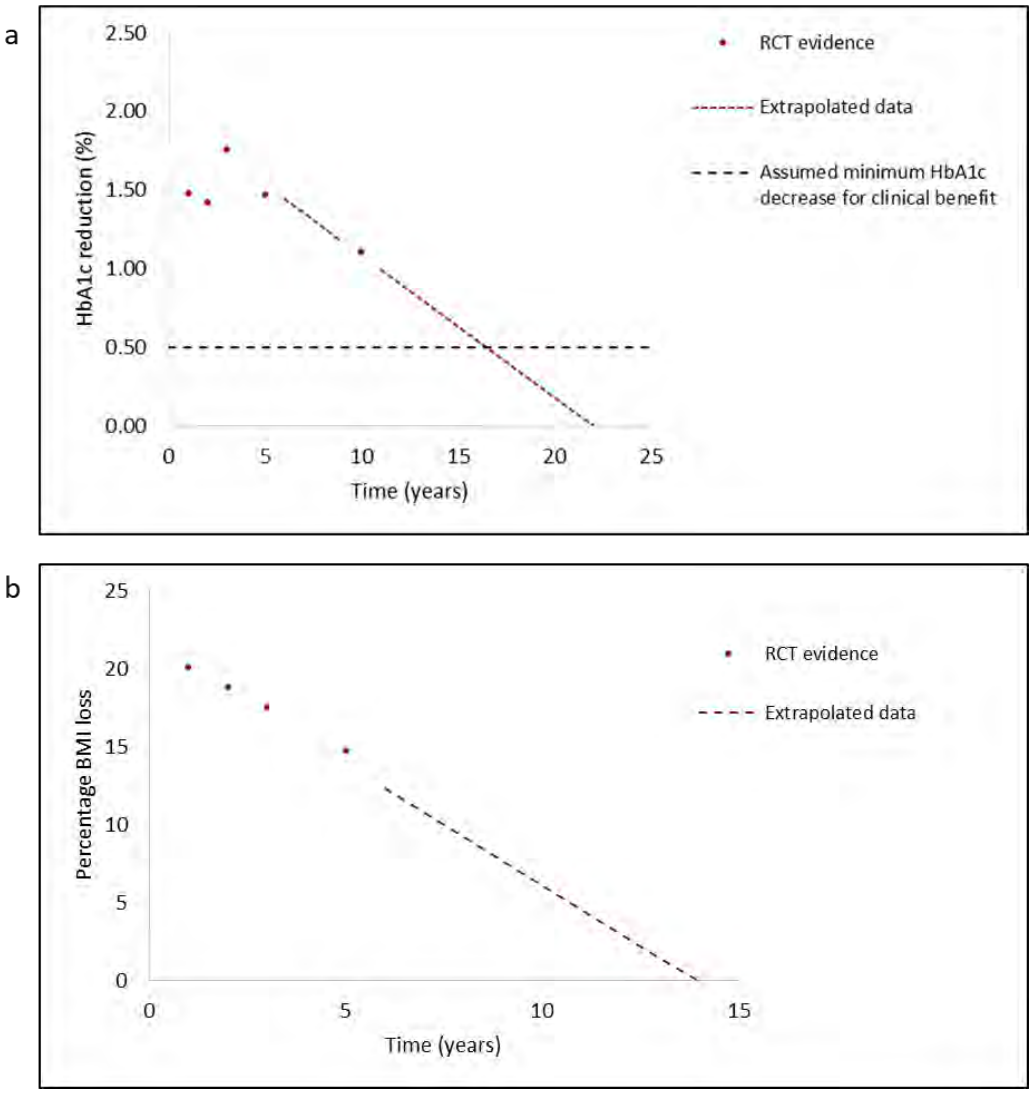
As per the HIPE Reporting Database and trends in international practice, it was assumed that patients with comorbid T2D and obesity in Ireland referred for metabolic surgery would undergo either LRYGB or LSG.[99]

As per the findings of the systematic review in chapter 4, there is no evidence of a clinically significant difference between LRYGB and LSG in terms of BMI or HbA1c reduction.[259, 266, 268, 271, 275, 277] Thus, for the purposes of this model, these procedures were assumed to have equivalent clinical effectiveness. Estimated mean differences in reductions in HbA1c and percentage BMI losses were based on pooled estimates for the comparison RYGB (reference procedure) versus best medical care. Eight RCTs reported on mean difference in HbA1c with up to ten years' follow-up data available.[168, 169, 249, 259-261, 263, 278] Evidence for mean difference in percentage BMI loss was derived from five RCTs which enrolled populations with class two obesity at baseline.[259, 260, 264, 272, 278] As a conservative approach, it was assumed that, after the last available time point of data reported from relevant RCTs, BMI and HbA1c values would continue to return to baseline linearly at the same rate as observed at previous time points (Figure 6.2). BMI was estimated to return to baseline on average after 13 cycles (or 13 years). It was assumed that there was no difference between metabolic surgery and best medical care cohorts for the remaining model cycles.

In the absence of high quality evidence from RCTs, the risk of stroke and MI was estimated based on the association between HbA1c and the risk of cardiovascular events in large observational datasets.[382, 383] As a conservative approach and with consideration to evidence of a decreasing treatment effect over time, it was assumed that most patients in the metabolic surgery cohort would not obtain an HbA1c value of <53 mmol/mol (7%). For the population with T2D and a BMI ≥30 kg/m^2, a HbA1c in the range 53 to 63 mmol/mol (7.0 to 7.9%) was estimated to be associated with a reduced risk of stroke (RR 0.92; 95% CI 0.83 to 1.02) relative to a HbA1c in the range 64 to 74 mmol/mol (8.0 to 8.9%).[383] Similarly, a HbA1c in the range 53 to 70 mmol/mol (7.0 to 8.6%) was estimated to be associated with a reduced risk of myocardial infarction (RR 0.85; 95% CI: 0.76 to 0.95) relative to a

HbA1c in the range ≥71 mmol/mol (~8.7%) for the population with T2D and a BMI in the range 35 to <40 kg/m^2.[382] Estimates of relative effects were applied to the baseline risk of stroke (0.0056%, 95% CI: 0.0051 to 0.0061) and myocardial infarction (0.0113%, 95% CI: 0.011 to 0.012) in the population with T2D; (Table 6.2).[384] In line with previous studies, a mean difference in HbA1c of ≥5.5 mmol/mol (0.5%) between the metabolic surgery and best medical care cohorts was considered the minimal clinically important difference (that is, the smallest clinical benefit of value to patients).[385-387] No cardiovascular benefit was assumed when the mean difference in HbA1c between the metabolic surgery and best medical care cohorts was <5.5 mmol/mol (0.5%) (reached on average after 16 cycles).

Figure 6.2 Projected mean difference in (a) HbA1c and (b) % BMI loss over time between the metabolic surgery and best medical care cohorts



Key: BMI – body mass index; HbA1c – glycated haemoglobin.

Sample sizes in RCTs included in the systematic review of clinical effectiveness and safety were considered too small to reliably estimate the frequency of post-surgical complications in patients with comorbid T2D and obesity undergoing metabolic surgery. Observational evidence suggests that surgical outcomes after bariatric surgery are not related to T2D status at baseline.[388, 389] While the risk of complications may be higher at the extremes of obesity, the risk of surgery-related complications, revision surgery and surgery-related mortality following bariatric and metabolic surgery were assumed to be equivalent - consistent with the conservative approach in this model. These risks were estimated from SOReg and the UK NBSR in the absence of a national bariatric surgery registry.[380, 381, 390] Surgery-related complication rates specific to RYGB and SG were used, and it was assumed that a metabolic surgery programme would comprise an equal mix of these procedures.

Anti-hyperglycaemic agents are associated with a risk of severe hypoglycaemia (that is, requiring emergency medical services including ambulance staff, emergency department attendance, and hospital admission). The risk of a severe hypoglycaemic event was estimated to be higher for insulin-treated T2D (0.037; 95% CI: 0.033 to 0.042), compared with T2D managed with secretagogues (that is, anti-hyperglycaemic medications that stimulate insulin secretion from the pancreas, such as sulfonylureas) (0.005, 95% CI: 0.004 to 0.007) or non-secretagogues (that is all other anti-hyperglycaemic medications excluding insulin and secretagogues) (0.002; 95% CI: 0.002 to 0.003).[391] Evidence from the systematic review of clinical effectiveness and safety did not indicate an increased risk of severe hypoglycaemia post-surgery in the population with comorbid T2D and obesity at baseline. Therefore, in the base case analysis no additional risk was assumed.

All-cause mortality was based on National Life Tables for Ireland in 2016, stratified by age and adjusted to account for the expected sex distribution of the cohort.[379] A relative risk of T2D-specific mortality (hazard ratio 1.41; 95% CI 1.07 to 1.83) was applied to the risk of all-cause mortality.

6.2.9.1 Transition probabilities

Evidence from RCTs indicates that metabolic surgery “resets” baseline glycaemic control (and consequently the associated anti-hyperglycaemic medication requirements), but following metabolic surgery HbA1C levels slowly increase again over time (see Chapter 4). In the model, treatment intensification was considered a surrogate for disease progression. Evidence from some, [167, 168, 249, 260] but not all,[259, 261] relevant RCTs suggest that de-intensification of diabetes treatment is uncommon in patients managed with best medical care. Only two RCTs comparing metabolic surgery with best medical care provided sufficient data to facilitate the

development of the model structure based on drug class.[249, 259] In the base case analysis, changes in medication use over time were estimated from the STAMPEDE trial.[259, 284, 291] Of note, data from the STAMPEDE trial suggest the possibility of movement between insulin and non-insulin agents at medium to long-term follow-up in the best medical care cohort,[259, 291] which contradicts the assumption of static or intensifying treatment over time. However, for the purposes of this model, it was assumed that sustained de-intensification of treatment outside the context of a RCT is unlikely.

As a conservative approach, the annual risk of progression was assumed to remain the same irrespective of the initial intervention (that is, metabolic surgery or best medical care), that is, it was assumed that transition probabilities were independent of the intervention.

The probability of mortality following stroke and myocardial infarction were estimated to be higher in the year of the event (0.165, 95% CI: 0.162 to 0.168 and 0.329 95% CI: 0.300 to 0.359 respectively) than in subsequent cycles (0.053, 95% CI: 0.052 to 0.055 and 0.064, 95% CI: 0.052 to 0.077, respectively).

Table 6.2 Transition probabilities, clinical effectiveness and safety input parameters

Parameter	Mean	95% CI	Distribution	Source
Transition probabilities				
No treatment to oral medication	0.116	(0.093 – 0.142)	beta	Schauer 2012; 2014; 2017[259, 284, 291]
Oral medication to GLP-1 RA	0.019	(0.003 – 0.048)	beta	Schauer 2012; 2014; 2017[259, 284, 291]
GLP-1 RA to insulin	0.140	(0.078 – 0.217)	beta	Schauer 2012; 2014; 2017[259, 284, 291]
Stroke to death	0.165	(0.162 – 0.168)	beta	Skajaa 2021(392)
Post-stroke to death	0.053	(0.052 to 0.055)	beta	Skajaa 2021[392]
MI to death†	0.329	(0.300 to 0.359)	beta	Koek 2007(393)
Post-MI to death	0.064	(0.052 to 0.077)	beta	Koek 2007[393]
Probability of no treatment at 1 year - BMC	0.000	(0.000 – 0.000)	beta	Schauer 2012(284)
Probability of using oral medication at 1 year - BMC	0.205	(0.096 – 0.343)	beta	Schauer 2012[284]
Probability of using GLP-1 RA at 1 year - BMC	0.410	(0.263 – 0.566)	beta	Schauer 2012(284)
Probability of using insulin at 1 year - BMC	0.385	(0.240 – 0.540)	beta	Schauer 2012[284]
Probability of no treatment at 1 year post-surgery	0.643	(0.546 – 0.734)	beta	Schauer 2012(284)
Probability of using oral medication at 1 year post-surgery	0.296	(0.210 – 0.390)	beta	Schauer 2012[284]
Probability of using GLP-1 RA at 1 year post-surgery	0.000	(0.000 – 0.000)	beta	Schauer 2012(284)
Probability of using insulin at 1 year post-surgery	0.061	0.023 to 0.116)	beta	Schauer 2012[284]
Annual risk of stroke	0.056	(0.005 to 0.006)	beta	Hayes 2013(384)
Annual risk of MI	0.0113	(0.011 – 0.012)	beta	Hayes 2013(384)
RR of myocardial infarction‡	0.851	(0.762 – 0.948)	lognormal	Edqvist 2019[382]
RR of stroke‡	0.920	(0.831 to 1.016)	lognormal	Shen 2020[383]
Probability of additional nutritional support, year 1	0.300	(0.215 – 0.393)	beta	Expert opinion
Probability of taking secretagogues	0.260	(0.202 - 0.323)	beta	Farmer 2021[373]
RR all-cause mortality T2D	1.410	(1.066 – 1.830)	lognormal	Paprot 2015[394]
Treatment-related complications				
Risk of cholecystectomy, year 1	0.017	(0.015 - 0.019)	beta	SOReg 2019[390]

Risk of cholecystectomy, year 2	0.020	(0.018 - 0.022)	beta	SOReg 2019[390]
Annual risk of cholecystectomy, years 3 to 5	0.009	(0.007 - 0.011)	beta	SOReg 2019[390]
Annual risk of cholecystectomy, years 6 to 10	0.007	(0.003 - 0.013)	beta	SOReg 2019[390]
Risk of hernia, year 1	0.004	(0.0029 - 0.0042)	beta	SOReg 2019[380]
Risk of hernia, year 2	0.005	(0.0036 - 0.0054)	beta	SOReg 2019[380]
Annual risk of hernia, years 3 to 5	0.004	(0.0027 - 0.0048)	beta	SOReg 2019[380]
Risk of perforation, year 1	0.002	(0.0011 - 0.0020)	beta	SOReg 2019[380]
Risk of perforation, year 2	0.001	(0.0006 - 0.0015)	beta	SOReg 2019[380]
Annual risk of perforation, years 3 to 5	0.000	(0.0001 - 0.0007)	beta	SOReg 2019[380]
Risk of stricture, year 1	0.003	(0.002 - 0.003)	beta	SOReg 2019[380]
Risk of stricture, year 2	0.002	(0.001 - 0.002)	beta	SOReg 2019[380]
Annual risk of stricture, years 3 to 5	0.001	(0.0002 - 0.001)	beta	SOReg 2019[380]
Risk of ulcer, year 1	0.007	(0.006 – 0.008)	beta	SOReg 2019[380]
Risk of ulcer, year 2	0.006	(0.005 – 0.007)	beta	SOReg 2019[380]
Annual risk of ulcer, years 3 to 5	0.004	(0.003 – 0.005)	beta	SOReg 2019[380]
Risk of obstruction, year 1	0.010	(0.008 – 0.011)	beta	SOReg 2019[380]
Risk of obstruction, year 2	0.016	(0.014 – 0.018)	beta	SOReg 2019[380]
Annual risk of obstruction, years 3 to 5	0.007	(0.006 – 0.009)	beta	SOReg 2019[380]
Risk of revision surgery	0.021	(0.019 – 0.022)	beta	NBSR 2020[381]
Risk of in-hospital mortality	0.0001	(0.00001 – 0.0002)	beta	NBSR 2020[381]
Risk of severe hypoglycaemia[§] - non-secretagogues	0.002	(0.002 – 0.003)	beta	Wang 2017[391]
Risk of severe hypoglycaemia - secretagogues	0.005	(0.004 – 0.007)	beta	Wang 2017[391]
Risk of severe hypoglycaemia - insulin	0.037	(0.033 - 0.042)	beta	Wang 2017[391]

Key: BMC – best medical care; GLP-1 RA - glucagon-like peptide-1 receptor agonist; HbA1c – glycated haemoglobin; HTA – health technology assessment; MI – myocardial infarction; NBSR - National Bariatric Surgery Registry; RR – relative risk; SOReg – Scandinavian Obesity Surgery Registry.
[†] Weighted for the sex distribution of the modelled population.
[‡] Applied when the mean difference in HbA1c was ≥5.5 mmol/mol (≥0.5%) between the metabolic surgery and best medical care cohorts.
[§] Requiring emergency medical services (ambulance staff, emergency department attendance and hospital admission).

6.2.9.2 Utility values

Utility is a measure of perceived health-related quality of life (HR-QoL) in a given health/disease state, with improvements or reductions in HRQoL translating into utility increments or decrements, respectively. Typically, values range from one (that is, full health) to zero (that is, death). Utility values were identified from studies included in the systematic review of cost-effectiveness and forward citation searching. Preference was given to utility values measured using generic preference-based methods such as the EQ-5D. However where unavailable, estimates from time trade-off methods were used.[326]

The model accounted for the impact of a range of factors on HR-QoL including treatment (that is, surgery-related complications, medication regimen complexity, treatment-related hypoglycaemia), treatment effects on clinical factors (that is, HbA1c, BMI) and long-term macrovascular complications (that is, stroke and myocardial infarction). Utility inputs are summarised in Table 6.3.

The cohort was assigned a mean utility at the outset of the model. Thereafter, changes in clinical characteristics resulted in changes in utility. As a conservative approach, it was assumed that patients in the "no treatment" health state would have the same HR-QoL as patients on oral medications due to the potential to progress to medically-managed T2D and the need for ongoing monitoring of glycaemic control in individuals with a history of T2D. The utility gain (that is, improvement in HR-QoL) associated with HbA1c reduction was assumed to be proportional to the degree of change (Table 6.3).[211, 395] The utility gain associated with BMI reduction for a population with comorbid T2D and obesity was estimated using the following equation:[395]

$$Utility\ change = -0.0086 + 0.022 \times Log(\%BMI\ loss)$$

HbA1c, representing an average of blood glucose values over a three month period, may not capture all aspects of blood sugar control that influence HR-QoL (for example, such as glycaemic variability).[396] To this end, treatment-related severe hypoglycaemic events were associated with a disutility (that is, a decrease in HR-QoL).

A disutility was applied for insulin use to account to for the inconvenience, lifestyle restrictions and the potential for occupational implications, weight gain and hypoglycaemic episodes associated with insulin therapy which may negatively impact HR-QoL.[10, 397, 398] A disutility was also applied for GLP-1 RA therapy to reflect that injectable agents may influence treatment preferences and HR-QoL.[399]

Table 6.3 Utility values

Parameter	Mean	95% CI	Distribution	Source
Baseline utility T2D	0.719	(0.713 – 0.725)	beta	Sullivan 2016[400]
Utility in post-stroke	0.569	(0.504 – 0.633)	beta	HIQA 2017[401]
Increment per unit decrease in HbA1c (%)	0.025	(0.022 – 0.028)	beta	Ridderstråle 2016[211]
Disutility of stroke†	0.164	(0.110 – 0.226)	beta	Beaudet 2014[402]
Disutility of MI	0.056	(0.036 – 0.080)	beta	Sullivan 2011[403]
Disutility of post-MI	0.037	(0.004 – 0.101)	beta	Sullivan 2011[403]
Disutility of surgery (applied for 3 months)	0.041	(0.030 – 0.054)	beta	McCormack 2005[404]
Disutility of GLP-1RA use	0.020	(0.015 – 0.026)	beta	Matza 2017[399]
Disutility of insulin use	0.040	(0.033 – 0.047)	beta	Ridderstråle 2016[211]
Disutility of severe hypoglycaemia	0.047	(0.045 – 0.049)	beta	Beaudet 2014[402]

Key: GLP-1 RA - glucagon-like peptide-1 receptor agonist; HbA1c – glycated haemoglobin; HTA – health technology assessment; MI – myocardial infarction.
† Weighted for the incidence of disabling and non-disabling stroke reported in the ABF 2020 Admitted Patient Price List.

6.2.9.3 Cost inputs

In accordance with national HTA guidelines, all costs are presented in 2021 Irish Euro (€).[326] An annual discount rate of 4% was applied to both costs and outcomes.[326]

Costs included the annual costs associated with anti-hyperglycaemic medication and the cost per episode of care associated with pre-operative, surgical and post-operative care, T2D-related complications (that is, stroke and myocardial infarction) and treatment-related hospitalisation (that is, post-surgical complications and severe hypoglycaemia). Costs associated with the treatment of other obesity-related comorbidities were not considered (Table 6.4).

Hospital inpatient costs and non-acute healthcare costs were obtained from relevant diagnosis related groups (DRGs) reported in the 2020 Healthcare Pricing Office (HPO) Admitted Patient Price List and the published literature specific to the Irish context.[405, 406] Resource use estimates including multi-disciplinary team assessment and dietetic support were informed by discussion with clinical experts. With consideration to guidance from the American Diabetes Association (ADA), it was assumed that patients with stable glycaemia would visit their GP twice per year, while patients with T2D-related biomarkers (that is HbA1c, total cholesterol, blood pressure) above treatment targets (estimated to be 32% of the population, see Chapter 3) or intensively managed T2D (patients managed with insulin) would visit their GP four times per year.[165, 176] It was assumed that these costs would be accrued by the HSE for 70% of patients under the Chronic Disease Management Programme.[177]

Medication-based health state costs reflect the estimated cost of combination therapy (mono-, dual- or triple therapy) within each health state based on prescribing patterns in the UK Clinical Practice Research Datalink (CRPD) database.[373] The average total cost per prescription of non-insulin anti-hyperglycaemic agents (including ingredient cost, dispensing fees and VAT, (where applicable)) was estimated from data recorded under the HSE-PCRS long-term illness (LTI) scheme in 2020, assuming a 28 day dispensing interval in line with guidance from the National Centre for Pharmacoeconomics.[407, 408]

Estimation of Irish-specific costs of insulin for a patient with T2D was challenging as indications for the use of medications (that is, T1D versus T2D) are not recorded by the HSE-PCRS. As a result, two methods for estimation of the cost of insulin were employed. Firstly, the mean total cost of each insulin type per dispensing episode was estimated from data recorded by the HSE-PCRS under the LTI scheme in 2020.

Secondly, approved insulins and their associated unit costs were identified from the HSE approved medications for diabetes mellitus (January 2022) and the PCRS list of reimbursable items, respectively.[409, 410] In the absence of robust national data, the mean daily dose of short-acting (51.5 international units (IUs)), long-acting (30.7 IUs) and premixed (47.3 IUs) insulins were based on usage by patients with T2D aged ≤60 years as estimated from a primary care database study in Germany, which accounted for the dose administered as well as pen priming, dosing errors and accumulation of insulin stores by patients.[411] The cost of each type of insulin (long-acting, fast-acting, premixed) was assumed to reflect a weighted average of available forms of long-acting (for example, degludec), fast-acting (for example, lispro) and pre-mixed insulins based on prescribing frequency recorded under the LTI scheme in 2020.[412] Due to the absence of Irish-specific estimates, the average proportion of patients using basal-bolus, basal or premixed insulin regimes was assumed to reflect usage in German primary care for both methods.[411] The first approach likely overestimates costs due to the inclusion of patients with T1D (who may require higher daily insulin doses) in the HSE-PCRS database, while the latter likely underestimates insulin use for the population with comorbid T2D and obesity due to the lower baseline BMI of the population recorded in the German primary care database (BMI ≥30 kg/m^2: 59%). In the base case analysis, the estimated cost of insulin per patient was based on the average cost of these two methods. All medication costs included the dispensing fee and were adjusted for the appropriate Framework Agreement Rebate, where applicable, in line with guidance from the National Centre for Pharmacoeconomics.[408]

It was assumed that a new needle would be used for insulin and GLP-1 RA administration in line with guidance from the HSE and manufacturers.[413, 414] A mixture of once-weekly and once-daily GLP-1 RAs was assumed based on prescribing frequency recorded under the LTI scheme in 2020.[407] The frequency of blood glucose monitoring for patients with T2D according to their treatment regime was based on recommendations from the HSE's Medicines Management Programme (MMP).[415] It was assumed that lancets and tests strips available at the reimbursement price recommended in the MMP *Preferred blood glucose test strips with associated meter(s) evaluation report* would be dispensed.[416]

For the budget impact analysis, non-oral medicines (that is, GLP-1 RAs and insulins) and consumables associated with drug administration or self-monitoring of blood glucose (that is, needles, lancets, blood glucose test strips) were subject to VAT at 23%.

Data from the HSE-PCRS were correct as of February 10th 2022.

Table 6.4 Cost inputs†

Parameter	Mean	Distribution	Source
Oral medication and consumables‡	€591	gamma	PCRS[229]
GLP-1 RAs and consumables	€2,276	gamma	PCRS[229]
Insulin and consumables	€1,446	gamma	PCRS; Kostev 2021[229, 411]
GP visit	€48	gamma	Smith 2021[406]
Pre-surgery MDT assessment	€157	gamma	Ready reckoner 2012, National Casemix Programme[417]
Dietetic consultation	€68	gamma	Smith 2021[406]
Psychologist assessment	€103	gamma	Smith 2021[406]
Metabolic surgery	€9,363	gamma	ABF 2020 Admitted Patient Price List[405]
MDT follow-up, year 1	€629	gamma	Ready reckoner 2012[417]
MDT follow-up, >1 year	€157	gamma	Ready reckoner 2012[417]
Biochemical and micronutrient monitoring	€30	gamma	National Clinical Programme for Pathology, HSE and expert opinion
Stroke (acute hospital care episode)	€9,764	gamma	HTA of mechanical thrombectomy[401]
Post-stroke (lifetime cost, post-acute hospital care episode)	€15,655	gamma	HTA of mechanical thrombectomy;[401] ABF 2020 Admitted Patient Price List[405]
MI	€9,191	gamma	ABF 2020 Admitted Patient Price List[405]
Reoperation/revision surgery	€8,672	gamma	ABF 2020 Admitted Patient Price List[405]
Hypoglycaemia requiring hospital admission	€2,885	gamma	ABF 2020 Admitted Patient Price List[405]
Hernia	€6,020	gamma	ABF 2020 Admitted Patient Price List[405]
Gastrointestinal obstruction	€3,714	gamma	ABF 2020 Admitted Patient Price List[405]
Gastrointestinal perforation	€2,937	gamma	ABF 2020 Admitted Patient Price List[405]
Laparoscopic cholecystectomy	€6,602	gamma	ABF 2020 Admitted Patient Price List[405]
Ulcer	€720	gamma	ABF 2020 Admitted Patient Price List[405]
Stricture	€2,885	gamma	ABF 2020 Admitted Patient Price List[405]
Skin-fold surgery	€5,731	gamma	ABF 2020 Admitted Patient Price List[405]

Key: ABF – Activity based funding; BMC – best medical care; GLP-1 RA - glucagon-like peptide-1 receptor agonist; HbA1c – glycated haemoglobin; HSE – Health Service Executive; HTA – health technology assessment; MDT – multidisciplinary team; MI – myocardial infarction; PCRS – Primary Care Reimbursement Service.
† Costs are presented in 2021 Irish Euro. Uncertainty in cost parameters is represented by 20% variation in the mean.
‡ Consumables include needles (where appropriate) and supplies for self-monitoring of blood glucose (that is, blood glucose test strips and lancets).

6.2.10 Model outputs

Incremental costs and QALYs were calculated by averaging the results of Monte Carlo simulations (10,000 iterations) which were then used to calculate the incremental cost-effectiveness ratio (ICER) – the incremental cost per QALY gained. In accordance with national HTA guidelines, the ICER was considered relative to willingness-to-pay (WTP) thresholds of €20,000 and or €45,000 per QALY, as appropriate.[326]

6.2.11 Assessment and quantification of uncertainty

Probabilistic and deterministic sensitivity analyses (PSA and DSA, respectively) were conducted to test the robustness of the model outputs.

6.2.11.1 Sensitivity analysis

Parameter uncertainty was assessed using a Monte Carlo simulation with 10,000 iterations. Each model parameter was defined by a statistical distribution to represent uncertainty in the mean parameter value. For each parameter, an appropriate statistical distribution was selected (for example, a beta distribution for a probability). Parameter values were then drawn as random variates from their specified distributions and the total costs and benefits were recalculated.

The total costs and QALYs for each simulation were recorded and used to quantify the proportion of simulations that were considered cost-effective with respect to the cost-effectiveness threshold (that is, €20,000). The output was presented on a cost-effectiveness plane. No specific guidance is available on the optimal number of simulations necessary to reach convergence.[418] Model convergence was assessed to ensure convergence was reached after 10,000 simulations.

One-way sensitivity analysis (OWSA) was conducted by fixing each parameter in turn at its upper and lower bounds, while all other parameters were held at the mean. The impact of extreme variation in single input parameters on the model output was presented on a tornado plot.

6.2.11.2 Scenario analyses

Scenario analysis was conducted to assess structural uncertainty in the model. These analyses varied model assumptions, or replaced a base case parameter with an alternative published data point (Table 6.5). A number of scenarios were modelled:

- *Adoption of alternative transition probabilities from an alternative RCT*.[249]
- *Increasing the risk of post-surgical complications*: In the base case analysis the risk of post-surgical complications was based on the mean rate of post-

surgical complications associated with SG and RYGB recorded in the SOReg. In general, data from SOReg indicate that RYGB is associated with a greater risk of post-surgical complications relative to SG.[380] The mean rate of post-surgical complications was based on RYGB only in a scenario analysis.

- *Inclusion of skin-fold removal surgery starting two years post-surgery*: Guidance from the British Association of Plastic Reconstructive and Aesthetic Surgeons (BAPRAS) recommends that patients should have reached a stable weight for 12 months prior to plastic surgery.[419] Thus, it was assumed that plastic surgery would not occur in the first two years post-metabolic surgery to allow adequate time for weight loss and a period of weight stabilisation. The probability of plastic surgery was based on data from the SOReg for the population with a baseline BMI of 35 to 39.9 kg/m^2 and was assumed to occur until year 10 as no follow-up data were available beyond this time point.[380] Utility increments associated with plastic surgery following massive weight loss were not identified.[420] As a conservative approach, no utility gain was assumed.
- *Removing the disutility associated with GLP-1 RA*: Previously, all GLP-1 RAs were administered subcutaneously. If semaglutide becomes widely available in Ireland as an oral formulation the disutility associated with injectable GLP-1 RA may no longer be applicable.[421] The disutility associated with GLP-1 RA administration was removed in scenario analysis to reflect the potential for oral administration.
- *No increment associated with a reduction in HbA1c*: Improvements in quality-of-life associated with metabolic surgery may be indirectly mediated through avoidance of long-term microvascular and macrovascular complications and reductions in treatment-related burden. As a conservative approach, and to avoid the possibility of overestimating improvements in HR-QoL related to reductions in HbA1c, it was assumed that there is no direct improvement in HR-QoL associated with a reduction in HbA1c.
- *No increment associated with a reduction in BMI*: BMI as a single measurement of obesity does not reflect the complexity of the disease.[23] While obesity is associated with an increased risk of cardiometabolic complications, it is a heterogeneous condition with considerable inter-individual variability in its clinical presentation. Current guidance recommends a comorbidity-based approach to patient selection for bariatric/metabolic surgery, based on the presence and severity of obesity-related complications, which better reflects the health status of an individual patient with obesity.[123] As a conservative approach, it was assumed that the benefits of surgery on HR-QoL related to changes in HbA1c only in patients with T2D and obesity.

- *Increasing the cost of micronutrient monitoring*: In the base case analysis, the cost of micronutrient monitoring was based on the panel of micronutrients typically monitored in patients post-bariatric surgery. A scenario was considered in which all patients underwent comprehensive non-routine monitoring, typically undertaken for patients who underwent malabsorptive procedures such as biliopancreatic diversion with duodenal switch, or in the presence of signs or symptoms.

Table 6.5 Input parameters used in scenario analyses

Scenario	Parameter	Value	Source
Alternative transition probabilities	No treatment to oral medication	0.130	Mingrone 2021
	Oral medication to GLP-1 RAs	0.186	Mingrone 2021
	GLP-1 RAs to insulin	0.052	Mingrone 2021
Increased risk of post-surgical complications	Risk of hernia, year 1	0.0050	SOReg 2019[380]
	Risk of hernia, year 2	0.0070	SOReg 2019[380]
	Annual risk of hernia, years 3 to 5	0.0037	SOReg 2019[380]
	Risk of perforation, year 1	0.0020	SOReg 2019[380]
	Risk of perforation, year 2	0.0020	SOReg 2019[380]
	Annual risk of perforation, years 3 to 5	0.0007	SOReg 2019[380]
	Risk of stricture, year 1	0.0020	SOReg 2019[380]
	Risk of stricture, year 2	0.0010	SOReg 2019[380]
	Annual risk of stricture, years 3 to 5	0.0007	SOReg 2019[380]
	Risk of ulcer, year 1	0.0110	SOReg 2019[380]
	Risk of ulcer, year 2	0.0100	SOReg 2019[380]
	Annual risk of ulcer, years 3 to 5	0.0060	SOReg 2019[380]
	Risk of obstruction, year 1	0.0180	SOReg 2019[380]
	Risk of obstruction, year 2	0.0300	SOReg 2019[380]
	Annual risk of obstruction, years 3 to 5	0.0145	SOReg 2019[380]
Plastic surgery starting in year 2 post-surgery	Plastic surgery, years 3 to 5	0.035	SOReg 2019[390]
	Plastic surgery, years 6 to 10	0.018	SOReg 2019[390]
No disutility associated with GLP-1 RA use	Disutility of GLP-1RA use	0.00	Assumption
No utility gain for HbA1c reduction	Increment per unit decrease in HbA1c (%)	0.00	Assumption
No utility gain for BMI reduction	$= -0.0086 + 0.022 \times Log(\%BMI\ loss)$	0.00	Assumption
Increasing the cost of micronutrient monitoring	Cost of biochemical monitoring	€200	Expert opinion

6.2.12 Model validation and calibration

Internal validation was conducted in accordance with HIQA's Internal Quality Assurance Framework. All model inputs, calculations, and model outputs were reviewed by a second economic modeller.

6.3 Results

6.3.1 Cost utility analysis

6.3.2.1 Base case analysis

The ICER reflects the mean ICER obtained by probabilistic sensitivity analysis with 10,000 simulations. Convergence testing indicated that the number of simulations was sufficient to provide a stable result (Supplementary Appendix A5.2). A stable estimate of the ICER was achieved after approximately 1,500 simulations.

Over a ten year time horizon, it is estimated that metabolic surgery would be associated with an additional cost of €3,701 (95% CI: €881 to €6,509) per patient, and a gain of 0.91 QALYs (95% CI: 0.75 to 1.06), corresponding to an ICER of €4,079 (95% CI: €946 to €7,418) per QALY gained. Thus metabolic surgery was considered cost-effective at a willingness to pay threshold of €20,000/QALY. When compared with best medical care over a ten year time horizon, metabolic surgery was cost-effective in 99.55% of simulations and cost-saving in 0.45% of simulations (that is, there were no simulations where metabolic surgery was not considered cost-effective, Figure 6.3).

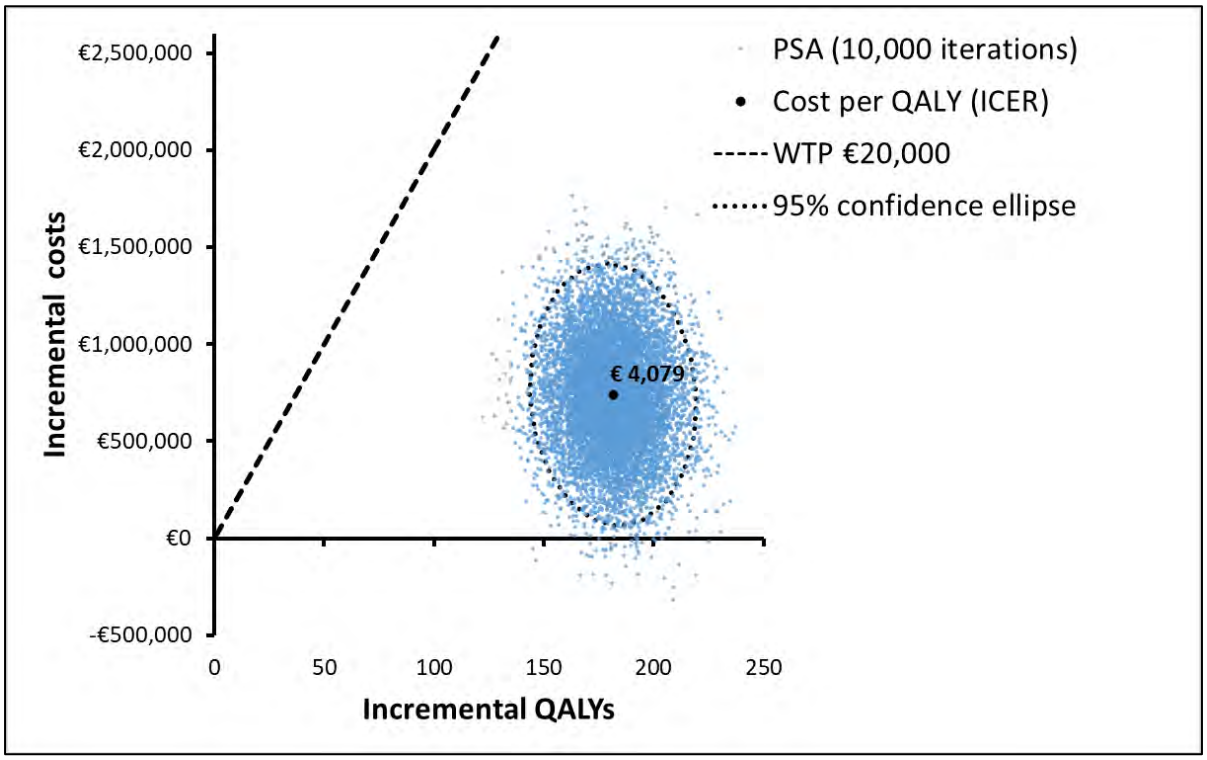
Results for other time horizons are presented in Table 6.6. Metabolic surgery became increasingly cost-effective or potentially cost-saving over time.

Table 6.6 Results of probabilistic sensitivity analysis†

Time horizon	Incremental costs (95% CI)	Incremental QALYs (95% CI)	ICER (95% CI)	Probability of dominance‡
10 years	€3,701 (€881 to €6,509)	0.91 (0.75 to 1.06)	€4,079 (€946 to €7,418)	0.0045
20 years	€804 (€-3,129 to €4,587)	1.18 (0.91 to 1.52)	€680 (Dominant to €4,054)	0.33
30 years	€-145 (€-4,769 to €4,202)	1.29 (0.97 to 1.76)	Dominant (Dominant to €3,483)	0.52
40 years	€-376 (€-5,306 to €4,152)	1.33 (0.99 to 1.85)	Dominant (Dominant to €3,410)	0.55

Key: ICER – incremental cost-effectiveness ratio; QALY – quality-adjusted life year.
† Incremental costs and QALYs are expressed per patient.
‡ Probability that metabolic surgery is cost-saving (that is, less costly and results in better outcomes) relative to best medical care.

Figure 6.3 Cost effectiveness plane for metabolic surgery compared with best medical care over a ten year time horizon



Key: ICER – incremental cost-effectiveness ratio; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life year; WTP – willingness to pay.

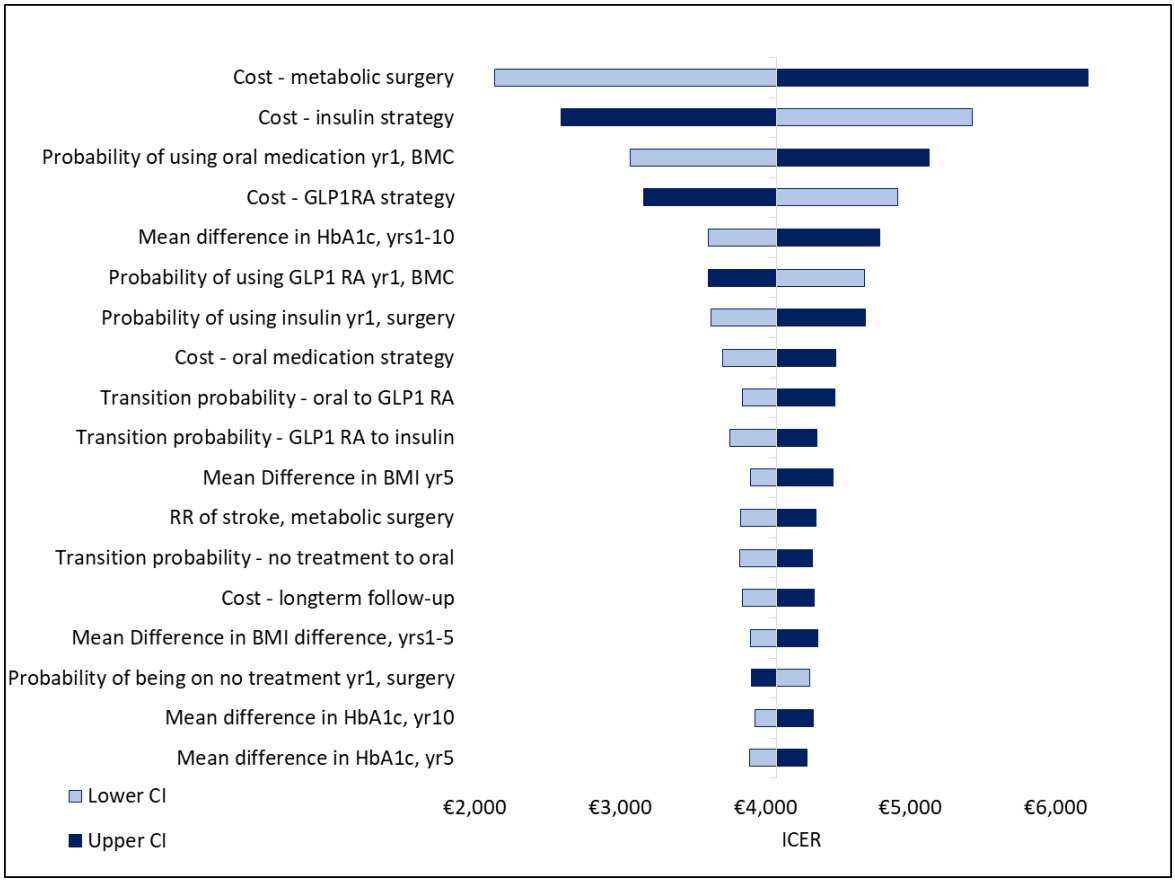
6.3.2.2 One-way sensitivity analysis

In the OWSA, all input parameters were varied and ranked in order of increasing influence on uncertainty in the ICER. Results are presented as tornado plots which provide a visual representation of the sensitivity of the model to the uncertainty associated with individual parameters. Although all parameters were varied in the analysis, only those that result in a ≥10% fluctuation from the mean ICER are presented.

OWSA demonstrated that the results were robust to variation in input parameters (Figure 6.4). The ICER did not exceed the WTP threshold of €20,000/QALY in any of the investigated sensitivity analyses. In the base case analysis, the ICER was most sensitive to the cost of metabolic surgery (95% CI: €2,135 to €6,221). Other influential parameters included medication costs (for example, insulin and GLP-1 RA) and parameters relating to changes in the pharmacological management of T2D (such as the probability of being on oral medication at year one in the best medical care cohort). Variation in the mean difference in HbA1c between metabolic surgery and best medical care cohorts also had a considerable impact on the ICER.

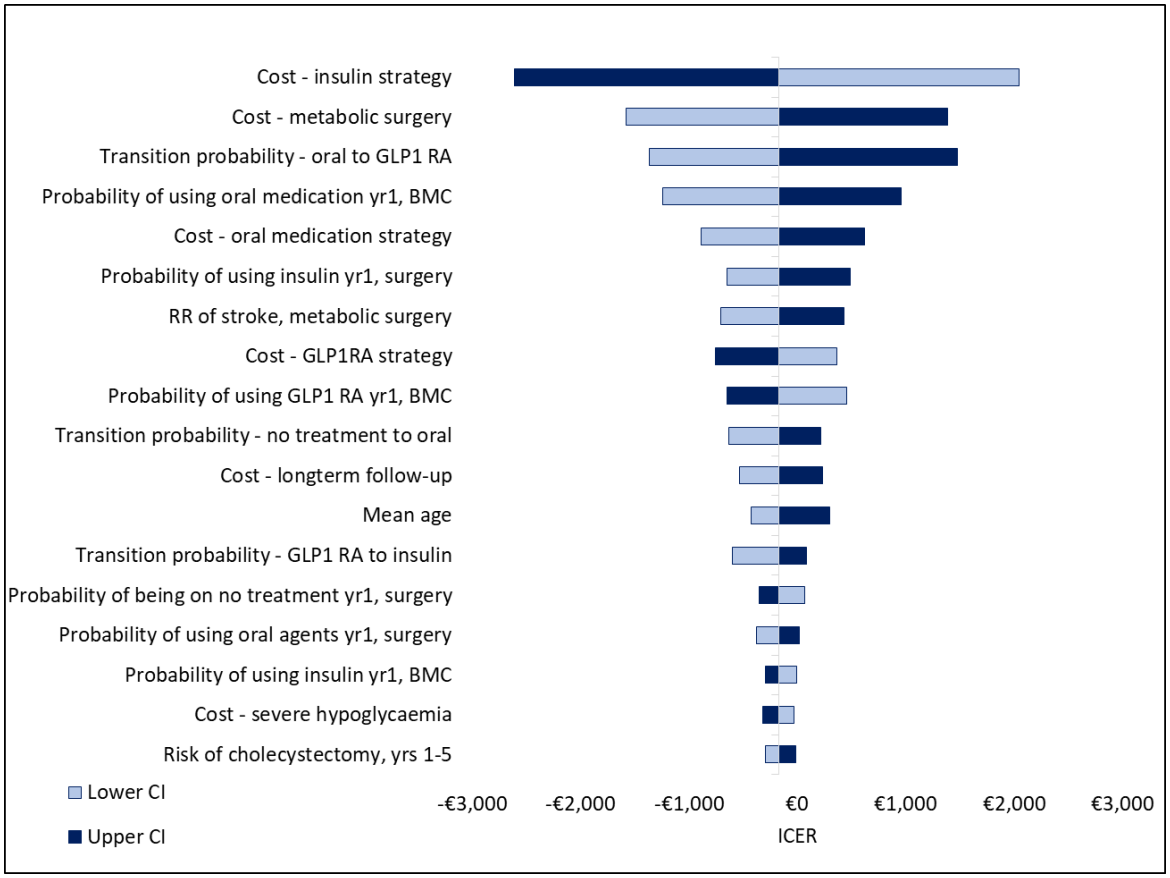
Over a lifetime time horizon, the mean difference in HbA1c became less influential as no clinically significant difference between the cohorts was assumed after an average of 16 cycles, based on extrapolation of RCT evidence (Figure 6.5).

Figure 6.4 Tornado plot of univariate sensitivity analysis over a ten year time horizon†



Key: BMC – best medical care; CI – confidence interval; GLP-1 RA - glucagon-like peptide-1 receptor agonist; RR – relative risk.
† Parameters are ranked in order of decreasing influence on the ICER. Only the most influential parameters are shown.

Figure 6.5 Tornado plot of one-way sensitivity analysis over a lifetime (40 years) time horizon†



Key: BMC – best medical care; GLP-1 RA - glucagon-like peptide-1 receptor agonist; RR – relative risk.

† Parameters are ranked in order of decreasing influence on the ICER. Only the most influential parameters are shown

6.3.2.3 Scenario analyses

Over a ten year time horizon, metabolic surgery remained cost-effective at a WTP threshold of €20,000/QALY in all investigated scenario analyses (Table 6.7). Even when the utility gain associated with a reduction in BMI and HbA1c was removed in a single scenario, assuming that all benefits of metabolic surgery on quality of life are indirectly mediated through avoidance of cardiovascular events and reductions in treatment-related burden, metabolic surgery was still considered cost-effective (ICER €17,462).

Table 6.7 Results of scenario analyses over a ten year time horizon

Scenario	Incremental costs	Incremental QALYs	ICER
Alternative transition probabilities for medication-based health states	€5,037	0.88	€5,717
Plastic surgery starting 2 years post-surgery	€4,638	0.92	€5,065
Increased risk of post-surgical complications	€3,922	0.92	€4,283
No disutility associated with GLP-1 RA administration	€3,733	0.88	€4,241
No utility gain associated with HbA1c reduction	€3,733	0.60	€6,182
No utility gain associated with a decrease in BMI	€3,733	0.53	€7,102
No utility gain associated with BMI and HbA1c reduction	€3,733	0.21	€17,462
Increasing the cost of micronutrient monitoring	€5,633	0.92	€6,152

Key: GLP-1 RA - glucagon-like peptide-1 receptor agonist; HbA1c – glycated haemoglobin; QALY – quality-adjusted life year.

Table 6.8 depicts the impact of variation in transition probabilities between medication-based health states on the ICER. Overall, variation in the proportion of patients transitioning between health states did not have a significant impact on the ICER over a ten year time horizon. In general, when more rapid treatment

intensification was assumed, the ICER was larger (that is, the intervention became less cost-effective). For example, a higher probability of moving from no treatment to oral medication results in an increase in the ICER relative to the base case analysis due to a reduction in cost-savings related to cessation of anti-hyperglycaemic medication use in the metabolic surgery cohort.

Table 6.8 Impact of changes in transition probabilities on the ICER†

Oral medication to GLP1-RA		GLP1-RA to insulin						No treatment to oral medication
		0.01	0.10	0.14	0.20	0.30		
	0.01	1,730	2,405	2,613	2,853	3,121	0.01	
	0.02	1,792	2,462	2,669	2,906	3,172	0.01	
	0.10	2,233	2,869	3,065	3,289	3,538	0.01	
	0.20	2,591	3,198	3,384	3,596	3,832	0.01	
	0.30	2,819	3,405	3,585	3,789	4,015	0.01	
	0.01	3,097	3,743	3,943	4,171	4,427	0.12	
	0.02	3,244	3,881	**4,077**	4,301	4,552	0.12	
	0.10	4,343	4,909	5,082	5,276	5,489	0.12	
	0.20	5,303	5,807	5,958	6,126	6,306	0.12	
	0.30	5,963	6,422	6,558	6,708	6,865	0.12	
	0.01	3,768	4,399	4,594	4,817	5,067	0.20	
	0.02	3,964	4,584	4,774	4,992	5,235	0.20	
	0.10	5,442	5,970	6,130	6,309	6,501	0.20	
	0.20	6,744	7,192	7,324	7,469	7,619	0.20	
	0.30	7,643	8,034	8,146	8,268	8,389	0.20	
	0.01	4,288	4,908	5,099	5,318	5,562	0.30	
	0.02	4,529	5,134	5,320	5,532	5,768	0.30	
	0.10	6,341	6,836	6,984	7,150	7,326	0.30	
	0.20	7,938	8,338	8,453	8,578	8,704	0.30	
	0.30	9,035	9,369	9,462	9,560	9,651	0.30	

Key: GLP-1 RA - glucagon-like peptide-1 receptor agonist.
† Value in bold represents the ICER when transition probabilities are set to their deterministic base case values.

6.3.2.4 Severe hypoglycaemic events avoided

The number of anti-hyperglycaemic medication-related severe hypoglycaemic events was also modelled for the metabolic surgery (n=200) and best medical care (n=200) cohorts. It was estimated that 35 severe hypoglycaemic events requiring hospital admission could be avoided over a ten year time horizon with the introduction of a metabolic surgery programme.

6.3.2 Budget impact analysis

For the purposes of the budget impact analysis, an annual cohort of 200 patients was assumed for five years. There is considerable uncertainty regarding the demand for metabolic surgery given the influence of factors such as patient acceptability and access to care on demand. Planned upscaling of capacity within the bariatric surgery service will bring the total number of procedures performed per annum to approximately 1,200. The annual cohort size is based on the assumption that approximately 17% of patients undergoing bariatric surgery have T2D pre-operatively and would therefore be eligible for metabolic surgery.[99]

The budget impact is directly proportional to the number of patients in the cohort, therefore a doubling in the size of the cohort would result in a doubling of the budget impact.

The budget impact is limited to the additional cost of providing a metabolic surgery programme including pre-, peri- and post-operative care. Existing capacity constraints related to staffing, infrastructure, and healthcare system design and delivery were not considered. Significant investment in the broader healthcare system may be necessary to support the provision of a sustainable and appropriately resourced programme. Potential organisational issues associated with the introduction of a metabolic surgery programme are described in chapter 7.

6.3.2.1 Base case analysis

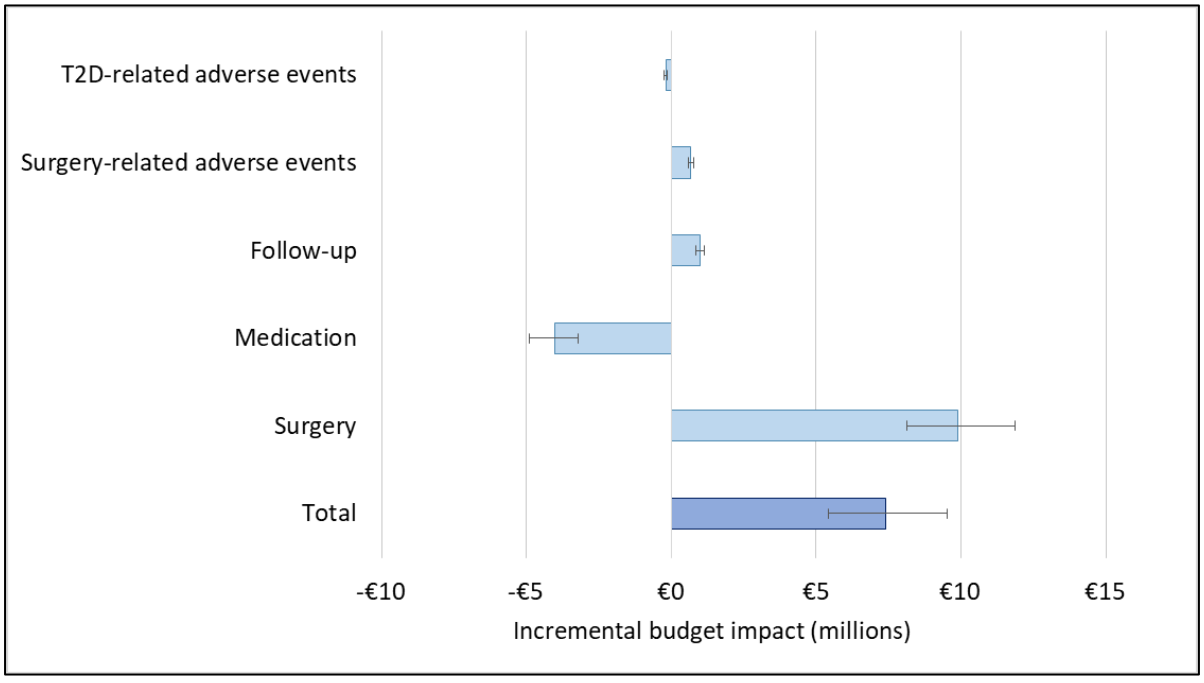
The incremental five-year budget impact was estimated at €7.39 million (95% CI: 5.41 to 9.54) (Table 6.9). The majority of expenditure over a five year time horizon directly relates to provision of surgery and the associated multidisciplinary support (Figure 6.6). Increased spending related to metabolic surgery was offset by a 24% reduction in the cost of anti-hyperglycaemic medication for patients in the metabolic surgery cohort relative to the best medical care cohort. Other costs including follow-up and surgery-related adverse events (that is, gastrointestinal perforation, obstruction, hernia, stricture, and gastrointestinal ulcer) comprised a small proportion of the total incremental budget impact with a small reduction in expenditure due to T2D-related adverse events (that is, stroke, myocardial infarction and severe hypoglycaemic events) avoided. Reductions in other T2D-related complications, such as amputation, progression to dialysis, were not included in the analysis.

Table 6.9 Five-year estimated budget impact (€ million)

Year	Metabolic surgery (95% CI)	Best medical care (95% CI)	Incremental cost (95% CI)
Year 1	2.44 (2.08 to 2.83)	0.45 (0.38 to 0.52)	1.99 (1.64 to 2.39)
Year 2	2.65 (2.29 to 3.05)	0.92 (0.78 to 1.07)	1.73 (1.36 to 2.14)
Year 3	2.87 (2.50 to 3.27)	1.40 (1.20 to 1.62)	1.46 (1.07 to 1.89)
Year 4	3.10 (2.73 to 3.51)	1.89 (1.63 to 2.17)	1.22 (0.79 to 1.67)
Year 5	3.36 (2.98 to 3.78)	2.37 (2.06 to 2.73)	0.99 (0.52 to 1.48)
Total	14.43 (12.59 to 16.44)	7.04 (6.05 to 8.11)	7.39 (5.41 to 9.54)

Key: CI – confidence interval.

Figure 6.6 Itemised five-year incremental budget impact



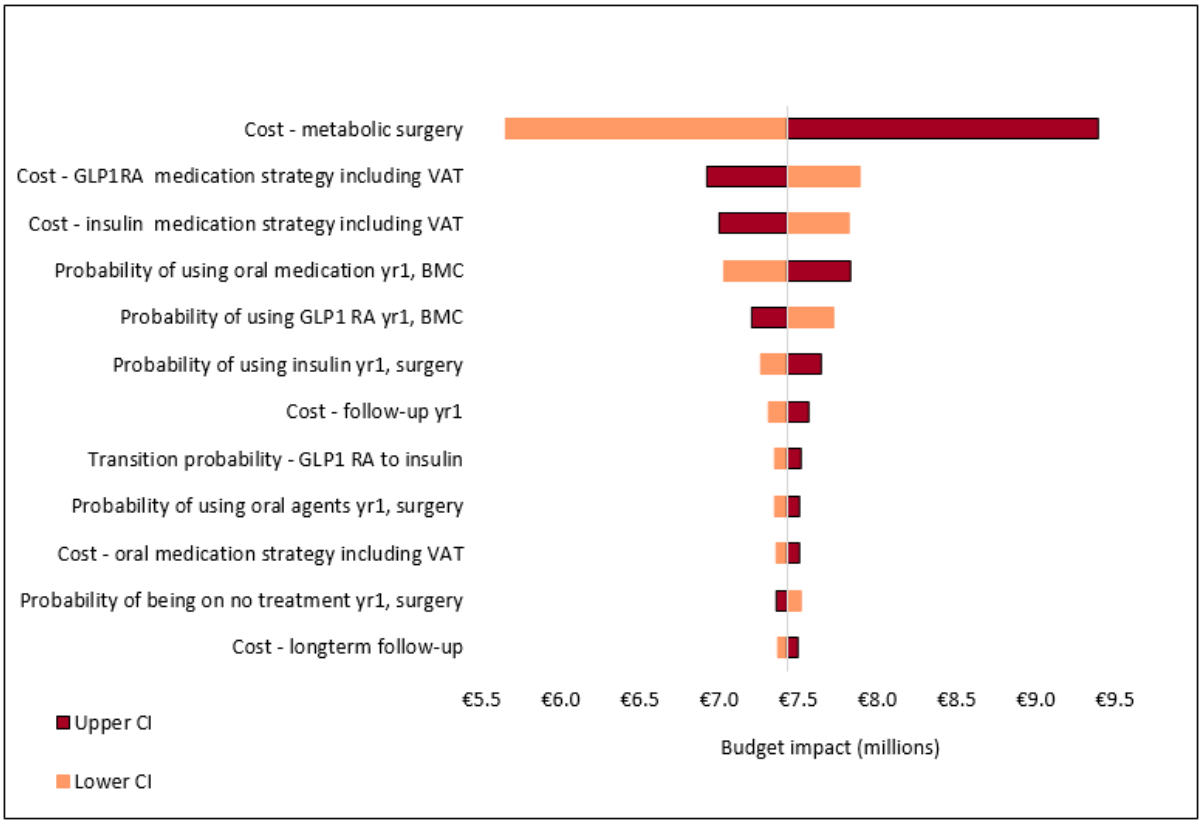
Key: T2D – type 2 diabetes**.**

Notes:
T2D-related adverse events include severe hypoglycaemic events, stroke and myocardial infarction. Surgery-related adverse events refer to gastrointestinal perforation, obstruction, hernia, stricture, gastrointestinal ulcer, cholecystectomy and revision surgery.

6.3.2.2 One-way sensitivity analysis

As in the CUA, one-way sensitivity analysis was undertaken to assess the impact of variations in input parameters on the five-year incremental budget impact analysis. Uncertainty relating to the cost of metabolic surgery was found to contribute most to uncertainty in the ICER.

Figure 6.7 Tornado plot of one-way sensitivity analysis for the five-year budget impact analysis†



Key: BMC – best medical care; CI – confidence interval; GLP-1 RA - Glucagon-like peptide-1 receptor agonists; VAT – value added tax.
† For the budget impact analysis, VAT was applied to the cost of non-oral medicines (that is, GLP-1 RA and insulins) and consumables associated with drug administration or self-monitoring of blood glucose (that is, needles, lancets, blood glucose test strips).

6.3.2.3 Scenario analyses

There is considerable uncertainty regarding the cost of pharmacological management of T2D due to the use of combination therapy by many patients, and the potential for confidential pricing agreements which may mean the price paid by the publicly-funded healthcare system (that is, the HSE) is lower than the published price. In scenario analyses, the cost of GLP-1 RA and insulin were varied by 20% in either direction. Results are presented in Table 6.10. The availability of anti-hyperglycaemic agents at a lower price than estimated in this analysis would result

in an increase in the incremental budget impact, due to lower cost offsets associated with reduced anti-hyperglycaemic medication use in the metabolic surgery cohort. A 20% reduction in the cost of both insulin and GLP-1 RA would translate into a 12% increase in the base case five-year total incremental budget impact.

Table 6.10 Results of scenario analyses for the five-year budget impact analysis (€ million)

Scenario	Total incremental cost (€ millions)	Divergence from base case† (%)
20% increase in the cost of GLP-1 RA	6.90	-7%
20% increase in the cost of insulin	6.98	-6%
20% increase in the cost of GLP-1 RA and insulin	6.48	-12%
20% decrease in the cost of GLP-1 RA	7.87	6%
20% decrease in the cost of insulin	7.80	6%
20% decrease in the cost of GLP-1 RA and insulin	8.26	12%

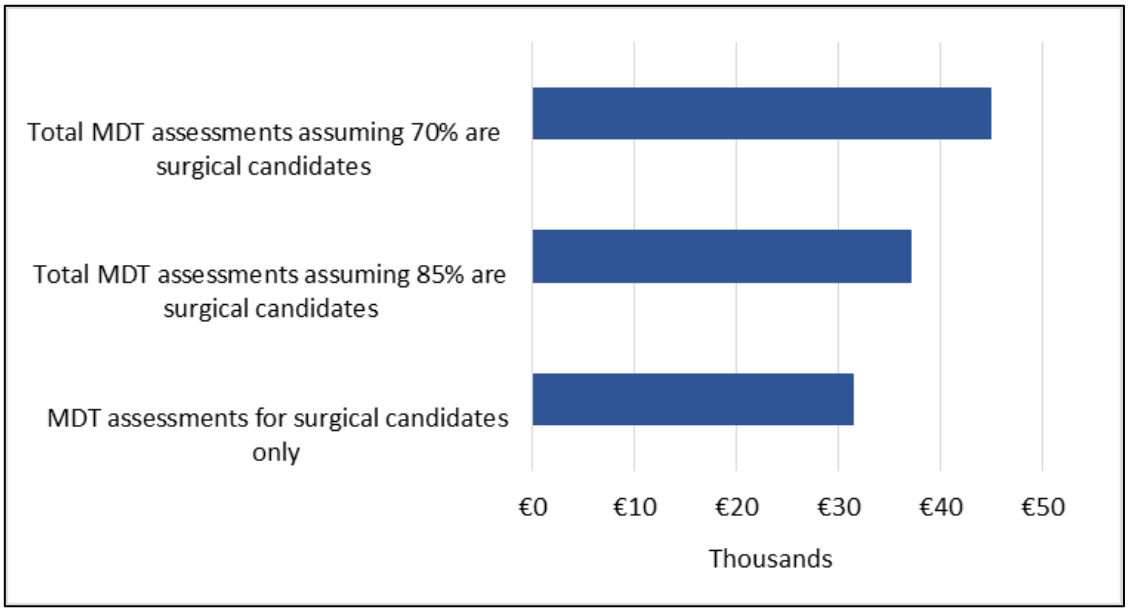
Key: CI – confidence interval.
† Percentage change in the total incremental budget impact over five years under the scenario analysis relative to the base case estimate.

Varying the progression rate from pre-operative multidisciplinary team assessment

Following pre-surgical screening, there may be a variety of reasons why a patient is not considered suitable for surgery, such as frailty or the presence of certain comorbidities. The contribution of MDT assessment costs to the overall budget impact will depend on the proportion of patients progressing to surgery. Based on evidence from the UK, it was assumed that 70 to 85% of patients would progress to metabolic surgery following MDT assessment.[422, 423] Up to 286 MDT assessments would be carried out to identify 200 surgical candidates, resulting in additional expenditure relating to pre-surgical assessment. In the absence of a current metabolic surgery service, it is challenging to estimate how many will be referred and what proportion might ultimately be considered suitable for surgery.

The proportion of patients progressing to surgery will depend on the availability of clear eligibility criteria and the capacity for pre-referral screening prior to presentation for MDT assessment. Without pre-referral screening or well defined referral guidelines, the number of patients referred for MDT assessment that are not surgical candidates will increase. If the outcome of the MDT assessment is considered time-limited, additional costs may accrue if there is a requirement for re-assessment prior to surgery in the context of lengthy (for example, greater than six months) surgical waiting lists.

Figure 6.8 Cost associated with pre-surgical assessment of metabolic surgery candidates



Key: MDT – multidisciplinary team.

Phased implementation

If a metabolic surgery programme was introduced on a phased basis over five years to allow time for the development of surgical capacity, the estimated budget impact would be €4.90 million over a five year time horizon.

6.4 Discussion

The economic model simulated the annual expected treatment costs and outcomes for patients with comorbid T2D and obesity managed with metabolic surgery compared with best medical care. Over a ten year time horizon, metabolic surgery was more costly, but more effective in terms of QALYs than management with best medical care (ICER €4,079; 95% CI: 946 to 7,418). In all simulations, metabolic surgery was below the WTP threshold of €20,000/QALY. Thus, metabolic surgery can be considered cost-effective when compared with best medical care for the management of T2D and obesity.

Existing CUAs in populations with T2D and obesity were largely undertaken prior to the publication of long-term follow-up data from relevant RCTs or used estimates of effect from national data sources, in addition to context-specific cost data. Therefore, our findings are not directly comparable. Nevertheless, despite variation in the input parameters used, the findings of this economic evaluation are largely consistent with previous CUAs comparing metabolic surgery with best medical care, specifically in the population with T2D and obesity where it has consistently been found to be a cost-effective or cost-saving intervention.[332-347] Although metabolic surgery was not found to be cost-saving in the present analysis the conservative approach adopted owing to a lack of long-term high-quality follow-up data has the potential to have underestimated the true effect of a metabolic surgery programme.

This CUA considers the cost-effectiveness of metabolic surgery compared with best medical care in the population with T2D and moderate to severe obesity, as this represents the population most commonly enrolled in RCTs comparing RYGB with best medical care with medium to long-term follow-up data. Previous CUAs of bariatric/metabolic surgery in the population with T2D and obesity have conducted subgroup analysis according to BMI at baseline.[340, 343, 348-352, 355, 360, 363] In line with recent recommendations proposing a comorbidity-based approach to candidate selection as opposed to traditional BMI-based criteria, BMI was not considered an appropriate measure of disease severity in the population with T2D and obesity.[123] In the context of demand exceeding available capacity, patient prioritisation will be a key challenge. More studies are needed to evaluate the relative benefits of metabolic surgery in different T2D sub-populations to address this knowledge gap.

Metabolic surgery is associated with high upfront costs which raises concerns regarding the budgetary impacts associated with the introduction of a metabolic surgery programme. For the purposes of the budget impact analysis, an annual cohort of 200 patients was assumed for five years. This may not be sufficient to meet demand; however, uptake rates are likely dependent on numerous factors

including patient acceptability, potential capacity constraints related to competition for resources with the existing bariatric surgery programme, and patient and provider education. Although metabolic surgery likely represents a cost-effective use of resources, an important consideration for policy makers is the capacity to provide ongoing long term post-operative monitoring and support for a growing cohort of patients. The estimated budget impact does not include the costs of training specialised personnel including nurses, surgeons and anaesthesiologists and appropriate specialist support including dieticians and psychologists. In addition, it was assumed that there are no capital investment costs associated with establishing additional theatre space or critical care facilities. Delivering metabolic surgery services within existing infrastructure and capacity constraints will be dependent on expansion to additional hospital sites for appropriately risk-stratified patients, in addition to the potential use of current centres equipped for bariatric surgery patients.

Limitations

The certainty of the results is limited by the availability of data to model all relevant clinical and economic consequences. A limitation of the study is the reliance on relatively short-term clinical trial data to make long-term projections. Given the uncertainty in the durability of the treatment effect over longer term time horizons, a time horizon of ten years was used in the base case analysis as a conservative approach.

Evidence from the systematic review of clinical effectiveness and safety did not suggest a clinically important difference in effectiveness between RYGB and SG. Thus, for the purposes of this CUA, both procedures were assumed to have equivalent clinical effectiveness. With the exception of one within-trial CUA,[344] previous CUAs conducted in the population with T2D and obesity to date have also not compared surgical procedures head-to-head, owing to a lack of long-term comparative data.

Owing to limitations in the evidence base, this model considered a limited set of T2D-related complications. Although not examined in relevant RCTs identified in the systematic review of clinical effectiveness and safety, we assumed that metabolic surgery would lead to a reduction in the incidence of stroke and myocardial infarction. This assumption is supported by evidence from long-term observational studies suggesting a decrease in the incidence of composite cardiovascular endpoints after bariatric/metabolic surgery;[308, 424-426] however, such evidence is not suitable for populating an economic model due to the difficulty assigning health state costs to heterogeneous clinical outcomes. For the purposes of this model, the

treatment effect of metabolic surgery on cardiovascular outcomes was assumed to be mediated through reductions in HbA1c only.[382, 384] Metabolic surgery may have additional beneficial effects on hard cardiovascular endpoints mediated through weight loss, improvements in cardiovascular risk factors, or through changes in inflammatory markers. In addition, this model assumed the same rate of stroke and myocardial infarction in the metabolic surgery and best medical care cohorts when the mean difference in HbA1c was above the specified minimal clinically important difference of 5.5 mmol/mol (5%). However, previous studies have shown that a period of improved glycaemic control can have long-term clinical benefits.[305, 306, 427] Thus the beneficial effects of surgery on the risk of cardiovascular events may be underestimated in this CUA. It is possible that reductions in health services utilisation related to the management of other T2D-related complications not considered in this economic evaluation (for example, chronic kidney disease) may result in additional cost-savings; however, long-term follow-up data were not available to support inclusion of microvascular outcomes in the model at this time.

Estimates of post-surgical complication rates were based on reports on bariatric surgery registry data, in the absence of evidence of surgical outcomes for the population undergoing metabolic surgery. This approach was considered reasonable as evidence from retrospective cohort studies indicates that T2D status does not influence the risk of surgical complications.[388, 389]

Previous economic evaluations have assumed a single health state for T2D.[335, 343, 348, 354, 361] However, T2D treatment regimens are heterogeneous in terms of both costs and medication-related burden which can impact quality-of-life. A strength of this analysis lies in the costing of medication-based health states to reflect the benefits of metabolic surgery that can be achieved even without T2D remission or in the case of T2D relapse. High attrition rates were noted with respect to RCTs that reported evidence of the long-term effectiveness of metabolic surgery and best medical care. Also complicating the estimation of transition probabilities to support medication-based health states is the continuous evolution of best medical care over time. Nevertheless, in a scenario analysis, substitution of alternative transition probabilities did not result in meaningful changes in the ICER.

Confidential pricing agreements as part of patient access schemes may be agreed between pharmaceutical companies and the HSE whereby pharmaceutical companies offer discounts or rebates that reduce the cost of a drug. Due to the potential for confidential pricing agreements for anti-hyperglycaemic agents, drug costs may be lower than presented. However, considerable variation in anti-hyperglycaemic medication costs in sensitivity and scenario analyses did not change the conclusions of this analysis. In addition, the cost of micronutrient monitoring may vary

dependent on factors such as the testing method in a given laboratory or changes in type of frequency of monitoring based on an identified clinical need at a patient level. Uncertainty associated with these inputs did not influence the conclusions of this analysis in the univariate sensitivity analysis.

Consideration of the societal perspective would likely render metabolic surgery more cost-effective or cost-saving by accounting for indirect costs (for example, productivity losses due to morbidity or mortality related to T2D and obesity, the cost of transportation to and from medical appointments). The payer perspective was considered most important in the context of this assessment to inform decision-making by the Health Service Executive. While it is acknowledged that the societal perspective is important, it is unlikely that consideration of indirect costs would change the conclusions of this analysis, but rather further strengthen the argument for a metabolic surgery programme at a broader societal level. Estimation of costs from the societal perspective would be associated with greater uncertainty as this data is not routinely collected, therefore data availability and quality are likely to be low. The societal perspective may also raise ethical issues because it places less weight on people not in the workforce.

The results are based on the assumption that the clinical effectiveness of metabolic surgery and best medical care do not change over the modelled time horizon. However, increased diffusion of other anti-hyperglycaemic medications associated with weight loss or adjuvant weight-loss medication may result influence estimates of cost-effectiveness. The net impact of additional interventions is currently unclear.

Conclusions

Metabolic surgery is cost-effective for the management of T2D and obesity when compared with best medical care in the Irish context. Replication of simulated costs and outcomes will be dependent on careful selection of candidates for metabolic surgery with consideration to their clinical need.

7 Organisational issues

Key points

- The delivery of a metabolic surgery programme for patients with comorbid T2D and obesity would depend on several critical enablers: scaling up of hospital capacity; health service delivery reform to allow follow-up care to be delivered in the community; patient and provider education; and the availability of specialist staff.
- It is estimated that treating a cohort of 200 patients per year would be associated with an estimated 230 multidisciplinary team (MDT) pre-operative assessments (including expertise in surgery, dietetics, psychology and endocrinology), 85 theatre days and 400 hospital beds days for the index admission. During the first year post-operatively, a minimum of 800 specialist MDT follow-up visits would be required.
- It would be important that the healthcare system is adequately resourced to undertake lifelong follow-up of these patients. Resource requirements for long-term follow-up would depend on organisational structures. Capacity for annual review would need to be factored into the staffing of specialist centres until discharge to primary care is considered appropriate. To achieve operational efficiency, long-term follow-up care for uncomplicated cases discharged to primary care may be incorporated into existing reviews for T2D management.
- The success of a shared model of care between primary care, community and hospital services will depend on adequate resourcing of community services; clear eligibility criteria and referral pathways.
- Without investment in community resources to support discharge of patients from acute hospital services, an imbalance would be created between an increasing number of patients requiring follow-up, and the availability of resources in metabolic surgery units. This would present a risk to the sustainability of the programme. Ongoing investment would be required as the size of the patient cohort increases.
- Development of key performance indicators (KPIs) would help support the delivery of a metabolic surgery programme through the collection of robust data to monitor outcomes and identify organisational challenges. Revisions to the care pathway should be driven by a review of the programme's KPIs, of the identified needs within the Irish healthcare system, and of changes in best practice guidelines.

- Should a decision be made to implement a national metabolic surgery programme, consideration should be given to the development of national disease registries for diabetes and metabolic surgery to support quality assurance processes, healthcare service planning in response to epidemiological trends and monitoring of patient outcomes. Consideration should be given to the variables recorded in other international registries to facilitate international collaboration and benchmarking.

7.1 Introduction

The aim of this chapter is to provide an overview of the potential organisational challenges associated with introduction of a metabolic surgery programme as part of the T2D clinical care pathway in Ireland. The approach taken was to outline requirements and challenges in providing the surgery within the context of a metabolic surgery programme that considers all aspects of care. As such, it outlines potential considerations in relation to the referral pathway, pre-operative assessment, the acute surgical care episode and the long-term follow-up of these patients. The estimated staffing and resource requirements for each of these phases are outlined as well as potential requirements for patient and provider education and considerations for the quality assurance of a metabolic surgery programme.

7.2 Organisation of chronic disease care

The HSE's Integrated Care Programme for the Prevention and Management of Chronic Disease aims to shift care for the management of chronic diseases such as T2D away from hospital-based services towards the community. Through the integrated care programme and the implementation of Sláintecare, it is intended that this shift in care will be facilitated by increasing access to specialist services in the community. Table 7.1 outlines the levels of community- and hospital-based care for patients with chronic disease. Management of chronic disease will primarily be delivered through GP-led primary care (Level 1), supported by community specialist services (Level 2).[428, 429] It is planned that six new geographically-based "Regional Health Areas" (RHA) will be established to facilitate the delivery of care closer to home.[428] Increasing access to specialist community-based services and the implementation of six RHAs are likely to be a key enabler to the implementation of a metabolic surgery programme by providing better access to a range of specialist services prior to the acute surgical episode and in terms of the medium- and long-term post-operative care of these patients, thereby reducing demands on acute hospital services.

Table 7.1 Levels of care

Level of care		Description	Examples of potential services
Community-based care	**Living well with chronic disease**		
	Level 0	Community-based services including education sessions, goal-setting and the development of action plans to support the prevention and/or management of chronic disease(s) and associated complications.	Educational support groups, online resources
	Community Healthcare Network		
	Level 1	GP care provided in the CHN.	GP, GP nurse, public health nurse
	Community Specialist Ambulatory Care hubs		
	Level 2	Community ambulatory care based in the ambulatory care hub in the community provides a further layer of support to the GP to care for patients in the community through access to diagnostics, diabetes structured patient education services and pulmonary and cardiac rehabilitation.	Dietetics, diabetes education and self-management support services
Hospital-based care	**Acute specialist ambulatory care hubs**		
	Level 3	Acute specialist ambulatory care delivered from the ambulatory care hub offers acute specialist services such as outpatient services and respiratory outreach.	Endocrinology, dietetics, psychology, physiotherapy, occupational therapy
	Hospital services		
	Level 4	Specialist hospital care for the management of complex issues. Community supports will be in place to facilitate timely discharge from hospital services.	Metabolic surgery MDT

Key: CHN – community healthcare network; GP – general practitioner; MDT – multidisciplinary team.

At present, patients with T2D who have a GP visit card or medical card (approximately 70% of patients with T2D) are managed as part of the Chronic Disease Management Programme by their GP. The Chronic Disease Management Programme comprises two GP consultations per annum specific to their T2D care.[239, 430] The consultations include a review of metabolic and cardiovascular indicators (including HbA1c, lipids, blood pressure and BMI), the patient's immunisation status, participation in retinopathy screening and a review of medications, as well as review and education in relation to health behaviours, symptomatic foot review and provision of education materials.[239] While it is intended that the majority of routine T2D care is provided in the primary care setting in Ireland, for patients with more complex needs, access to additional specialist services is required, which are mainly delivered in secondary and tertiary care settings.[230]

7.3 T2D clinical care pathway

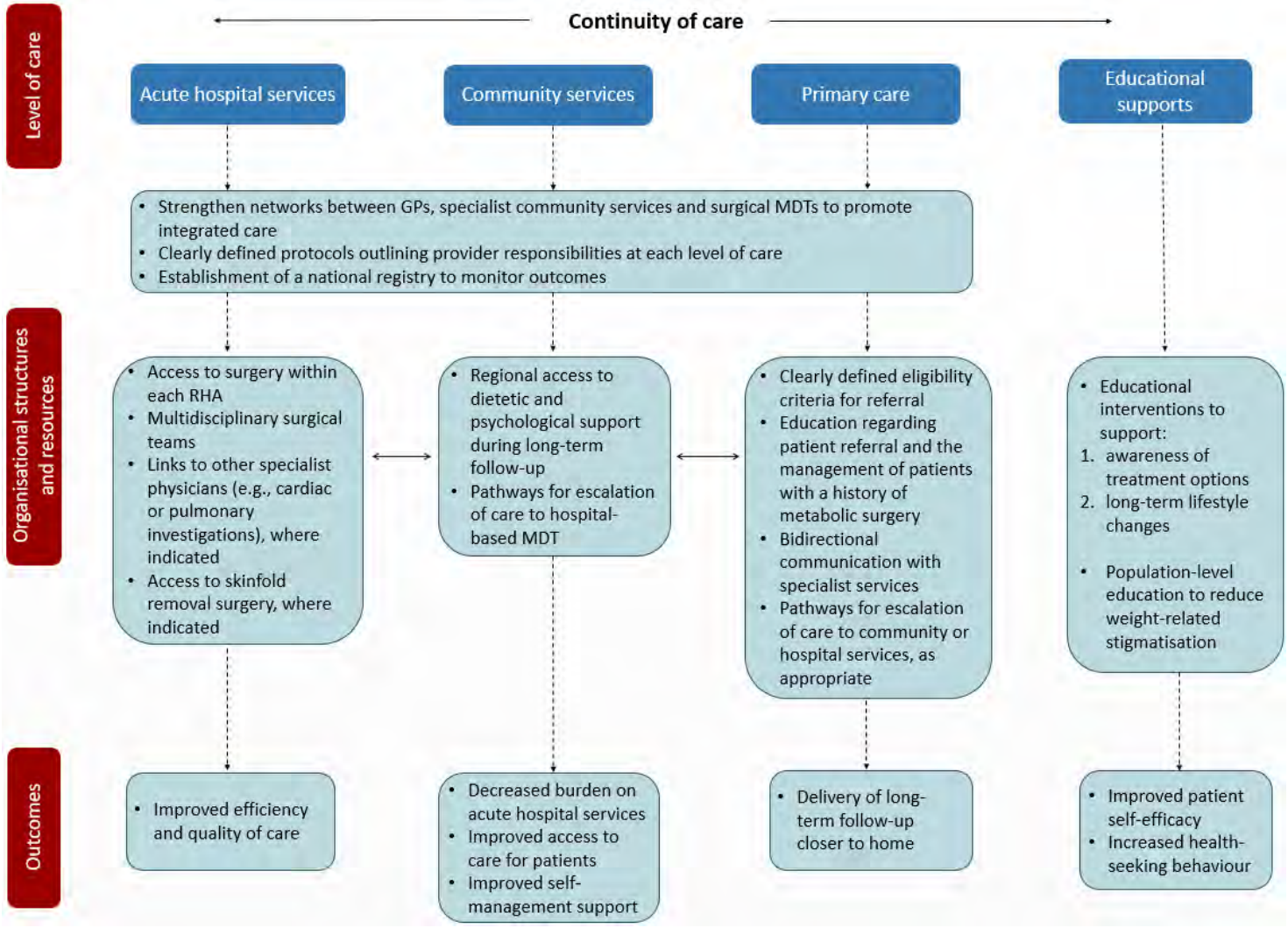
7.3.1 Metabolic surgery

Metabolic surgery is a recommended treatment option for T2D in patients with comorbid obesity in international clinical practice guidelines.[7, 9] However, metabolic surgery is not currently integrated into the clinical care pathway for T2D in Ireland. There is potential for patients with comorbid T2D and obesity to access surgical care through the bariatric surgery service; however, as identified in Chapter 2, the number of procedures undertaken through this service is limited resulting in significant waiting lists as demand greatly exceeds available capacity. While providers will liaise with the patient's primary care provider and refer to endocrinology services, where appropriate, as noted, this care is not formally integrated with T2D management.

Evidence from the systematic review of clinical effectiveness and safety indicates that, for patients with comorbid T2D and obesity, metabolic surgery is an effective treatment option with an acceptable safety profile (see Chapter 4). Metabolic surgery has also been found to be cost-effective in this population over a relatively short time horizon (see Chapter 6). In light of these findings, metabolic surgery would likely represent an efficient use of resources. In addition to allowing for the integration of long-term follow-up with standard T2D care, inclusion of metabolic surgery in the T2D treatment algorithm is likely to increase its visibility to clinicians and patients as a valid treatment option, potentially increasing the number of referrals for metabolic surgery.

As described in the following sections, provision of metabolic surgery as part of the T2D clinical care pathway would require coordination of care across multiple levels. Some of the key organisational structures and resources required to deliver care as part of a metabolic surgery programme are highlighted in Figure 7.1 and are discussed with respect to patient referral, pre-operative assessment, acute surgical care and longer-term post-operative care.

Figure 7.1 Organisational structures and resources needed to support a metabolic surgery programme



Key: MDT – multidisciplinary team; RHA – regional health area.

1.1.1.1 Referral

Consideration should be given to the development of standardised eligibility criteria and referral pathways. While criteria for metabolic surgery will differ to those for bariatric surgery, consideration should be given to the implementation of a comorbidity-based approach rather than traditional BMI-centric referral criteria. Such an approach would be in line with the Model of Care for Obesity and international best practice guidelines for both metabolic and bariatric surgery.[123, 230] As more evidence becomes available, updates to the referral criteria may be necessary.

As noted in Chapter 2, T2D control above treatment targets is not necessarily a requirement for referral for multidisciplinary team (MDT) assessment in international guidelines. However, in the context of demand exceeding available capacity, prioritisation of patients for metabolic surgery with consideration to clinical need would likely be necessary. While data to inform patient prioritisation were not identified in the systematic review of clinical effectiveness and safety (see Chapter 4), algorithms for patient prioritisation based on clinical need have been proposed based on expert opinion.[123]

Consideration should be given to the capacity required within acute hospital services to screen referrals for metabolic surgery. Assessment of all potentially eligible candidates by surgical MDTs in hospital outpatient departments may put excessive pressure on these services resulting in long waiting lists and challenges for the provision of high-quality care for patients already enrolled in the programme. Depending on demand for surgery and the capacity of surgical MDTs, consideration could be given to the use of community-based specialist services for initial assessment and onward referral for surgical MDT review, depending on the outcome of the assessment.

It is not known how many patients would be eligible for and wish to avail of metabolic surgery. The proportion of eligible patients that proceed to surgery, will likely be influenced by potential facilitators and barriers to referral. The development of referral guidelines, structured referral forms, and educational interventions delivered by specialist clinicians may be effective in supporting penetration of metabolic surgery into the T2D care pathway and reducing inappropriate referrals, including referral of patients who do not wish to pursue surgical care. Barriers to referral from primary care to metabolic surgery services may include lack of clear eligibility criteria, concerns regarding long-term outcomes, and lack of support from specialist services in the management of medical and surgical complications.[431-433] Perceived stigma, lack of education regarding the benefits of metabolic surgery on

T2D control, and inaccessibility of services may contribute to a lack of health-seeking behaviour among the population with comorbid T2D and obesity.[431, 434]

Should a decision be made to resource a metabolic surgery programme, patients with comorbid T2D and obesity may be eligible for surgery through both the metabolic surgery and bariatric surgery pathways. This population should be referred for metabolic surgery, so that long-term follow-up could be aligned with a shared model of care for the management of chronic disease (see section 7.3.1.4) and to facilitate consistent monitoring and recording of outcomes for all patients with comorbid T2D and obesity (see section 7.6.2).

1.1.1.2 Pre-operative assessment

Specialist MDTs are required to assess the suitability of referred patients for metabolic surgery. If implemented, ideally a metabolic surgery programme should be adequately resourced for the timely assessment of referrals to prevent clinical deterioration of patients while awaiting surgery and to avoid the need for multiple visits during the pre-operative phase due to clinical data becoming outdated.

British Obesity and Metabolic Surgery Society (BOMSS) standards recommend that the specialist surgical MDT should, at a minimum, comprise bariatric/metabolic surgeon(s), a specialist dietician, a specialist nurse and a psychologist experienced in the management of bariatric/metabolic surgery patients.[435] For the population with comorbid T2D and obesity, an endocrinologist should also be present on the MDT.

For selected patients, additional tests or consultations with other disciplines may be indicated to determine suitability for surgery such as upper gastrointestinal endoscopy, pulmonary and cardiovascular assessments.[436-439] Again, consideration should be given as to whether capacity to provide specialist investigations is available within existing resources in the hospital or region within which care is being provided.

No guidance was identified specific to requirements for psychological assessment of patients with comorbid T2D and obesity undergoing metabolic surgery. In the absence of such evidence, consideration could be given to the adoption of the recommendations that have been developed for the psychological assessment of bariatric surgery patients. This would include requirements for appropriate psychological assessment protocols to be in place that take consideration of the resources available regionally and the psychosocial needs of the individual patient.[440] The timing, duration, frequency and intensity of the psychological support will also depend on the underlying psychosocial needs of a patient. For patients with untreated mental health issues identified during psychological

assessment that do not represent a clear contraindication to surgery, but which have the potential to undermine the patient's ability to adhere with life-long behavioural changes and adversely impact outcomes of surgery, consideration will be needed as to how necessary psychological interventions and support will be provided within the context of the programme.(441) Ongoing psychological support may be needed for some patients.

Patient education

Metabolic surgery requires a commitment to lifelong behavioural changes and adherence to follow-up care. It is important that patients are fully informed about the implications of having metabolic surgery. To facilitate informed consent, patient education prior to surgery may include information on:(437)

- available procedure options, as well as the expected outcomes of each procedure
- the risks and benefits including post-operative treatment targets
- necessary behavioural changes (for example, diet, exercise, vitamin and mineral supplementation)
- the expected course of post-operative care and signs and symptoms of complications.

Pre-operative biochemical monitoring

Guidelines from the British Obesity and Metabolic Surgery Society (BOMSS) recommend blood testing to investigate and correct nutritional deficiencies prior to surgery, where necessary, and to facilitate monitoring of relative changes in biochemical parameters in the post-operative period.(442)

Assessment of surgical risk and care needs

Bariatric surgery services are currently provided in Model 4 hospitals which are typically affiliated with a university, provide care to acute medical and surgical patients, and have on-site access to an emergency department and higher level intensive care unit. As described in detail in the next section (7.3.1.3), introduction of metabolic surgery at additional lower acuity hospital sites (for example, Model 3 hospitals which care for undifferentiated acute medical and surgical patients, and have on-site access to an emergency department and lower level intensive care unit) may be necessary to support adequate patient access.

Risk assessment protocols should be established to risk-stratify patients pre-operatively in order to determine the appropriate hospital site for surgical intervention.[437] The appropriate hospital site for an individual patient will depend on the expected care needs post-surgery, ranging from high acute (for example, hospital ward) to critical care (for example, high dependency unit (Level 2) or critical care unit (Level 3)).[435, 437] Robust inter-hospital transfer agreements would be required for hospitals without critical care facilities undertaking metabolic surgery in patients considered at low-surgical risk.[435] For patients with expected or planned requirements for post-operative critical care, on-site critical care facilities should be available.[435]

Some patients with a diagnosis of obesity can safely use standard furniture, equipment and supplies available in inpatient and outpatient settings.[443] However, depending on an individual's physical characteristics (for example, weight distribution, restricted access for tracheal intubation or reduced mobility), specialised equipment may still be necessary for patients below the maximum weight capacity of standard furniture and equipment.[443] In the context of this assessment, bariatric care needs refers to the considerations needed to provide safe and sensitive care for individuals with obesity for whom standard clinical procedures, furniture, equipment or supplies may not be appropriate, or with unique care needs related to obesity and its associated complications. Key considerations for facilities managing patients with bariatric care needs may include:

- equipment and furniture (for example, examination tables, wheelchairs) with appropriate weight capacity and dimensions to support and accommodate the patient
- appropriately sized supplies (for example, gowns, blood pressure cuffs, needles)
- the physical environment (for example, doorways, passageways, increased floor space)
- Training of staff in the management of patients with bariatric care needs and the use of bariatric equipment.[435, 437, 438, 443-446]

Assessment of an individual patient's bariatric care needs during pre-surgical work-up will determine whether the procedure needs to be carried out in a centre specifically equipped for the management of patients with Class III obesity (BMI≥40kg/m^2) with suitably modified equipment, or if care can be provided in a Model 3 hospital with standard equipment.

1.1.1.3 Acute surgical care episode

Should a decision be made to develop a metabolic surgery programme, consideration should be given to the potential for surgery to be delivered in each RHA in order to provide national coverage. Greater coverage would be important to reduce inequities related to geographic inaccessibility which may be a barrier to metabolic surgery uptake and in particular regular engagement with long-term follow-up care for patients living in poorly serviced areas.

There is limited international evidence on the optimal organisation of service delivery for metabolic surgery patients. With consideration to the volume of patients in need of treatment and requirements for lifelong follow-up the hub-and-spoke organisation design may be appropriate.[447, 448] The network could include "hubs" which offer a full range of services, complemented by secondary establishments or "spokes" which offer more limited services. It is assumed that, if appropriately resourced, existing Model 4 hospitals that act as tertiary referral sites for the bariatric programme (that is, Ireland East Hospital Group (St. Columcille's Hospital/St. Vincent's University Hospital) and University Hospital Galway) would also be suitable sites for the provision of metabolic surgery as they currently provide consultant-led multidisciplinary weight management services and are equipped to manage patients with more complex needs.

However, screened surgical candidates are currently waiting a minimum of four years for access to bariatric surgery services due to lack of resources both in terms of specialist staff and access to theatre space in these hospitals.[230] This includes potentially competing for acute surgical resources with other medical specialties such as oncology and emergency services which must take priority. This has presented a challenge for timely access to scheduled care such as bariatric surgery. It would be important that a metabolic surgery programme does not exacerbate current waiting lists for bariatric surgery candidates.

Given the existing challenges within Model 4 hospitals, if a decision were made to proceed with a metabolic surgery programme, consideration could be given to the establishment of additional sites using existing infrastructure at Model 3 hospitals within each RHA which are appropriately resourced with respect to the relevant MDT specialities.

7.3.1.1 Post-operative care

Short-term follow-up

Should a decision be made to implement a metabolic surgery programme, it is assumed that the surgical follow-up care would be consistent with the current standard of care for patients following bariatric surgery comprising hospital-based specialist dietetic and surgical follow-up at six weeks, 12 weeks, six months and 12 months post-surgery. The frequency of follow-up may be adapted according to the procedure performed, severity of co-morbidities and the needs of an individual patient.

Consistent with the international literature, it is assumed that the core MDT would assess whether input from other disciplines (for example clinical psychology or physiotherapy) is required with access provided, where appropriate.[449, 450] The level of support needed is likely to vary dependent on the individual patient and surgical procedure undertaken (for example, more complex procedures such as biliopancreatic diversion with duodenal switch). Based on expert opinion, approximately 30% of patients accessing bariatric surgery in Ireland at present require additional specialist post-operative dietetic support for six weeks post-surgery. It is likely that a similar proportion of patients undergoing metabolic surgery will require additional nutritional support to assist them in adapting to behavioural changes post-surgery. Resource requirements will be dependent on demand for these services.

Once discharged from hospital, while under the care of the surgical MDT, it is assumed that patients would continue to have their diabetes managed in primary care by their GP. Consistent with best practice, it is assumed that there would be close communication between the surgical MDT and GP, particularly with respect to any ongoing monitoring that is required, the management of complications that arise and when and how to escalate care .[450]

UK NICE guidelines recommend that patients remain under specialist surgical care for two years post-surgery, prior to discharge to primary care under a shared model of care for chronic disease management.[450, 451] In the Netherlands patients may remain under the care of the surgical MDT for up to five years post-surgery.[449] Patients with a higher risk of metabolic and biochemical complications or who undergo higher risk surgical procedures (for example, biliopancreatic diversion with duodenal switch) may require lifelong follow-up in the specialist centre. The timing of discharge from the metabolic surgery unit, where appropriate, should be considered carefully as discharge could coincide with weight regain or relapse of T2D

and thus happen at a time when more intensive support is required. Best practice guidelines recommend that patients should only be discharged from specialist care if glycaemic status is stable on the advised treatment regimen (that is, pharmacological, dietary and exercise).[450]

Medium- to long-term follow-up

A national metabolic surgery programme, if established, should consider how patients will be provided with access to ongoing support to promote long-term adherence to necessary behavioural changes so to achieve optimal patient outcomes. With consideration to the accumulating number of patients with a history of metabolic surgery that will require long-term follow-up care, it is important that long-term care can be delivered outside of acute hospital-based services for appropriately risk-stratified patients to ensure that care is provided at the lowest level of acuity necessary. This would help to ensure ongoing capacity within hospital services to treat new patients and support the sustainability of the programme.[452] This said, it is recognised that some patients with complex needs may require higher levels of support from the metabolic surgery MDT in Model 4 services in the medium- to long-term.[431]

In contrast to many patients accessing bariatric surgery services, as outlined in Section 7.2, patients with T2D who are medical card or GP visit card holders have the option to be enrolled in the HSE's Chronic Disease Management Programme. The Chronic Disease Management Programme includes access to two dedicated appointments per annum specific to the management of their T2D. Therefore, for this cohort of patients there would be an opportunity to integrate post-surgical follow-up care with existing consultations to reduce the burden on patients and providers.

While there is agreement in the international literature that a shared model of care should be used for the long-term follow-up of patients with a history of metabolic surgery, the optimal organisation of the pathway is uncertain.[431, 450] O'Kane et al. proposes four shared models of care to support long-term follow-up of patients with a history of metabolic/bariatric surgery (Table 7.2).[450]

Common elements between each model of care include:

- provision of a discharge summary with a long-term follow-up plan involving all appropriate healthcare professionals
- an annual review
- ongoing communication between levels of care

- the ability for a GP to refer back to a specialist centre
- submission of follow-up data to a national registry.

Should a metabolic surgery programme be established, different models may be implemented within and between regions in Ireland with consideration to regional variation in access to and demand for services or an individual patient's needs. In all the models, the specialist MDTs may be co-located at the original metabolic surgical unit or the MDT may provide the long term follow-up at affiliated regional hospitals. Clearly defined protocols outlining provider responsibilities, protocols for information exchange between levels of care and escalation of care would be required to facilitate coordinated care transitions and reduce inappropriate variation in practice.

Loss to follow-up is noted as a considerable challenge, particularly two years post-surgery.[449] Delivery of care closer to home would likely increase engagement by removing barriers associated with travel or time off work. Achieving and maintaining competency in the management of patients with a history of metabolic surgery including micronutrient monitoring, screening for post-surgical complications and monitoring for decreased effectiveness of medications due to changes in drug pharmacokinetics (that is, how a drug is affected as it moves through the body) may be challenging in the context of low patient volumes in primary care and lack of specialist training.[449, 453, 454] At present, there are no specific services to support GPs to undertake long-term follow-up care of post-metabolic surgery patients. Discharge of patients from hospital services to primary care would be dependent on adequate resourcing of community services to support GPs, bidirectional communication channels between levels of care, establishment of criteria requiring referral back to specialist services and appropriate governance frameworks. While a number of proposed shared care models (Table 7.2) could result in an increased workload for GPs (for example, preparation for annual reviews, extended consultation times and updating the patient record), it should be noted that the number of metabolic surgery patients per GP practice would be very low. These increased care requirements may be offset by reductions in health service utilisation related to T2D-related complications in patients with a history of metabolic surgery owing to improvements in glycaemic control.

In primary care, the patient is responsible for the cost of the appointment unless the patient has a Medical Card or GP Visit Card. System changes resulting in the reorganisation of care from hospital to primary care settings may have financial implications for patients not currently eligible to be managed as part of the Chronic Disease Management Programme due to out-of-pocket expenses associated with GP visits. Out-of-pockets expenses for some patients may contribute to poor compliance

with follow-up care and adverse health outcomes. Other financial barriers to engagement with long-term follow-up care may include the cost associated with vitamin and mineral supplementation which may contribute to poor adherence in the long-term. Consideration could be given to mechanisms to provide vitamin and mineral supplementation for patients with T2D with a history of metabolic surgery for whom cost represents a significant barrier.

Hospital-centric post-operative follow-up is not designed to meet the demands of patients with immediate concerns or requiring a greater level of support. Routine access to dietetic support in the community may decrease avoidable readmissions secondary to dehydration and malnutrition.[449] Potentially avoidable emergency department visits following bariatric/metabolic surgery have been shown to represent a significant course of inefficient resource use and excess healthcare spending in other countries.[455-457] While capacity building within the community to support patients in adapting to behavioural changes post-surgery will be associated with additional investment, this may be offset by a reduction in requirements for emergency department and secondary care attendance.

Situations may arise where shared care arrangements cannot be agreed or where problems have arisen within the agreement with the potential for the safety and quality of patient care to be adversely affected (for example, staff shortages in primary or community care). In those case, the responsibility for the patient's management including monitoring and prescribing should remain with the specialist service until discharge is considered appropriate.

Table 7.2 Proposed shared models of care for medium- to long-term follow-up of metabolic surgery patients

Description	Patient roles and responsibilities	GP roles and responsibilities	Specialist service roles and responsibilities	Surgical team roles and responsibilities
Model 1: Shared care between GP and specialist services (supported transfer of follow-up)				
▪ The patient's condition is stable ▪ Follow-up is shared between the GP and specialist centre ▪ Annual review undertaken in a specialist centre ▪ Capacity for annual review would need to be factored into the staffing of specialist centres	▪ Involved in the discharge decision and agree to the shared care arrangement ▪ Agree to adhere to lifelong behavioural changes ▪ Attend follow-up appointments with specialist team and GP ▪ Inform GP and specialist team of plans to relocate so that care can be transferred	▪ Carry out annual check-up including HbA1c, weight, blood tests and screening for complications ▪ Refer the patient back to the community or hospital-based specialist services if any new complications are identified	▪ Carry out an annual review including nutritional status, psychological health and any other complications identified by the GP or patient ▪ Provide additional support when requested by the GP ▪ Inform the GP if the patient does not attend appointments	▪ Provide the GP with a discharge summary including most recent results, any complications, changes to medications, requirements for and guidance on the interpretation of blood tests, nutritional supplements and details of the community specialist service care which care is being shared ▪ Send discharge summary to the community specialist services ▪ Outline details of complications that should trigger referral back to the metabolic surgery service
Model 2: GP follow-up supported by specialist services (transfer of follow-up)				
▪ Patient's condition is stable ▪ Follow-up by the GP only ▪ The GP refers the patients for an annual nutritional review with a dietician	▪ Involved in the discharge decision and agree to the shared care arrangement ▪ Agree to adhere to behavioural lifestyle changes ▪ Engage with an annual specialist nutritional review ▪ Inform GP and specialist team of plans to relocate so that care can be transferred	▪ Carry out annual check-up including HbA1c, weight, blood tests and screening for complications ▪ Refer the patient back to the community or hospital-based specialist services if any new complications are identified ▪	▪ Provide the GP with a protocol for annual review including psychological health and screening for complications ▪ Perform an annual review of the patient's dietary and nutritional intake ▪ Provide additional support when requested by the GP ▪ Inform the GP if the patient does not attend appointments	▪ Provide the GP with a discharge summary including most recent results, any complications, changes to medications, requirements for and guidance on the interpretation of blood tests, nutritional supplements and details of the community specialist service care to be contacted for specialist support ▪ Send discharge summary to the community specialist services ▪ Outline details of complications that should trigger referral back to the metabolic surgery service

Model 3: Joint appointments in primary care (integrated follow-up)				
▪ Joint follow-up by specialists and GP in the community ▪ Capacity for annual review would need to be factored into the staffing of specialist centres	▪ Involved in the discharge decision and agree to the shared care arrangement ▪ Agree to adhere to lifelong behavioural changes ▪ Attend joint follow-up appointments with specialist team and GP when arranged ▪ Inform GP and specialist team of plans to relocate so that care can be transferred	▪ Organise required blood tests prior to the joint annual review with a specialist ▪ Refer the patient back to the community or hospital-based specialist services if any new complications are identified ▪	▪ Arrange for specialist staff (a dietitian, specialist nurse or physician) to perform an annual review of the patient jointly with GP in a community setting including annual blood tests, weight, review of comorbidities, nutritional status, psychological health and any other complications ▪ Provide additional support when requested by the GP	▪ Provide the GP with a discharge summary including most recent results, any complications, changes to medications, requirements for and guidance on the interpretation of blood tests, nutritional supplements and details of the community specialist service with which care is being shared ▪ Send discharge summary to the community specialist services ▪ Outline details of complications that should trigger referral back to the metabolic surgery service
Model 4: Specialist follow-up				
▪ Follow-up with specialist team ▪ Capacity for annual review would need to be factored into the staffing of specialist centres	▪ Involved in the discharge decision and agree to the shared care arrangement ▪ Agree to adhere to lifelong behavioural changes ▪ Attend follow-up appointments with specialist team ▪ Inform the GP and specialist team of plans to relocate so that care can be transferred	▪ Continue to review T2D status as part of chronic disease management (HbAc1, monitoring micro- and macro-vascular complications) ▪ Refer the patient back to the community or hospital-based specialist services if any new complications are identified	▪ Perform an annual review that includes blood tests, weight, assessment of nutritional status, psychological health and any other complications identified by the patient or GP ▪ Provide additional support when requested by the GP	▪ If the specialist service is not located in the metabolic surgery unit, provide the specialist service with a discharge summary including the most recent results, any complications, changes to medications, requirements for blood tests and nutritional supplements ▪ Provide the GP with a discharge summary (blood tests and nutritional supplements for information only) ▪ Outline details of complications that should trigger referral back to the metabolic surgery unit

Key: GP – general practitioner; HbA1c – glycated haemoglobin; T2D - type 2 diabetes.
Proposed models of care adapted from O'Kane et al.[450] 'Guidelines for the follow-up of patients undergoing bariatric surgery'.

Support groups

Group sessions supervised by a healthcare professional may also be used to provide effective and efficient support to patients outside of scheduled appointments. Where provided, consideration could be given to combining group support sessions for bariatric and metabolic surgery patients, particularly in regions where demand for services is lower.

In the absence of guided support groups, patients will likely use online resources to address unmet information needs which may not be in line with best practice or individualised to a patient's specific needs.

Biochemical monitoring and nutritional supplementation

It is recommended that blood tests are carried out at three, six and 12 months post-operatively in the first year, and annually thereafter.[442, 458] The type and frequency of nutritional monitoring and supplementation may need to be individualised following malabsorptive procedures or if the patient reports signs/symptoms suggestive of deficiency.[102, 442, 452, 459]

Monitoring for micronutrient deficiencies could be aligned with monitoring of HbA1c and other cardiometabolic markers as part of standard T2D care after the first post-operative year. If a metabolic surgery programme is implemented, consideration should be given to how support will be provided to GPs for interpretation of results of non-routine biochemical monitoring, including the treatment strategy to correct nutritional deficiencies (for example, guidance documents tailored to the information needs of GPs).

Skinfold removal surgery

For patients who undergo metabolic or bariatric surgery, consideration must be given to referral to a plastic surgeon for patients with clinically-significant redundant skinfolds once weight loss has stabilised. Such skinfolds impact quality-of-life (both psychosocial and physical burden) and are associated with a risk of infection.[419]

Data from the 2019 annual report from SOReg indicate that the probability of plastic surgery increases with increased weight loss post-operatively.[390] In patients with percentage total weight loss over 40%, almost half of the patients underwent plastic surgery at ten years' follow-up. Of note, the mean pre-operative BMI of patients presenting for metabolic surgery may be lower compared with the pre-operative BMI of patients presenting for bariatric surgery,[17] as a consequence the need for skinfold removal surgery may be lower when compared with patients accessing

bariatric surgery services. Requirements for plastic surgery will therefore likely vary depending on the characteristics of the patient cohort, and may vary between specialist centres and regional hospitals.

Surveillance

LSG may be associated with an increased risk of developing de novo Barrett's Oesophagus post-operatively relative to LRYGB.[460] However, the risk of progression to upper gastrointestinal malignancy in this population remains unclear.[460] With increasing use of LSG in Ireland and internationally, consideration should be given to the possibility of requirements for endoscopic surveillance for patients considered at risk of developing Barrett's Oesophagus post-operatively. A recent position statement from the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) recommended a single screening endoscopy one year post-operatively following LSG, and subsequently every two to three years, depending on the outcome of the initial surveillance test.[460] While efforts are underway to reduce waiting lists for endoscopy in Ireland,[461] potential requirements for endoscopic surveillance for patients post-LSG may need to be factored into projected service demands.

Bariatric surgery has been noted as a risk factor for reduced bone mineral density.[314] Where there is a clinical concern that a patient may be at risk of or experiencing loss of bone mineral density, diagnostics such as a DEXA scan could be considered to assess whether specific intervention is required.

Medical tourism

Medical tourism can present a significant challenge for healthcare services. Patients who seek privately-funded elective surgery abroad may do so on the basis of self-referral. Challenges may therefore arise if complications occur following their return to Ireland or with respect to the post-operative monitoring requirements. While there is evidence that Irish residents are availing of bariatric surgery abroad, no information is available on the indication for surgery (that is, weight loss or T2D control), the treatment pathway (for example, referral mechanisms or long-term follow-up) or the extent to which those travelling would meet the eligibility criteria for bariatric/metabolic surgery in Ireland.

Based on evidence of superior clinical effectiveness and safety, and surgical expertise in Ireland, a metabolic surgery programme would comprise LRYGB and LSG. Patients accessing care abroad may undergo less effective procedures such as LAGB, which has been associated with an increased risk of procedure-specific post-operative complications, including band slippage and band erosion. Patients who

previously accessed care abroad may not have access to follow-up care abroad, but also are not under the care of a MDT in Ireland during follow-up. Consequently, patients with post-surgical complications following surgery abroad present at Irish emergency departments which impacts existing limited resources. As highlighted in Chapter 6, provision of a metabolic surgery programme in Ireland would be a cost-effective use of resources. A decision to resource such a programme would also help to ensure that eligible patients would have timely access to safe and effective care that is appropriate to their needs, and consistent with best practice in terms of both the procedure provided and the necessary follow-up care.

7.4 Resource requirements

While the incremental budget impact of a metabolic surgery programme was outlined in Chapter 6, the purpose of this section is to provide details of the specific resources that were considered and that would be necessary for the delivery of a comprehensive programme. Consistent with the budget impact analysis, the resource requirements have been developed based on an assumption of 200 new patients undergoing metabolic surgery each year, with the requirements for post-operative long-term follow-up and monitoring accruing accordingly. Additional infrastructural requirements such as operating theatres were not factored into the budget impact analysis based on the assumption that, nationally the additional procedures could be performed within the existing physical infrastructure. However, that assumption is contingent on services being reorganised to facilitate introduction of metabolic surgery services at additional hospital sites. In the event that additional operating theatre capacity is not available at other hospital sites, it may be necessary to consider building additional surgical theatre capacity to ensure timely access and minimise disruption to other services.

7.4.1 Staff

In planning the implementation of a metabolic surgery programme, the availability of trained specialist staff would need to be considered. Staff shortages may represent a capacity constraint with regard to both access to the initial surgery and the provision of adequate follow-up care. Shifting of follow-up care from acute hospital services to community settings may require expansion of the specialist workforce to compensate for loss of economies of scale. Table 7.3 summarises the estimated acute hospital service resource requirements to support a metabolic surgery programme. These services are disaggregated into scheduled and unscheduled care and by the components of the care pathway.

As outlined in Chapter 6, it is assumed that, approximately 85% of patients referred for pre-surgical MDT assessment will be both suitable for and consent to surgery. Therefore to identify 200 surgical candidates, approximately 235 patients would require pre-surgical MDT assessment. Assuming that an MDT assessment would comprise two hours total time per patient, this would equate to an estimated total of 470 hours of pre-surgical MDT assessment. The surgical MDT assessment would comprise individual review by a surgeon, an endocrinologist, a dietitian and where appropriate and clinically indicated, a psychologist. Sites may differ in how this is provided, whether all assessments for a patient occur as part of a single outpatient visit or if the components of the assessment are delivered sequentially by the different disciplines within the MDT. The process will likely to be influenced by local capacity and practice arrangements. The number of patients progressing from pre-surgical assessment to surgery will be dependent on the availability of clear referral criteria.

With respect to acute surgical care, consideration must be given to the resource requirements for the primary procedure as well as potential requirements for revision surgery and skin-fold removal surgery. Depending on the specific procedure, two to three surgeries per day may be conducted by a surgeon at a single site. Resource requirements are presented at a programme level as the level of surgical activity at a given centre will be dependent on regional demand, existing surgical capacity and the availability of designated capacity for elective surgical patients. A national programme operating across multiple sites would require surgical theatre and recovery facilities access for two days per week for an estimated 40 weeks per year in order to carry out 200 procedures annually. Based on the systematic review of clinical effectiveness (Chapter 4) it was assumed mean length of stay would be two days, therefore equating to 400 surgical bed days per annum. In the longer term, capacity for revision surgery would need to be factored into the overall level of surgical activity (Table 7.3). Additional staff resources would be required to support this level of activity. Based on resource requirements for the bariatric surgery service operating in St Vincent's University Hospital, healthcare staff resource requirements for the acute surgical care of 200 patients under a national metabolic surgery programme are presented in Table 7.4 below. Additional support staff, such as porters, will also be required. However, the extent to which new staff would be required will depend on the volume of operations carried out at a given hospital site, the skills mix and existing capacity at that site. Specific staffing requirements will need to be determined at a hospital or hospital group level. Requirements for endocrinology expertise may be underestimated as requirements would be greater in a metabolic surgery programme.

Access to operating theatres would be required to treat emergent post-surgical complications. Based on data from SOReg, severe complications requiring re-intervention and cholecystectomy are estimated to occur in 3% and 4% of patients post-surgery, respectively.[380, 390] Requirements for surgery to remove excess skin-folds are likely to vary according to the degree of weight loss.[390] Following implementation of a metabolic surgery programme, requirements for plastic surgery are unlikely to be necessary for two years to allow sufficient time for weight loss and weight stabilisation post-surgery.

As outlined in Section 7.3.1.4, it was assumed that patients would receive four hospital-based specialist dietetic and surgical outpatient follow-up visits at six weeks, 12 weeks, six months and 12 months post-surgery. While local arrangements may differ, assuming 200 surgical patients, this would equate to 800 outpatient surgical MDT appointments (or 800 hours) if the patient were to see all members of the team at a single OPD appointment. Additional nutritional support provided by a specialist dietitian may be necessary for some patients in the early post-operative period. An estimated additional 200 surgical MDT outpatient appointments would be necessary for the annual review of patients in their second year post-surgery. When developing a metabolic surgery programme, consideration must be given to the length of MDT follow-up required for a typical patient. Capacity for annual review for a growing cohort would need to be factored into the staffing of specialist centres if appropriately risk-stratified patients are not discharged to primary care.

For patients post-metabolic surgery, access to community supports may facilitate optimal patient outcomes and reduce unplanned healthcare utilisation (for example, emergency department visits). Staffing requirements of ambulatory care hubs would need to be proportionate to local population needs. However, it is not possible to estimate population needs at a local level in the absence of robust national level data regarding the burden of disease. Therefore, in the event of a metabolic surgery programme being established, service roll out may need be carried out on a phased basis to determine demand for services and identify any needs for organisational restructuring.

Table 7.3 Estimated acute hospital service resource requirements to support a metabolic surgery programme

Component of care pathway	Patients (n)	Staff resources	Assumptions	Capacity requirements
Scheduled care				
Pre-surgical assessment	235	Surgeon, endocrinologist, dietitian, psychologist	▪ Assume MDT assessment occurs during a single 2-hour patient visit ▪ Assume 85% of referrals for MDT assessment are surgical candidates[422]	▪ 235 surgical MDT outpatient consultations (470 hours)
Peri-operative care	200	Surgeon, specialist nursing staff	▪ 2 to 3 surgeries per day (equating to 2 days per week, for 40 weeks assuming all surgeries at a single hospital site) ▪ Mean LOS: 2 days ▪ Approximately 2% of patients may require revision surgery in the medium- to long-term. Revision surgeries should be considered in overall capacity after year one	▪ Theatre access for 200 procedures (approximately 80 theatre days) 400 surgical bed days
MDT follow-up	200†	Surgeon, dietitian, psychologist	▪ Follow-up at 6 weeks, 12 weeks, 6 months and 12 months ▪ Assume MDT assessment occurs during a single patient visit	▪ 800 surgical MDT outpatient visits in year one
Additional nutritional support	60	Dietitian	▪ Assume 30% require additional nutritional support post-surgery comprising 1 consultation per week for 6 weeks post-surgery	▪ 360 outpatient dietician visits
Unscheduled care				
Readmission	12	ED staff; specialist nursing staff	▪ Assume 5-6% of patients require readmission[380] ▪ LOS dependent on severity of complications	▪ 10-12 readmissions per cohort of 200 surgical patients. LOS dependent on the severity of the complication
Post-surgical complications requiring reoperation	6	Surgeon; specialist nursing staff	▪ 3% of patient have a severe complication requiring re-intervention (Clavien-Dindo>3b)‡[380]	▪ Estimated additional 2 days of access to surgical theatre per annum ▪ LOS dependent on complication severity/ clinical condition of the patient
Cholecystectomy	8	Surgeon; specialist nursing staff	▪ Up to 4% of patients require cholecystectomy during long-term follow-up[390]	▪ Estimated additional 2-3 days theatre time for reoperation per annum ▪ LOS dependent on complication severity/ clinical condition of the patient

Revision surgery	4	Surgeon; specialist nursing staff	▪ Approximately 2% of patients undergoing LRYGB or LSG require revision surgery(381)	▪ Estimated additional 1-2 days theatre time for reoperation per annum ▪ LOS dependent on complication severity/ clinical condition of the patient
Community care				
Long-term specialist follow-up	200†	Dietitian, psychologist	▪ Community-based long-term follow-up care should be available for all patients	▪ Long-term follow-up may be provided in the community for the majority of patients
Primary care	200†	GP; practice nurse	▪ Assumed that patients will visit the GP 2 to 4 times per year, depending on T2D control ▪ Blood tests will be required to monitor HbA1c, cardiovascular risk factors and micronutrient status	▪ 400 to 800 GP consultations per year per cohort of 200 patients ▪ Blood tests twice per year, or as required

Key: ED – emergency department; GP – general practitioner; LOS – length of stay; LRYGB – laparoscopic Roux-en-Y gastric bypass; LSG – laparoscopic sleeve gastrectomy; MDT – multidisciplinary team.
† Estimated patient numbers during year one. The size of the cohort requiring MDT follow-up, long-term specialist follow-up and access to primary care will increase over time.
‡ The Clavien-Dindo system is used to grade the severity of post-surgical complications, consisting of 5 severity grades based on the therapy used to treat the complication. A grade IIIb complication is defined as "Intervention under general anaesthesia".(462)

Table 7.4 Estimated staff resource requirements for a National Metabolic Surgery Programme

Healthcare staff resources	Whole-time equivalent
Consultant bariatric/metabolic surgeon	3.0
Consultant anaesthetist	1.0
Consultant plastic surgeon	1.5
Consultant endocrinologist	1.5
Theatre nurse	3.0
Staff nurse	3.0
Bariatric clinical nurse specialist	1.0
Dietitian	1.0

7.5 Patient and provider education

7.5.1 Physician-targeted interventions

Access to metabolic surgery for patients will be dependent on referral of patients with comorbid T2D and obesity from primary care or specialist services to MDTs for assessment. Provider knowledge and perceptions about metabolic surgery may affect the accessibility of such services to patients. Concerns regarding the management of long-term medical and surgical complications may represent a barrier to initial referral. Physician-targeted interventions would be needed to support penetration of metabolic surgery into the T2D clinical care pathway.

To facilitate learning and development, e-learning modules on the management of metabolic surgery patients could be developed and made accessible to other healthcare professionals who may come into contact with patients with a history of metabolic surgery (for example, emergency department staff, general practice nurses).

7.5.2 Patient education

In the population with T2D, self-management education and support interventions have been shown to result in improvements in glycaemic control in the short term.[463]

Patient-level perceived barriers could influence uptake of metabolic surgery which may include lack of awareness of the role of metabolic surgery in the treatment of

comorbid T2D and obesity and perceptions of metabolic surgery as an extreme treatment option or last resort.[433] Given evidence of the effectiveness of education and support interventions in the population with T2D,[463] consideration could be given to the development of educational interventions to promote acceptance of metabolic surgery as a valid treatment option among patients with comorbid T2D and obesity who would meet the criteria for surgery.

A list of reliable online resources should be identified and provided to patients to consult as part of their pre- and post-operative education to support patients in adhering to behavioural changes. Online education could improve patient engagement by minimising barriers such as time, distance and cost. Where more individualised advice is needed, consideration should be given to the provision of telephone or video consultations which may produce healthcare system benefits in terms of more prudent use of finite resources for face-to-face consultations. In developing education interventions consideration would need to be given to the integration of metabolic surgery educational interventions with existing education initiatives for the population with T2D.

Anti-hypertensive and diabetes-related medications may be stopped or dose-modified in the immediate post-operative period.[450] Other medications may also need dose modification due to changes in drug pharmacokinetics. During the post-operative period, patients would need clear, individualised guidance with respect to the reduction and/or cessation of their anti-hyperglycaemic or other medication(s) and should be provided with a glucose metre and test strips to facilitate self-monitoring of blood glucose prior to discharge post-surgery.

7.6 Quality Assurance

7.6.1 Key performance indicators

Should a metabolic surgery programme be established, consideration should be given to the development of key performance indicators (KPI). These would support its delivery through the collection of robust data to monitor outcomes and identify organisational challenges. The KPIs could encompass the patient experience, clinical outcomes (for example, mortality, post-surgical complications), organisational structures (for example, surgeon and institutional volumes) and processes (for example, length of time on the waiting list, proportion of referred patients considered surgical candidates, loss to follow-up). Standards of surgical practice specific to bariatric/metabolic surgery outlined by Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP) and the European

Accreditation Council for Bariatric Surgery (EAC-BS), may be used to inform the development of context-specific KPIs.[437, 464]

Outcomes of bariatric/metabolic surgery have been shown to be volume-dependent, with a general trend towards improved quality of care with higher surgical volumes.[437, 438, 465, 466] However, the minimum volume threshold is unclear and is likely more applicable to complex bariatric/metabolic surgery cases. While minimum volume requirements are recommended by some organisations;[435, 437, 464] guidance from BOMSS recognises that minimum volume requirements could represent a barrier to the establishment of new centres. While a volume-outcome relationship may exist under certain circumstances and might be important, volume requirements should consider the technical complexity of the particular surgery and the experience of the surgeon and MDT. Of note, monitoring of surgical outcomes should consider the surgical activity at a given hospital site. Comparison of surgical outcomes between surgical centres may not be appropriate in circumstances where surgical training or complex cases are directed towards specialist centres.

Revisions to the care pathway should be driven by a review of the programme's KPI's, identified needs within the Irish Healthcare system as well as changes in best practice guidelines.

7.6.2 Establishment of national disease registries

Ireland does not have a national register for diabetes. Without accurate information on the proportion of the population with comorbid diabetes and obesity, healthcare service planning is challenging. Consideration should be given to the establishment of a national diabetes register to support healthcare services planning and monitoring of epidemiological trends. Consideration should also be given to how such a national diabetes register could integrate with existing infrastructures, such as the Diabetic RetinaScreen IT infrastructure.

Should a national metabolic programme be established, consideration should be given to the establishment of a national metabolic surgery registry to monitor patient outcomes in order to inform and support quality assurance processes, and how such a register could be integrated with a national diabetes register. Hospitals currently carrying out bariatric surgery in Ireland submit data to the National Bariatric Surgery Register (NBSR) in the UK. However, submission of data to the NBSR is not mandatory and may therefore not include all cases.

Eighteen countries included in the IFSO 5th global registry report have a national bariatric surgery register, including nine European countries: Austria, Belgium, France, Italy, The Netherlands, Norway, Sweden, Turkey and The United

Kingdom.[99, 467] These data include patients with and without pre-operative T2D. There is no universally implemented set of common data elements to be recorded in bariatric surgery registries resulting in considerable variation in reporting standards in bariatric surgery registries internationally. Variables commonly reported across these 18 national registries (≥50% agreement) are outlined in Table 7.5 below. Consideration should be given to the variables recorded in other European registries and used in the IFSO global registry, to align with best practice, facilitate participation in future international collaborative studies and international benchmarking.[99, 467]

Table 7.5 Variables recorded in international bariatric surgery registries

Domain	Variable
Healthcare system	Healthcare institution/Hospital ID
Patient	Patient ID
	Date of birth
	Sex
Pre-operative assessment	Date of initial consultation
	Weight
	Height
	Comorbidities (including hypertension, type 2 diabetes, sleep apnoea, GERD, osteoarthritis, cardiovascular disease, liver disease, mobility, PCOS, depression)
	Blood tests including HbA1c and dyslipidaemia
	Risk of pulmonary embolism
	Smoking status
	History of bariatric surgery (including procedure type)
Surgery	Surgeon ID
	Pre-operative weight
	Date of operation and discharge
	Procedure type including surgical approach
	Details of other operations
Complications	Date of complication
	Timing of complication (e.g. peri-operative, post-operative, 30-days follow-up)
	Details of post-operative complication (e.g. gastrointestinal perforation, bleeding)†
	Requirements for re-admission
	Type of re-intervention including surgical approach
	Date of re-admission and discharge
	Patient discharge status (home or step-down facility)
Follow-up	Date of follow-up
	Weight
	Comorbidity status including medication requirements or medical treatment (e.g. hypertension, type 2 diabetes, sleep apnoea, GERD, osteoarthritis, cardiovascular disease, liver disease, mobility, PCOS, depression)
	Malnutrition including prescribed supplementation

Source: Apkinar 2021.[467]
† including classification of severity.

If established, it would be important that clear protocols are put in place regarding the responsibility for submission of data to the national registry (for example, the GP, community-based specialist services or the surgical MDT) to prevent duplicate or missing entries for patients transitioning between levels of care. Administrative support would likely be necessary to assist healthcare professionals in submitting data to the registry to reduce the risk of incomplete or missing data entries.

Similarly, if developed, it would be important that key stakeholders are involved in the development of the registry, so that it reflects the needs of policy-makers, clinicians, patients and researchers. The following aspects should be considered to ensure best use and sustainability of the registry:[449, 468]

- establishment of a governance structure for management of requests relating to registry-based studies or collaboration in a coordinated registry network or (for example independent steering committee, ethics committee, advisory board)
- establishment of a single contact point within the registry for handling data requests and data access conditions
- development of a policy for collaborations with external organisations, including, for example, policy for data sharing and data analysis and a publication policy
- establishment of a supportive function for ethical and legal aspects of collaborations such as ethical approval of registry-based studies or compliance with national and European legislation (for example, the European Union General Data Protection Regulation (EU GDPR))
- recruitment and training of staff for data coding and input
- provision of a scientific and technical function to support registry-based studies which may include support relating to data extraction, management and analysis
- development of processes for the identification of changes in evidenced-based practice requiring updates to measured process and outcome indicators
- frequent independent audit to monitor data quality.

7.7 Discussion

Translation of results from randomised controlled trials into clinical practice will be dependent on the provision of end-to-end care in settings accessible to patients. In the context of a potential national metabolic surgery programme, this may require reform of health service delivery in Ireland. Integrated care pathways are needed to optimise available resources and facilitate better coordination of care by providing healthcare services at the lowest appropriate level of complexity, with responsive, connected services, in line with the current HSE National Service Plan objectives and the Enhanced Community Care (ECC) programme.[428, 429]

In order for metabolic surgery to penetrate into the T2D clinical care pathways many conceptual and practical barriers would need to be addressed including misconceptions regarding the use of metabolic surgery as a last weight-loss intervention or a last resort, inadequate resourcing of community services and poor coordination of care between levels of care.

Four different shared care models have been proposed for consideration should a decision be taken to proceed with a national metabolic surgery programme. The optimal service delivery design would be dependent the resources available within the community to support GPs in undertaking long-term follow-up care in addition to the needs of an individual patient. Transfer of medium- to long-term follow-up care from hospital services to primary care may be associated with improved access and convenience for patients, [469] which may support engagement with long-term follow-up. However, in the absence of training and support, quality of care and health outcomes may be compromised if this care demands competencies beyond those routinely required of general practitioners.[470] Shifting the delivery of long-term follow-up care for patients with a history of metabolic surgery from acute hospital settings to the community as part of a shared model of care will raise challenges associated with the need for investment in community-based services, training of staff, the development of protocols outlining provider roles and responsibilities where care is shared between providers and clear criteria for referral, discharge and escalation of care. Without appropriate investment in community resources to support patient discharge from acute hospital services in the medium- to long-term, an imbalance will be created between an increasing number of patients requiring follow-up in the face of a stable number of clinicians and support staff in metabolic surgery units. This presents a risk to the sustainability of a high quality service. It would be important that KPIs relevant to all levels of care are identified and audited to identify and address any important risks to the quality of care.

An assessment of approaches to the organisation of bariatric surgery in England, France, Sweden and The Netherlands carried out by the Belgian Health Care Knowledge Centre (KCE) in Belgium reported that handover procedures from specialist follow-up to primary care can be heterogeneous, resulting in follow-up care that is insufficient or unsystematic. The assessment highlighted the need for collaborative working arrangements between healthcare professionals but also noted that given the additional burden associated with the lifelong follow-up of patients following surgery, GPs may feel insufficiently compensated for the time invested in the management of post-bariatric surgery patients.[449] High attrition rates have been reported during follow-up of bariatric surgery patients. Given that patients with comorbid T2D and obesity are already engaged with the healthcare system for their T2D management, the risk of attrition is likely to be lower in this population. Nonetheless, the aforementioned organisational challenges will need to be considered to ensure patient and physician satisfaction with a metabolic surgery programme, if implemented.

As noted, parallels can be drawn between bariatric and metabolic surgery pathways. It is important to consider the possibility of sharing resources with the bariatric surgery service which may produce efficiencies. While the primary indication for bariatric (weight loss) and metabolic surgery (T2D control) differs, many of the resource requirements between these pathways will be similar (for example, dietetics and psychology). Thus, sharing of resources would likely increase efficiency and reduce costs provided that organisational workflow is properly designed and adequately resourced to support both pathways.

In addition to organisational barriers, many conceptual barriers would need to be addressed to support penetration of metabolic surgery into the T2D clinical care pathway. Educational interventions directed towards both patients and providers may be necessary to address misconceptions regarding the use of metabolic surgery primarily as a weight-loss intervention or a last resort as these may contribute to a lack of health-seeking behaviours and reluctance to refer among patients and healthcare providers, respectively. Specific consideration would need to be given to the development of guidance oriented towards GPs on the management of patients with a history of metabolic surgery including monitoring for post-operative complications, guidance on the interpretation of blood tests, and the impact of metabolic surgery on the bioavailability and metabolism of oral drugs which may influence prescribing choices post-surgery.[453, 471]

Should a decision be made to implement a national metabolic surgery programme, it would be important to update the T2D clinical care pathway to include metabolic surgery to increase its visibility as an appropriate treatment option for patients with

comorbid T2D and obesity. Ongoing refinement of the care pathway would be needed with consideration to the organisational challenges relating to the specific roles and responsibilities of healthcare providers at each level of care identified during phased roll-out, changes to evidence-based criteria for referral and discharge and outcomes of KPI monitoring.

An important limitation of the evidence base for the systematic review of clinical effectiveness and safety must be considered (see Chapter 4). Although data from numerous RCTs suggest that metabolic surgery is more effective than best medical care alone, pharmacological treatments available at the time RCTs were conducted have been superseded by newer classes of pharmacological agents. While medication alone in comparison with metabolic surgery will likely be insufficient to produce long-term diabetes control and weight loss in all patients, the availability of more effective pharmacological treatment options may require reconsideration of treatment pathways including the sequence or timing of interventions, referral criteria, or the use of multimodal treatment strategies that may produce better outcomes by prolonging the benefits of surgery.[472, 473] T2D clinical care pathways will require ongoing refinement in line with changes in best practice recommendations and the evolving needs of service users and providers.

8 Ethical considerations

Key points

- In terms of the benefit-harm balance, the proposed metabolic surgical programme will result in a higher proportion of patients achieving treatment targets and a reduced risk of developing complications of T2D. The harms of surgery relate primarily to the significant dietary changes required post-surgery and the generally irreversible nature of the intervention.
- Patients may have unrealistic expectations regarding the outcome of the procedure and the impact it may have on their day to day life. The pre-operative assessment process will have to ensure that patients have a clear understanding of the purpose and impact of the intervention.
- The perception of T2D and obesity as issues of lifestyle could lead to stigma about the intervention that may create a reluctance to seek treatment. There is a risk of a perception that individuals have failed treatment.
- A metabolic surgery programme will have similar specialist resource requirements to bariatric surgery in terms of staff and facilities. There is a risk that the introduction of a metabolic surgery programme may reduce capacity for bariatric surgery, thereby creating inequities for candidates for bariatric surgery.
- The primary outcomes reported in clinical trials were intermediate outcomes of diabetes remission and reductions in HbA1c, rather than improved quality of life or long-term reduction in complications or mortality. However, despite the limited data available, the intervention is considered a cost-effective use of resources.

8.1 Overview

This chapter outlines the main ethical issues that should be considered in relation to the introduction of a metabolic surgery programme for the treatment of type 2 diabetes (T2D) in patients with obesity. The chapter content was developed broadly in line with the structure described in the European network of HTA (EUnetHTA) Core Model.[474] The ethical issues relating to a technology must be assessed with reference to the prevalent social and moral norms relevant to the technology, and also with respect to the technology assessment itself.

While governments have an obligation to protect the health and wellbeing of citizens, this must be achieved in a manner that is equitable, non-discriminatory, transparent, and, as far as possible, non-coercive. The moral value that societies attribute to the consequences of implementing a technology is affected by socio-political, cultural, legal, religious and economic differences. It must be also borne in mind that the balance of benefits and harms to individuals and the wider population may be viewed differently over time as a reflection of societal and cultural changes.

T2D is commonly associated with overweight and obesity, which contribute to the development of insulin resistance. Metabolic surgery is, in essence, bariatric surgery carried out with the intention of treating T2D. As such, this analysis will focus on metabolic surgery as directed at treating T2D rather than weight loss. However, as obesity is a critical risk factor for T2D and because bariatric surgery is more common, much of the available literature on ethical issues for this surgery relates to bariatric surgery and obesity rather than to T2D and its treatment.

8.2 Benefit-Harm balance

As reported in Chapter 2, T2D often goes undiagnosed for years as insulin resistance and the associated hyperglycaemia typically develop gradually over time. The impacts are often not severe enough in the early stages of the disease for affected individuals to notice any of the classic symptoms of diabetes. As a result, there is often a lengthy pre-diagnostic period during which patients may not experience T2D-related complications or the associated reduction in quality of life.

For diagnosed patients, there is a treatment burden associated with T2D and those with medically-treated T2D are at risk of hypoglycaemic events. Metabolic surgery is largely targeted at reducing T2D-related complications in the long-term as a result of short- or medium-term improvements in glycaemic control. Metabolic surgery may be seen as a drastic treatment option for patients who perceive their health to be good. Surgery is invasive and, as with any procedure, there is a risk of complications

which may be considered more harmful than the risks associated with best medical care. However, it should be noted that metabolic surgery is considered here as a treatment option for those with T2D who are above treatment targets despite best medical care. As such, the cohort who would be eligible for surgery will likely be experiencing reductions in quality of life due to treatment and or complications associated with T2D.

8.2.1 Benefits

The benefit of metabolic surgery is connected to the improvements in metabolic endpoints which may translate into a reduced risk of a broad range of T2D-related complications. Reduced complications will lead to improved quality of life and decreases in healthcare utilisation in the long-term, providing benefits to both the individual patient and to the wider healthcare system.

Metabolic surgery can also have positive effects on the household of the person undergoing surgical treatment. For example, it may encourage behaviour change by the whole household to support the person who underwent surgery. Furthermore, people with more severe complications of diabetes may require assistance in the activities of daily living either from a family member or other carer. The impact of surgery may defer or eliminate some of those severe complications to the extent that the need for supportive care is reduced or eliminated.

An important aspect of the medical treatment of T2D is the use of medication. The options available for treatment include oral and injectable agents. There is an inconvenience and the risk of injection-site reactions associated with injectable agents, which has implications for quality of life. One of the findings of the systematic review of clinical effectiveness was that metabolic surgery was associated with an increased proportion of patients moving from injectable treatments to oral or no treatment.

There is evidence that Irish patients currently go for bariatric surgery in the private system or abroad. It is not known if patients currently seek metabolic surgery (that is for the treatment of their type 2 diabetes) abroad; however, the following issues would also be relevant. Where patients access bariatric surgery abroad, it is often done without the support or involvement of clinicians in Ireland. For example, it may be sought for cosmetic reasons and without the knowledge of the patient's GP. Aside from concerns about the quality of care received, the patient may have limited or no follow-up care from the surgical team. Once they have returned to Ireland, they may require support from their GP who has not been provided with any information regarding their surgery or requirements for follow-up care. Any surgical

complications arising are likely to be treated in an Irish hospital, again in the absence of any records regarding the original procedure. By providing a metabolic surgery programme in Ireland, it may reduce the demand for treatment abroad, thereby ensuring that patients who meet the eligibility criteria for surgery can access this as part of an integrated programme that considers also the long-term follow-up and monitoring necessary for their optimal care.

Surgery may also have positive effect on other patients as, in the long-term, a reduction in healthcare utilisation associated with management of T2D-related complications could mean more resources will be available for the healthcare system.

8.2.2 Harms

Metabolic surgery requires almost instantaneous behavioural changes, particularly in terms of diet. As a consequence, metabolic surgery patients do not have an opportunity to introduce behavioural changes on a phased basis and, as mealtimes can have important influences on the structure of our daily lives and socialising, this can create challenging social situations for patients after surgery. Moreover, some procedures can lead to malabsorption and micronutrient depletion with associated consequences. While the impact of micronutrient depletion can be managed, it is an adverse consequence of surgery.

On a personal level, the enjoyment and comfort associated with food may be decreased due to the necessary dietary changes. Food and eating are phenomena with strong cultural value and may be integral to an individual's sense of self. Bariatric surgery may enforce changes in people's eating habits and preferences in profound ways that could be considered harmful.[475] However, the changes in eating habits may also ultimately be considered to be positive if linked to improvements in health-related behaviours and well-being.

As the surgical approach is fundamentally bariatric surgery, it is associated with weight loss that typically peaks 12 to 24 months after surgery. Weight loss can lead to body image issues for some patients that lose weight and have excess skinfolds post-surgery. If patients require access to plastic surgery to remove excess skin-folds where medically-indicated, a lack of access may contribute to suboptimal outcomes, particularly in terms of quality of life. Of note, patients included in the randomised controlled trials of metabolic surgery tended to have a lower baseline BMI than those undergoing bariatric surgery, and hence the need for skinfold removal may be limited.

Based on the evaluation of clinical effectiveness, the main surgical methods were considered equivalent in terms of reductions achieved in HbA1c and BMI. However, there are differences in the procedures in so far as some are considered reversible (for example, certain banding techniques), while other procedures are permanent. Reversibility appears to be a morally relevant difference, especially as surgery does not cure the condition, but rather improves glycaemic control.[475] Not all studies achieved statistically significant reductions in HbA1c, and patients failing to achieve a clinically significant improvement in their T2D status may regard reversibility as important. Patients who do not perceive direct benefits of surgery, but experience the marked impact on diet may feel that treatment reversal is preferable. The evaluation of clinical effectiveness indicated that improvements in HbA1c and BMI diminished over time, to the extent that eventually a patient may return to the same levels as if they had received best medical care. Again, a patient may, at that point, feel that reversal may be preferable. However, most RCTs showed substantial improvements in both HbA1c and BMI and only a very small proportion of patients might fail to achieve improvements in one or other marker. It is important to note that reversibility applies primarily to banding techniques, which were not included in the systematic review of clinical effectiveness or the model of cost-effectiveness, and may not achieve the same treatment effect as the included surgical techniques. Furthermore, like any procedure, reversal is not risk-free for the patient. The irreversibility of the procedure is unlikely to present significant ethical challenges as, based on bariatric surgery, only a minority of patients regret their decision to undergo surgery.[476, 477] A five-year post-operative telephone survey in Poland (n=104) found that only 3% of patients expressed dissatisfaction with their decision to undergo bariatric surgery.[477] However, inadequate access to skin-fold removal surgery may influence post-operative treatment satisfaction.[478] The potential for decision regret underscores the importance of informed consent pre-surgery, including realistic expectations, necessary behavioural adaptations, and potential harms.

Another issue related to the hidden or unintended consequences of metabolic surgery is that the threshold for eligibility may inadvertently become a goal for patients not meeting the eligibility criteria. For example, an individual may seek to increase their HbA1c or BMI to achieve eligibility, thereby exposing themselves to harm. It is important that access is based on clinical need with consideration to an individual patient's treatment targets, T2D history and comorbidities, rather than on generic criteria.

8.3 Autonomy

Autonomy is the right of individuals to make informed decisions about their own medical care. Respect for patient autonomy means that doctors have a duty to provide competent patients with the opportunity to make an informed decision about their medical treatment. Autonomy is the foundation for informed consent and requires competence and adequate information.

8.3.1 Informed consent

The issue of informed consent is shaped by the knowledge needed to understand the risks and the benefits of metabolic surgery. Low educational level or poor health literacy could affect the capability of some surgical candidates to properly understand all of the information, giving rise to unrealistic expectations and inadequate decision making.[479] It could be challenging to adequately inform patients about the risks, side-effects and expected consequences of surgery. Ensuring patients are fully informed is important because the intervention is not immediately lifesaving, is mostly irreversible, and the treatment requires the patient to permanently and significantly change their eating habits.[480] Expectations may be also guided by potentially unreliable or misleading information sources such as through the internet, television, and by word of mouth. Misplaced expectations may lead patients to overestimate the amount of weight loss anticipated after surgery and underestimate the duration and impact of the recovery phase.

The importance of ensuring that the patient has understood the implications of surgery implies the need for a careful assessment process before the decision to operate. The use of assessment clinics to determine the suitability of individuals for surgery should limit the risk of a patient misperceptions, although poor understanding may still lead to increased pressure for referral to the assessment clinics. For this reason, consideration should be given to how metabolic surgery would be publicised as a potential treatment and what information would be provided in a primary care and community setting to manage patient expectations and demand for referral. There may also be limited awareness among people with T2D about the purpose and potential of metabolic surgery. Patient education around the benefits of metabolic surgery for T2D treatment could lead to increases in demand for surgery beyond the realisable capacity within the system. It would be important for such patient education to foster realistic expectations about the extent of the programme and the lead in time from initial referral to assessment to surgery.

Information disclosure terminology and the choice of terms like “diabetes surgery”, “diabetes cure”, “metabolic surgery”, “diabetes remission”, “resolution” "lifestyle

diabetes", and “biochemical remission” are relevant and not without value. It could be the difference between informing patients that bariatric surgery is “diabetes treatment” to that it is a form of “enforced behavioural therapy” which can “require many years of psychiatric support in behaviour modification”, where exact indications and contraindications to surgery are not yet defined.(481)

It should be noted that bariatric surgery is already provided within the public and private healthcare systems in Ireland. While bariatric and metabolic surgery may be considered interchangeable terms, the latter implies that it is part of an overall treatment approach to T2D while the former is focused on weight reduction. The distinction becomes important in terms of the nature of follow-up care. A person with T2D that accesses bariatric surgery may not have their T2D status monitored under the assumption that it is a distinct issue, and hence they may receive disjointed care. Therefore, the role of a patient’s GP as the primary gate keeper to accessing care in the secondary care system is important to minimise the risk of disjointed care. Patient autonomy may be influenced by the marketing and attitudes of health professionals. Marketing may be widespread and does not necessarily give a balanced view of the benefits and harms of the surgery treatment and may also conflate bariatric and metabolic surgery. The role of healthcare personnel is also crucial as negative stereotypes can influence judgment and decision-making around patient care.(480)

8.3.2 Stigma

Stigma in relation to T2D comes mainly from obesity as T2D is frequently referred to as a “lifestyle disease”. It is related to the perception that obesity (one of the risk factors for T2D) is a choice under individual control and responsibility, so overweight or obesity are seen as a consequence of a lack of willpower or self-control. Conversely, biological, genetic and environmental factors may be overlooked despite being significant contributors to the development of T2D. As metabolic surgery may be considered where metabolic markers are above target, there may also be a perception that these are patients who have failed in their treatment, and that this may be due to poor adherence to treatment. It is important to acknowledge that not all therapies are effective or suitable for all individuals, and that where metabolic markers are above target, it may not be a reflection of the individual, but rather about finding the most appropriate treatment for that patient given their history, disease status, context and preferences.

On the other hand, bariatric surgery has been described as “surgically-induced starvation by malabsorption or gastric restriction” with social and aesthetic significance. The social perspective relates to the perceived lack of responsibility and

self-control. The aesthetic perspective relates to body image and weight, which are overt indicators. A rapid change in body weight may make surgical intervention evident to others. Bariatric surgery may therefore support stigmatisation. Weight bias and stigma can result in discrimination, and undermine human and social rights, and damage the health of afflicted individuals. People with obesity or overweight are vulnerable to stigma or discrimination that can cause physical and psychological problems and can affect social life, workplace, employment, education and relation within families. That a person has diabetes may not be evident. Having metabolic surgery may lead to weight changes that are apparent. Some patients may worry that such overt changes may draw attention and be mistakenly interpreted as bariatric rather than metabolic surgery.

Weight stigma arises from a variety of sources using incorrect and inaccurate language and imagery in relation to overweight and obesity. It can lead to a perception that individuals are solely responsible for their obesity. Furthermore, public health campaigns about obesity often underline the quality and value of prevention as a preferable option to treatments, such as pharmacotherapy or surgery, which are often considered more expensive.[482] Public health campaigns may frame prevention and treatment as mutually exclusive options, whereas they should be directed toward two distinct populations, with different needs.

The availability and promotion of metabolic surgery as a viable and effective treatment option may validate obesity as a medical issue needing surgical intervention. That is, perception may shift to appreciate that diet or pharmacological treatment may be insufficient and that it is a significant issue for which surgical intervention may be the best option for some individuals. A change in perception may lead to reduced stigma in relation to obesity and its treatment not just for patients with comorbid T2D but also more generally.

8.3.3 Psychological assessment

Due to the large number of people with comorbid T2D and obesity, the cohort would not be considered a particularly vulnerable population subgroup. However within this subgroup, there may be patients with mental health issues or socio-economically disadvantaged patients who may be at risk of poorer outcomes from surgery or at risk of being unjustly discriminated against. Psychiatric comorbidity could be relevant for some patients when assessing competence to consent and affect therefore decision-making autonomy. In this case, acquisition of a valid informed consent prior to surgery may be challenging due to a lack of information and understanding, reduced voluntariness, and diminished decision making capacity. Identification of patients for whom this could be an issue can readily be addressed as part of the

assessment process. However, protocols will be needed to determine how to resolve cases where informed consent could be an issue.

Psychological consultation prior to bariatric surgery plays a role in assisting patients to better prepare for surgery through multidisciplinary treatment planning. As such, inclusion of a mental health specialist with skill in evaluating patients and families may be warranted as part of preparation for metabolic surgery. The inclusion of the wider family may be important in ensuring that those living with the patient are prepared to provide the necessary support for the patient to adhere to the post-surgical diet. The MDT should explain the purpose, nature and method of the pre-surgical evaluation. If psychosocial assessment serves a gatekeeping function, ethical issues may arise if the assessment itself is perceived by patients as a form of coercion and the evidence of the role of psychosocial assessment as predictors of bariatric surgery outcome should be assessed.[480, 483] The psychological consultation can be useful to determine whether a patient may have psychiatric comorbidities that may impact on recovery or may be adversely impacted by the intervention. For example, if a patient has an underlying eating addiction, then there is a risk that post-surgery they may experience addiction transfer. Due to the dietary changes, the patient may no longer obtain comfort from food, and therefore they may substitute another type of addiction, such as gambling or alcohol.[484] However, the evidence in relation to addiction transfer is unclear.[484, 485] Psychological assessment can help identify whether supports need to be put in place post-surgery to reduce the risk of addiction transfer.

Despite the presence of psychiatric comorbidity, patients could be motivated to seek surgery to gain a sense of control over their medical problems and thereby improve psychological and quality-of-life. Some patients may feel that they gain control because surgery limits their choice and imposes control over their eating habits.

8.4 Respect for persons

As T2D is recognised as a chronic disease and patients eligible for metabolic surgery are already accessing medical treatment, the procedure does not overtly affect human dignity. However, patients may receive negative sentiment and experience stigmatisation due to a lack of knowledge about indications for metabolic surgery amongst the wider public. Stereotypes and prejudices result in discrimination directed at a person's appearance based on body weight. This raises the challenging question of whether bariatric surgery (in part) is the solution to a social problem of unsound attitudes toward people who are overweight or obese. The purpose of metabolic surgery is not to address appearance, but to treat T2D. However, that

distinction may not be clear to the wider public and so patients could be subject to discrimination and prejudice associated with weight-loss surgery.

The use of strict eligibility criteria could be detrimental to integrity if it is associated with discouraging honesty. For example, patients may answer psychological screening questions in a way they believe will lead to them being considered eligible for surgery.

There is a potential for metabolic surgery giving rise to a conflict with religious beliefs. In individuals with T2D, fasting of any type may increase the risk of hypoglycaemia. Regular meals are important to maintain blood sugar control which may be difficult to achieve for patients wishing to practice religious fasting. Equally, the nature of the diet required post-surgery may make it challenging to fast. Arguably this applies equally to all people with T2D, irrespective of whether they undergo metabolic surgery or follow best medical care. Religious beliefs may also influence a patient's attitudes towards or acceptance of what they consider cosmetic surgery for removal of excess skinfolds. However, it is acknowledged that the typically lower BMI of patients undergoing metabolic surgery may mean that there is limited need for skinfold removal.

The provision of metabolic surgery may increase the attention on weight and the "obesity epidemic," and may contribute to the burden of being obese. When metabolic surgery has become an option, it may be harder to be obese by choice. That is, the implication will be that if someone with T2D cannot achieve lower weight through diet, then they should do so by surgery.

8.5 Justice and equity

Justice and equity are relevant principles of healthcare ethics, and the introduction of a new technology may influence the justness and equity of the healthcare system. Justice reflects the need for a fair and equal distribution and allocation of healthcare resources in society based on the fact that the resources are finite, the respect of individual rights, and the upholding of morally established and accepted laws.[486] While economic evaluation and the concept of cost-effectiveness explicitly consider efficient use of finite resources, this does not automatically imply equal or equitable use of those resources.

Obesity and T2D follow a socio-economic gradient such that the least well off are most likely to be obese and have T2D. Those with lower socio-economic status are also more likely to experience complications of diabetes.[487] Socio-economic differences in health and healthcare are often considered unjust, and unequal access to treatment of T2D and obesity is a justice and health inequality problem. Justice

also requires coherence of the healthcare system so that T2D and metabolic surgery are treated similarly to other relevantly comparable conditions and treatments.[480] Metabolic surgery is bariatric surgery directed at those with T2D, and therefore it may be considered to have similar ethical implications to bariatric surgery, which is currently provided in Ireland.

From an organisational point of view, there is no immediate change in the organisation of care for patients as they will continue to be monitored by their GP, even if they are in T2D remission. As patients who have undergone metabolic surgery require lifelong monitoring, the post-surgical follow-up in the secondary care setting will be analogous to that provided for patients undergoing bariatric surgery. Continuity of care must be provided for patients both during the immediate post-surgical period and over the longer term. While follow-up care may initially take place in the hospital, it will eventually have to transfer to the primary care or community setting. For patients discharged to their GP for ongoing monitoring, it is important that referral pathways exist for escalation of care if necessary.

In relation to equity, T2D is classified as a chronic disease and creates entitlement through the long-term illness scheme. Thus people with T2D can be divided into a hierarchy of those eligible for a medical card (entitled to GP visits and medications, free at the point of access), those with a GP visit card (entitled to GP visits free at the point of access), and those with neither. All have long-term illness scheme cover, which entitles the patient to certain drugs, medicines and approved appliances for free from their pharmacy. Any treatment pathway that involves additional GP visits or medications may therefore accrue costs to the patient where they do not have a medical or GP visit card, and be considered to introduce inequities.

There may be a variety of barriers that could limit access to metabolic surgery.[488] At present, some of the population accessing bariatric surgery may have T2D but, for a variety of reasons, they may be considered low priority for surgery on the basis of BMI alone. For example, strict inclusion criteria and guidelines may mean that patients with a higher BMI are given priority for surgery. Furthermore, a lack of awareness about metabolic surgery and its benefits for people with T2D may mean that some people with T2D may not seek information or consider it as a potential treatment. A lack of awareness may not be across the board, and may be concentrated in certain subgroups based on ethnicity, gender or age. However, the provision of metabolic surgery for T2D in ethnic minorities and those of lower socio-economic status could reduce inequalities and discrimination. It is important that if a metabolic surgery programme is introduced, that consideration is given to how information on it as a treatment option will be disseminated to people with T2D and ensure that information is available to all, irrespective of socioeconomic status,

ethnicity, gender or age. A lack of information or barriers to accessing surgery may result in some patients seeking treatment privately or abroad, which can create challenges for the quality and continuity of care.(489)

At present, while there is limited access to bariatric surgery within the publicly funded healthcare system, there is no formal bariatric surgery programme in Ireland. The introduction of a fully-funded metabolic surgery programme for patients with comorbid T2D and obesity could result in inequities in access. That is, a patient with a BMI of 35 Kg/m^2 and T2D may be able to access surgery sooner than a patient with a BMI of 35 Kg/m^2 of higher, but without T2D. While it may be possible to prioritise patients within a programme to ensure they are treated according to need, it is not possible across programmes. However, if the metabolic surgery programme is fully resourced to take place alongside bariatric surgery and not to reduce the capacity for bariatric surgery, then it should result in a net increase in access to surgery. Although not considered in this assessment, it cannot be assumed that the health benefits and cost-effectiveness of bariatric and metabolic surgery are equivalent.

A programme of metabolic surgery will involve the procedure being provided by a number of surgeons across a range of institutions. There may be a learning curve associated with metabolic surgery, such that a more experienced surgeon may be able to complete more operations per annum and may take on more complex cases. Similarly, there may be a volume-outcome relationship at both the surgeon and institutional level such that a higher volume of procedures is associated with improved outcomes. Risk related to the surgeon's experience and the institution's procedural volume, as well as perceived bias related to the surgeons' relationship with industry, is not always disclosed. Another point to note is that there are a number of procedures that come under the umbrella term of metabolic surgery. A specific surgeon or hospital may have a preference for one surgical approach over others, which may limit choice for patients. It may also mean that the type of surgery available may differ depending on where you live in the country.

8.6 Ethical consequences of the HTA

The main ethical consequences of the HTA itself primarily relate to equitable resource distribution and the timing of the assessment.

8.6.1 Implications of the HTA

A HTA gathers a broad range of evidence and provides an assessment of that evidence. The advice produced by the HTA provides a robust basis for decision-making regarding the introduction of a technology. The availability of a HTA can be

considered a detailed de facto business case which supports the development of an implementation plan and national roll-out of a service. The National Clinical Programme for Obesity does not have evidence from a HTA to support implementation of a bariatric surgery programme, and at present there is no defined programme. Having the support of a HTA means that a metabolic surgery programme may be better resourced, and therefore patients with obesity who do not have T2D may not get the same level of access to care. The main concern is that bariatric and metabolic surgery may be considered in competition with each other because of the overlap in resources required in terms of staff and theatre space. By increasing the volume of metabolic surgery, it may effectively reduce the capacity available for bariatric surgery unless additional staff are recruited and theatre capacity is made available or utilised. While more effective management of patients with T2D has wider benefits for healthcare resources, it may still displace care for patients awaiting bariatric surgery.

8.6.2 Timing of the HTA

A health technology assessment is an evaluation of the evidence available at a point in time. The timing of a HTA can have a number of consequences for the findings of the assessment. For example, the evidence for clinical effectiveness may be immature at the time of the assessment, of the technology itself may be evolving and not be entirely representative of the technology that will be used in the medium to long term.

The timing of this particular HTA is not unimportant. The randomised controlled trials used to determine the efficacy of metabolic surgery take years to design, recruit, run and report. For example, one of the largest trials included in the systematic review of clinical effectiveness and safety was registered with ClinicalTrials.gov in 2008.[278, 282, 288, 289] The trial included four sites that began recruiting between 2008 and 2011. The first publication, reporting 12 month follow-up data, was published in 2013. Subsequent publications reported two-year follow-up in 2015, three-year follow-up in 2016, and five-year follow-up in 2018. During that time period there were marked advances in the medications available to treat T2D such that the definition of best medical care had changed. For example, newer anti-hyperglycaemic agents have become available and more widely used, changing the profile of the effectiveness, risk of adverse events and cost of best medical care. From this one example it can be seen that the available evidence may be based on outdated practice, creating challenges for interpreting the applicability in light of current practice. It should also be noted that alternative surgical approaches may also be developed, which may offer benefits over the techniques used in the available trials.

Another significant aspect of the timing of a HTA is the duration of follow-up available for trial outcomes. Particularly for a chronic disease such as T2D, where the treatment is not considered curative, understanding the longer-term impact of a treatment can be critical. The short-term impact of an intervention on outcomes may bear little relation to the longer-term impact. In the case of T2D, changes in HbA1c and BMI can be considered as intermediate outcomes that are predictive of changes in quality of life, morbidity and mortality. However, the association with the outcomes of interest may be poorly understood or subject to substantial uncertainty. In the case of metabolic surgery, the uncertainty is compounded by the small sample sizes used in many of the studies. One trial has reported outcomes at 10 years, while the others have reported outcomes at five years or less. To account for the uncertainty in longer-term impact, the base-case analysis of the economic evaluation was reported based on ten year follow-up, but it was apparent that extrapolation to longer-term follow-up suggested that the intervention may be more cost-effective than estimated in the base-case analysis.

The timing of a HTA can also have significant implications for the estimated costs of treatment, particularly in relation to pharmacological agents. The costs associated with newer anti-hyperglycaemic medications may be high now, but are likely to decrease over time. The nature of the medications is also changing, with oral formulations planned for treatments that are currently only available in injectable form. Such a change will have implications for costs, but also for acceptability to patients. The design and efficacy of weight-loss medications are also changing, and treatments may become available in the short to medium term that will increase the effectiveness of pharmacological therapy, and therefore reduce the relative effectiveness of surgery.

Regarding the evidence generation, the absence in Ireland of a registry data for T2D or metabolic surgery could be an ethical obstacle in terms of monitoring safety outcomes. Metabolic surgery has been shown in numerous RCTs to be significantly more effective than best medical care. It could be considered unethical to withhold a therapy proven to be clinically and cost-effective from research subjects with a serious medical condition. Future RCTs may therefore not be considered ethical, however evidence gaps remain in relation to the long-term outcomes of metabolic surgery. As metabolic surgery is very effective, small sample sizes are sufficient to demonstrate efficacy. As a consequence, these trials are underpowered to detect differences in secondary and safety endpoints. Alternative study designs such as pragmatic RCTs or carefully controlled observational studies may be necessary to address research gaps. There are also limitations associated with alternative study designs as those who choose surgery may differ from those who do not in observational studies. The data recorded in observational studies may not include all

of the relevant confounders or characteristics needed to appropriately adjust analyses for differences in the case and control arms.

8.6.3 Outcomes considered in the HTA

The outcomes used in the economic model were influenced by the outcomes reported in the RCTs that were included in the systematic review of clinical effectiveness and safety. The trials had a focus on T2D remission, and changes in HbA1c and BMI as their primary outcomes. As already stated, these may be considered as intermediate outcomes and do not directly measure the impact of metabolic surgery on the quality or quantity of life of treated individuals. For the purposes of the economic model and to simplify the representation of the treatment pathways, patients were put into mutually exclusive disease states based on type of pharmacological treatment, and whether or not they had experienced a stroke or myocardial infarction. To recognise the differences in treatment, disutility values were applied to recognise the differing impacts on adverse events and quality of life associated with each treatment. These data did not come from the supporting RCTs but rather from a variety of sources. As health-related quality of life outcomes are infrequently recorded in RCTs, it is common practice to obtain utility data from a wide range of sources. While this may be viewed as a weakness, as is common practice, the utility values were subject to sensitivity analysis to determine the impact on the estimated cost-effectiveness of varying those values.

Another point to note is that recently, there have been changes in the approach to defining eligibility criteria for metabolic surgery away from being BMI-based towards a focus on clinical need. In this case, clinical need is determined by looking at a range of markers including HbA1c, cholesterol and blood pressure. While treatment targets are set for these markers, they are not intended for use as thresholds for eligibility. Consideration of metabolic surgery as a therapeutic option for an individual patient should be based on the individual patient's treatment targets. In the absence of detailed individual patient data, it was not feasible to create an individual-level microsimulation model that incorporated data on all of the relevant biomarkers. Instead, the model was focused on HbA1c and BMI as the key indicators that could impact on treatment decisions and quality of life.

8.7 Discussion

This chapter considered the ethical issues that might arise with the introduction of a metabolic surgery programme in Ireland for the treatment of patients with comorbid T2D and obesity.

In terms of the benefit-harm balance, the proposed surgical programme will result in patients moving to less intensive T2D therapy. The outcome of surgery is an increased likelihood of patients achieving target values for HbA1c, with an associated reduction in risk of developing complications of T2D. The harms of surgery relate primarily to the significant dietary changes required post-surgery and the generally irreversible nature of the intervention.

In relation to informed consent, there is a risk that patients will have unrealistic expectations regarding the outcome of the procedure and the impact it may have on their lifestyle. Metabolic surgery may also be conflated with bariatric surgery, with a consequent focus on weight loss rather than the treatment of T2D. The pre-operative assessment process will have to ensure that patients have a clear understanding of the purpose and impact of the intervention, as well as realistic expectations. The perception of T2D and obesity as issues of lifestyle could lead to stigma about the intervention that may create a reluctance to seek treatment.

The introduction of a metabolic surgery programme could be associated with concerns about equity. The programme would require similar resources to bariatric surgery in terms of staff and facilities, and may therefore reduce capacity for bariatric surgery. The availability of a HTA to support a decision regarding a metabolic surgery programme may be to the detriment of bariatric surgery, as there is no equivalent evidence review and cost-effectiveness analysis available.

Finally, the timing of the assessment impacts on the available data to evaluate the clinical effectiveness of the intervention. While a number of randomised controlled trials have been published, the sample sizes have been small and the duration of follow-up available has generally been limited. The primary outcomes recorded were also in relation to intermediate outcomes of diabetes remission and reductions in HbA1c, rather than improved quality of life or long-term reduction in complications or mortality. The landscape of treatment alternatives is also evolving such that the comparators used in the available trials may no longer fully reflect best medical care. However, despite the limited data available, the intervention has been shown in this report to be a cost-effective use of resources.

9 Discussion

9.1 Introduction

A health technology assessment (HTA) is intended to support evidence-based decision-making in regard to the most efficient use of resources in the healthcare system. The aim of this HTA was to establish the clinical, cost-effectiveness and budget impact of metabolic surgery compared with best medical care (typically, pharmacotherapy combined with a short-term behavioural intervention).

9.2 Interpretation of the evidence

Comorbid T2D and obesity are associated with multiple metabolic complications leading to increased morbidity, mortality, and financial burden for individuals and the healthcare system. Although a range of treatment options are available, T2D remains a leading cause of blindness, end-stage renal disease, lower limb amputation and cardiovascular disease.

Despite advances in pharmacological management in recent years, successful management of T2D remains an important challenge globally,[236] necessitating investigation of additional treatment options. Weight management is an integral part of T2D care. Weight loss can result in improvements in glycaemic control and reduce medication requirements in patients with T2D and overweight or obesity.[9] The traditional concept of reserving metabolic surgery for persons exceeding a certain BMI threshold is rapidly evolving.[7, 9] It is now known that bariatric surgery is associated with additional metabolic benefits beyond weight loss in patients with obesity-related comorbidities such as T2D, even at lower levels of obesity. Of note, treatment options and guidelines for the management of T2D are continuously evolving, with substantial ongoing innovation in this area. Data from the studies included in this review have consistently shown the superiority of metabolic surgery over best medical care alone as the most effective means of obtaining substantial and durable improvements in glycaemic control and weight loss in individuals with comorbid T2D and obesity. However, a notable limitation of these trials is that they pre-date the widespread use of a number of new, effective medication classes (Chapter 4) which may alter our understanding of the relative benefit of surgery.

While a considerable proportion of patients who initially enter T2D remission following metabolic surgery may relapse over time, the recurrent T2D is generally less severe in terms of HbA1c levels and medication requirements. That is, even in the setting of T2D relapse, a legacy effect may exist. Evidence from The Diabetes and Aging Study, the UK Prospective Diabetes Study (UKPDS) and the Steno-2 Study

indicate that the health benefits of a period of improved glycaemic control may have sustained beneficial effects in terms of the risk of T2D-related complications and mortality.[305, 306, 427]

The majority of the RCT evidence to support the effectiveness of metabolic surgery relates to reductions in BMI and improvements in HbA1c levels. HbA1c predicts the risk of microvascular and macrovascular outcomes in diabetes and is recognised by the European Medicines Association (EMA) and Food and Drug Administration (FDA) as a surrogate marker for preventing diabetes complications.[490] Data from high-quality RCTs regarding the impact of metabolic surgery on hard clinical endpoints are emerging.[168, 249] Evidence from one RCT suggests that the incidence of T2D-related complications is lower among metabolic surgery patients compared with best medical care at ten years' follow-up.[249] In a second RCT, metabolic surgery was more effective than best medical care at slowing or arresting decline towards end-stage kidney disease when compared with best medical care at two years' follow-up.[168] However, RCTs powered to detect hard clinical endpoints are lacking owing to the fact that only small sample sizes are required to detect the typical primary endpoints of change in HbA1c or T2D remission as a result of the expected large effect size. Consequently, the majority of the evidence base for the impact of surgery on hard clinical endpoints is derived from observational evidence. Long-term mortality analysis (mean follow-up 7.1 years) of a retrospective cohort study conducted in Utah reported a 92% reduction in diabetes-specific mortality among the RYGB group when compared with control subjects.[491] Evidence from a meta-analysis including 174,772 participants investigating the effect of bariatric/metabolic surgery on survival outcomes indicated that survival benefits are much more pronounced for people with a diagnosis of T2D prior to surgery than those without; median life expectancy was 9.3 years (95% CI: 7.1 to 11.8) longer for patients with diabetes in the surgery group than the non-surgical group, while the life expectancy gain was 5.1 years (95% CI: 2.0 to 9.3) for patients without diabetes.[492] Observed mortality benefits are likely related to the decreased incidence of microvascular and macrovascular complications among patients with T2D and obesity compared with non-surgically treated comparison groups.[308, 424, 425] The marked clinical and associated economic benefits of surgery in the subpopulation with T2D supports the argument for dedicated funding for a metabolic surgery programme for this patient subgroup, to ensure that access is available to patients most likely to derive a benefit from surgery.

It is worth noting that achieving T2D remission (HbA1c < 6.5% without T2D medication) with behavioural interventions, with or without pharmacotherapy is possible, but improvements are often not sustained. Such interventions may include one or more of the following components: nutritional therapy, increased exercise,

psychological counselling, or peer support. In the DiRECT (Diabetes Remission Clinical Trial) study, 36% of patients with T2D (mean HbA1c: 60 mmol/mol (7.7%); mean time since diagnosis: 3 years) assigned to a weight management programme (comprising total diet replacement phase using a low energy formula diet (825 to 853 kcal/day), followed by structured food reintroduction of 2 to 8 weeks, and an ongoing structured programme with monthly visits) were in T2D remission at two years' follow-up compared with 3.4% in the control group.[493] However, these results may not be replicable in T2D populations with higher mean HbA1c levels or a longer history of disease. Long-term T2D remission with behavioural intervention and or medical treatment has yet to be demonstrated. Potentially, the future approach for patients with comorbid T2D and obesity will be nutritional and exercise interventions for all patients, pharmacological management of T2D and obesity for many, and metabolic surgery for the growing number of patients with comorbid T2D and obesity at risk of T2D-related complications or who are refractory to or intolerant of less invasive approaches. For many diseases, treatment approaches are considered in terms of sequential lines of therapy. This approach may be less applicable to the choice between pharmacotherapy and metabolic surgery in the treatment of comorbid T2D and obesity, where earlier intervention with the most effective therapy for an individual patient may be important to reduce the risk of progression or development of T2D-related complications.[427, 494] The optimal sequence of interventions is yet unclear and may evolve as other treatment options become available.

The health benefits of metabolic surgery must be carefully weighed against the possible complications which can include nutritional deficiencies and gastrointestinal complications such as obstruction or ulceration. Fortunately, over the past two decades, the overall risk associated with these procedures has declined as a result of increased surgical experience and training, adoption of the laparoscopic approach, changes in the procedures performed, improved care pathways (in particular, long-term follow-up and monitoring and the development of best practice guidelines) and quality assurance processes.[495] As a consequence of the improved safety profile, it has become possible to operate on higher-risk patients. According to the National Bariatric Surgery Registry (NBSR) 2020 report, surgeons are now operating on patients with more severe disease and consequently higher mortality risk scores.[381] Despite this, in-hospital mortality rates and complication rates have continued to decline over time.[381] With consideration to the potential for a reduced incidence of T2D-related complications post-surgery, earlier intervention with metabolic surgery to treat comorbid T2D and obesity could reduce the need for higher-risk or more costly interventions later in life to treat T2D-related complications.[496]

Improved clinical outcomes in this population have the potential to translate into lower healthcare resource use and thus lower costs associated with healthcare service provision. In the Irish-specific cost-utility analysis, compared with best medical care, metabolic surgery was found to be a highly cost-effective intervention for the treatment of comorbid T2D and obesity over a ten-year time horizon. These findings are consistent with those of the international literature. In all 30 studies included in the systematic review of economic evaluations (see chapter 5), metabolic surgery was cost-effective or even cost-saving in the population with comorbid T2D and obesity relative to best medical care. It is important to note that, consistent with best practice recommendations, a conservative approach was adopted for the purposes of modelling, biasing the results against the intervention (metabolic surgery) in circumstances where assumptions were necessary. For example, a lifetime horizon is often considered appropriate for HTAs, as the majority of technologies have costs and outcomes that impact over a patient's lifetime.[371] However, this cost-utility analysis estimated the clinical and economic impact of introducing a metabolic surgery programme over a ten-year time horizon in the base case, corresponding to the longest available duration of follow-up in relevant RCTs,[249] to minimise the dependency of the ICER on data projections. Over longer time horizons, the probability of the intervention being cost-saving increased. The model considers a limited number of T2D-related health states based on the best available evidence for metabolic surgery at the time of analysis. Therefore, there is an underestimation of the potential benefit related to plausible improvements in a broad spectrum of T2D-related complications consistent with the use of HbA1c to predict the risk of microvascular and macrovascular outcomes in diabetes. Despite adoption of a conservative approach, no scenario was identified in which metabolic surgery would not be considered cost-effective, suggesting that the intervention is at least cost-effective, if not cost-saving in the long-term. In considering the cost-effectiveness of metabolic surgery compared with best medical care, it is important to note that newer, more effective anti-hyperglycaemic agents were not available at the outset of RCTs with long-term follow-up. While this may have the potential to reduce the effect size of metabolic surgery compared with best medical care, this may not translate into an increase in the ICER (that is, metabolic surgery being considered less cost-effective), as newer anti-hyperglycaemic agents are considerably more expensive, relative to long-established agents at the time of analysis.[227, 375]

Based on the findings of this assessment, the challenges faced by the potential introduction of a metabolic surgery programme in Ireland are unlikely to be related to issues associated with clinical effectiveness, safety or cost-effectiveness. The challenge lies in instituting and managing a metabolic surgery programme so that it

does not unintentionally displace existing healthcare service activities, in particular, bariatric surgery. At present, there are two consultant-led multidisciplinary weight management services which deliver both medical and surgical treatments to adults with obesity: Ireland East Hospital Group (IEHG: St. Columcille's Hospital/St. Vincent's University Hospital) and Saolta Hospital Group (University Hospital Galway).[158] In order to ensure that metabolic and bariatric surgery services do not compete for resources, consideration should be given to the establishment of metabolic surgery services at additional Model 3 hospitals, ideally in a way that would provide an equitable geographic distribution of services. IFSO guidelines suggest that surgeons carrying out metabolic or bariatric surgery should undertake at least 25 to 50 procedures annually to ensure patient safety and quality of care.[464] However, guidance from British Obesity & Metabolic Surgery Society (BOMSS) highlights that while a volume-outcome relationship may exist, such thresholds should not be prohibitive to roll-out at new centres.[435] Determining the number of surgeries for a safe and effective service is challenging as it depends on a range of factors, including: the experience of the surgeon, the number of related procedures carried out by the surgical team, the range and complexity of procedures offered, and the patient population.

The surgical procedures that would be undertaken as part of metabolic surgery are not novel procedures. While the provision of the surgery is unlikely to be associated with significant clinical or organisational challenges at a hospital-level, if the programme is not to displace existing surgical activity, additional staffing will be required. Specific staffing requirements will need to be determined at a hospital or hospital group level. At a programme level, the principle challenges relate to the delivery of the surgery within the context of a cohesive programme that provides timely pre-operative MDT screening and review and long-term post-operative follow-up. Consideration could be given to the phased introduction of metabolic surgery services to allow for development of surgical capacity and to facilitate identification and resolution of organisational challenges. In the longer term, optimal service delivery would integrate follow-up care with standard T2D management in primary care to simplify the patient pathway, thereby producing operational efficiencies. Key enablers of discharge to primary care will be the development of clear pathways for escalation of care where complications occur and adequate support from community services. Such a structure would align with the roll-out of the Enhanced Community Care programme, whereby GPs will be supported by community specialist teams to undertake the long-term care of patients with chronic disease, such as patients with comorbid T2D and obesity.[429] A challenge will be the long-term management of patients who are not eligible for the Chronic Disease Management Programme. Patients ineligible for this programme would have to pay out-of-pocket for follow-up

care following discharge from hospital-based services, which may present a barrier to accessing care, increasing the risk of loss to follow-up and the potential for reduced quality of care. In practice, establishment of a metabolic surgery programme should be an evolving process, driven by a review of a broad range of organisational and patient-centred KPIs, identified needs within the Irish healthcare system, as well as changes in international best practice guidelines relating to the management of comorbid T2D and obesity.

Access to bariatric surgery varies widely across Europe, despite a relatively similar burden of obesity, and in general, there is insufficient capacity to meet demand in publicly funded healthcare systems.[99, 497, 498] It has been estimated that access to bariatric surgery in Ireland only meets a small proportion of clinical need.[4] On average, 16.9% of the population undergoing bariatric surgery have T2D pre-operatively in Europe.[99] This suggests a potential under-representation of patients with T2D among those accessing surgery, given that a higher prevalence of T2D is expected in the BMI range typically considered eligible for bariatric surgery.[99] Integration of metabolic surgery into the T2D clinical care pathways, as proposed by international experts,[7] may facilitate improved access for the subpopulation with comorbid T2D and obesity, for whom metabolic surgery is known to be associated with considerable clinical and economic benefits.

Appropriate quality assurance mechanisms and governance frameworks would be necessary to optimise the long-term effectiveness and safety of the programme. Although establishment of a dedicated metabolic surgery registry may be preferred, consideration could be given to recording metabolic surgery outcomes as part of an existing system such as the HSE's Chronic Disease Management Programme to facilitate monitoring of outcomes and healthcare service quality. However, as noted previously, not all patients with T2D are managed as part of this programme, which would result in an incomplete dataset. Centralised monitoring of outcomes for all patients with comorbid T2D and obesity may not be possible within existing IT infrastructure. This gap reinforces the need for a national T2D registry which captures outcomes for all patients with T2D.

9.3 Strengths and limitations

This assessment has a number of notable strengths. A robust approach to the assessment process was employed with the publication of a protocol for the HTA,[499] adherence to national and European best practice guidelines in Health Technology Assessment,[326, 371, 378, 408, 474] and the establishment of an Expert Advisory Group (EAG) comprising a broad range of key stakeholders to support the assessment. All chapters were reviewed and updated in line with recommendations from the EAG.

Despite these strengths, this assessment has some limitations which should be considered in the interpretation of the evidence.

Estimates of the size of the population eligible for metabolic surgery presented in this assessment are associated with considerable uncertainty. It is important to note that estimates of the eligible population were based on a diagnosis of comorbid T2D and obesity only. A proportion of those with comorbid T2D and obesity will be ineligible for surgery due to contra-indications related to comorbidities or age, while others that meet the criteria for surgery may choose not to access it, therefore the population that would undergo metabolic surgery if it was available would be smaller. Even if robust estimates of the size of the eligible population were available, given the elective nature of the surgery, precise estimation of uptake rates is not possible owing to the influence of patient and clinician acceptability on demand for metabolic surgery. A cross-sectional study of patients with T2D (n=1,167) presenting to outpatients clinics in Greece reported that only 39.3% of patients considered eligible for surgery had been informed about metabolic surgery as a treatment option.[500] In the context of this assessment, demand was estimated with consideration to current waiting lists for bariatric surgery in Ireland. It is estimated that approximately 1,000 screened surgical candidates are awaiting access to bariatric surgery in Ireland, reflecting that existing demand greatly exceeds available capacity. In Europe, on average, 17% of bariatric surgery patients have a diagnosis of T2D preoperatively,[99] while in Ireland it was 24% between 2009 and 2019. There may be a variety of reasons for the observed difference, and it should be noted that the proportion in Ireland is subject to substantial variability from year to year due to small numbers. An annual cohort of 200 patients was used in this HTA as a pragmatic choice with consideration to existing demand for bariatric surgery among patients with T2D and minimum volume thresholds. As it was assumed that a metabolic surgery programme would not require capital investment in terms of operating theatres or ICU capacity, the cohort size has no implications for the estimate of cost-effectiveness, only the estimated budget impact. The budget impact is directly proportional to the patient cohort size, therefore a doubling the number of patients would result in a doubling of the budget impact. Regional access to surgery, acceptable waiting times, integration of metabolic surgery into standard T2D management, appropriately-resourced community-based supports and educational interventions targeting patients and clinicians may serve to increase demand for metabolic surgery by improving the acceptability of the initial surgery and long-term care requirements.

Although a large body of RCT evidence was available for surrogate markers of clinical effectiveness (for example, HbA1c), the systematic review of clinical effectiveness and safety was limited in its ability to answer questions regarding the

effectiveness of metabolic surgery on morbidity and mortality due to the small sample sizes and relatively short-term follow-up of included RCTs. Nevertheless, the effect size in terms of HbA1c reduction is indicative of a reduced risk of T2D-related complications. Observational evidence consistently demonstrates clinically significant reductions in T2D-related complications. Larger randomised trials of metabolic surgery compared with best medical care are unlikely to be possible owing to numerous barriers to research including challenges associated with patient recruitment and retention, ethical issues associated with assigning patients to a comparator group that is now known to be less effective and the need for a multicentre consortium to ensure generalisability of results.[260] In recognising that such data are unlikely to be generated, this HTA highlights that there is currently sufficient high-quality evidence to support a decision to provide a metabolic surgery programme and that such a decision would be consistent with ensuring that patients have timely access to a highly cost-effective treatments.

There are numerous complications associated with T2D that can take many years to emerge, including acute myocardial infarction, stroke, diabetic retinopathy, diabetic foot, nephropathy and peripheral neuropathy. The economic model explicitly accounted for the risk of acute myocardial infarction and stroke and also a range of intervention-related adverse events. However, other longer-term complications were not included due to the challenges in estimating the change in risk associated with a period of reduced HbA1c and BMI. Furthermore, some of those complications may already be present to a greater or lesser extent in patients undergoing metabolic surgery, so the impact of the intervention may be less pronounced for those patients. Long-term complications can have marked effects on the individual and on the healthcare system. While those impacts are not captured in the model, they must be acknowledged. For the patient, complications of diabetes are associated with reduced health-related quality of life.[501, 502] The presence of complications may also have cost implications for the individual through out-of-pocket medical care expenses and an impact on the ability to work. Complications of diabetes impact the healthcare system generally through the resources required to manage them. A 2012 UK study estimated that the cost of treating and managing T2D was £1.8 billion in a year, while the equivalent cost for dealing with complications of T2D was £7.0 billion.[503] An intervention that reduces the risk of patients developing complications of T2D could generate substantial benefits for patients and the healthcare system over the longer-term. As such, the cost-effectiveness estimates presented in this report may be a substantial underestimate of the longer-term benefits of the intervention for the individual, for the healthcare system and at a societal level, should the potential impact on productivity also be considered.

In estimating the budget impact associated with the potential introduction of a metabolic surgery programme, the cost of acute hospital care was estimated using diagnosis-related group (DRG) costs, which include all overheads associated with the provision of care, including staffing. Requirements for additional staff would be a function of the number of surgeries carried out and where the procedures are provided, as the capacity constraints related to human resources will differ between hospitals/hospital groups.

9.4 Conclusions

Metabolic surgery is a highly effective and safe means of obtaining clinically significant and durable improvements in glycaemic control and weight loss in patients with comorbid T2D and obesity, when appropriate patient selection and long-term follow-up are ensured. Based on the results of this assessment, a metabolic surgery programme would be an efficient use of resources as even based on very conservative estimates, it would be considered highly cost-effective relative to best medical care. Provision of a metabolic surgery programme would be associated with additional costs in the short-term predominantly driven by the upfront cost of providing surgery. As such, additional staff would be required to provide these procedures to avoid existing surgical care being displaced. Implementation of a metabolic surgery programme may give rise to organisational challenges and opportunities associated with the development of integrated care for people with comorbid T2D and obesity. Metabolic surgery would likely reduce the burden of diabetes on the healthcare system in the longer-term owing to potential reductions in acute and chronic T2D-related complications.

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Appendix 1

Table A1.1. International guidance on indications of bariatric or metabolic surgery

Country	Advising body	Indications for metabolic or bariatric surgery		
		Class I obesity (with T2D)	Class II obesity (with comorbidity)	Class III obesity
Belgium	KCE 2019[12]	BMI of 30 - <35 kg/m^2 for persons with T2D and obesity	BMI ≥35 kg/m^2 in combination with the following obesity-related disorders: severe, difficult-to-treat hypertension, T2D or OSA.	BMI ≥40 kg/m^2
Denmark[115]	DHA 2017[49]	NR	BMI >35 kg/m^2 and obesity-related diseases	BMI >40 kg/m^2
England	NICE 2014[11, 504]	Consider an assessment for bariatric surgery for people with a BMI of 30–34.9 who have recent-onset T2D†.	▪ BMI 35-40 kg/m^2 and other significant disease (for example, T2D or high blood pressure) ▪ Expedited assessment for people with a BMI ≥35 who have recent-onset T2D	▪ BMI of ≥40 kg/m^2 ▪ First-line option for adults with a BMI of >50kg/m^2, in whom surgical intervention is considered appropriate.
France	HAS 2020[505]; 2019[97]; 2009[506]	NR	BMI ≥ 35 kg/m² associated with at least one comorbidity that may be improved after surgery including: ▪ high blood pressure ▪ OSA ▪ severe respiratory disorders ▪ severe metabolic disorders, in particular T2D ▪ disabling ic-articular diseases ▪ NASH	BMI ≥ 40 kg/m²
Germany	DGAV 2018[13, 507]	BMI ≥ 30 kg/m² to <35 kg/m² and T2D if individual target values, as determined from the National Disease Management Guideline on the Treatment of T2D, have not been achieved.	▪ BMI ≥35 kg/m^2, in the presence of one or more obesity-associated comorbidities. ▪ Patients with T2D with a BMI ≥ 35 kg/m² to <40 kg/m² if their individual target values, as determined from the National Disease Management Guideline on the Treatment of T2D, have not been achieved.	▪ BMI ≥ 50 kg/m2 (primary indication) ▪ BMI ≥40 kg/m2 without any comorbidities or contraindications, when conservative treatment options have been exhausted.

Ireland	RCPI[230]	BMI >30kg/m^2 with: ▪ Significant/severe/ uncontrolled obesity related end organ disease ▪ Significant/severe obesity/ uncontrolled related psychological symptoms ▪ Significant/severe/ uncontrolled functional limitations ▪ Significant/severe/ uncontrolled impairment of well being	BMI ≥35 kg m2 with co-morbidities such as type 2 diabetes.	BMI ≥40 kg m2
Norway	NIPH 2014[113]; 2014[508]; 2018[119]	Not yet recommended due to insufficient long-term evidence.	BMI ≥ 35 kg/m^2 with at least one obesity related comorbidity.	BMI ≥ 40 kg/m^2
Scotland	SIGN 2010**[103, 509]**	Obese adults with T2D should be offered individualised interventions to encourage weight loss (including lifestyle, pharmacological or surgical interventions) in order to improve metabolic control		
		NR	BMI ≥35 kg/m2 and the presence of one or more severe comorbidities which are expected to improve significantly with weight reduction (severe mobility problems, arthritis, T2D).	
Spain	SECO 2013[104]; 2015[510]; 2016[118]	BMI 30-35 kg/m2 who meet the following requirements: ▪ evaluated by an endocrinologist, in the context of an interdisciplinary team, other forms of diabetes have been ruled out (T1D, LADA, MODY) ▪ show a progressive deterioration of glycaemic control (HbA1c >7.5%) despite optimized conventional treatment (especially in those with other comorbidities that are not adequately controlled (arterial hypertension, OSA)) with the usual treatment.	BMI ≥35 kg/m2 if associated with major morbidities. Minor comorbidities that may be improved with surgical treatment, such as reflux disease, cholelithiasis, hypertension or others, should be considered on an individual basis	BMI ≥40 kg/m2
Sweden	FHI 1992;[114] Socialstyrelsen 2015[106]	NR	▪ BMI 35-40 kg/m^2 with high-risk comorbidities (accepted co-morbidities vary dependent on the region)	BMI ≥40 kg/m^2

			▪ People with T2D and BMI of 35– 40 kg/m² in cases where there is a difficulty controlling blood sugars and risk factors.	
Switzerland	SMOB 2018;[116] ASEMO 2016[117]	NR	BMI of ≥ 35 kg/m² with two years of adequate weight loss therapy that was unsuccessful.	▪ BMI ≥40 kg/m2 ▪ Consider bariatric surgery as the 1st treatment for a patient with a BMI >50 kg/m2.
The Netherlands	NHG 2010[511]; 2018[105]	NR	BMI between 35 and 40 with co-morbidity.	▪ BMI ≥40 kg/m² ▪ Consider bariatric surgery as the 1st treatment for a patient with a BMI >50 kg/m².
Canada	Obesity Canada 2020[71]; Diabetes Canada Clinical Practice Guidelines Expert Committee 2018[14]	Patients with poorly controlled T2D and BMI between 30 and 35 kg/m² despite optimal medical management.	BMI ≥ 35 kg/m2 with at least 1 adiposity-related disease.	BMI ≥ 40 kg/m²
Regional or international guidance				
Europe	EAES 2020[8]	BMI ≥ 30–35 kg/m² and T2D and/or arterial hypertension with poor control despite optimal medical therapy	BMI ≥35–40 kg/m² with associated comorbidities that are expected to improve with weight loss	BMI ≥40 kg/m²
International	IDF 2016[512]	*Considered* for patients with T2D and BMI 30.0–34.9 kg/m2 if hyperglycaemia is inadequately controlled despite optimal treatment with either oral or injectable medications.	*Recommended* to treat T2D in patients with BMI 35.0–39.9 kg/m2 when hyperglycaemia is inadequately controlled by lifestyle and optimal medical therapy.	*Recommended* to treat T2D in patients with BMI ≥40 kg/m2
	ADA/EASD 2018	Considered for those with a BMI of 30.0–34.9 kg/m2 (27.5– 32.4 in people of Asian ancestry) who do not achieve durable weight loss and improvement in comorbidities with reasonable non-surgical methods.	Adults with T2D and BMI of 35.0–39.9 kg/m2 (32.5–37.4 kg/m2 in people of Asian ancestry).	Adults with T2D and BMI ≥ 40.0 kg/m2 (BMI ≥ 37.5 kg/m2 in people of Asian ancestry) or (2) a
United	ACCE/ACE	Patients with BMI of 30 to 34.9 kg/m2 with	Patients with a BMI of ≥35 kg/m2 and 1 or	Patients with a BMI of ≥40 kg/m2

States	2016[28]	diabetes or metabolic syndrome may also be considered for a bariatric procedure	more severe obesity-related complications, including T2D, hypertension, obstructive sleep apnoea, obesity-hypoventilation syndrome, Pickwickian syndrome, nonalcoholic fatty liver disease or nonalcoholic steatohepatitis, pseudotumor cerebri, gastroesophageal reflux disease, asthma, venous stasis disease, severe urinary incontinence, debilitating arthritis, or considerably impaired quality of life	without coexisting medical problems
	ADA 2020[122]	Adults with T2D and BMI 30.0–34.9 kg/m2 (27.5–32.4 kg/m2 in Asian Americans) who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with tested efficacious nonsurgical methods.	BMI 35.0–39.9 kg/m2 (32.5–37.4 kg/m2 in Asian Americans) who do not achieve durable weight loss and improvement in comorbidities with nonsurgical methods.	BMI ≥40 kg/m2 (BMI ≥37.5 kg/m2 in Asian Americans)

Key: AACE - American Association of Clinical Endocrinologists; ACE - American College of Endocrinology; ADA - American Diabetes Association; ASEMO - Swiss Association for the Study of Obesity; ASMBS - American Society for Metabolic and Bariatric Surgery; DGAV - German Society for General and Visceral Surgery; DHA - Danish Health Authority; DSS - Diabetes Surgery Summit; EAES - European Association of Endoscopic Surgery; EASO - European Association for the Study of Obesity; ESPCOP - European Society for the Peri-operative Care of the Obese Patient; FHI - Swedish National Institute of Public Health; HAS - Haute Autorité de santé; IDF – International Diabetes Federation; IFSO-EC - European Chapter of the International Federation for the Surgery of Obesity and Metabolic Disorders; KCE - Belgian Health Care Knowledge Centre; LADA – latent autoimmune diabetes in adults; MODY – maturity-onset diabetes of the young; NASH – Non-alcoholic steatohepatitis; NHG - Dutch College of General Practitioners; NICE - National Institute for Health and Care Excellence; NIPH - Norwegian Institute of Public Health; OMA - Obesity Medicine Association; OSA – obstructive sleep apnoea; RCPI – Royal College of Physicians of Ireland; SECO - Spanish Society for Obesity Surgery; SIGN - Scottish Intercollegiate Guidelines Network; SMOB - Swiss Society for the Study of Morbid Obesity and Metabolic Disorders; TOS - The Obesity Society.

† The guideline development group considered that recent-onset type 2 diabetes would include those people whose diagnosis has been made within a 10-year time frame.

Appendix 2

Analysis of TILDA data

A cross sectional analysis of the first wave (2009-2011) of The Irish Longitudinal Study on Ageing (TILDA) was conducted with two specific objectives:

- to estimate the proportion of population with comorbid T2D and obesity
- to estimate the proportion of the population with comorbid T2D and obesity and T2D control above treatment targets.

TILDA is a nationally representative cohort study of community-dwelling adults aged 50 years and over. The study design is described in detail elsewhere. Participants completed a computer-assisted personal interview (CAPI) administered by trained social interviewers, which included questions on self-report doctor-diagnosis of chronic conditions. Those who completed the CAPI were invited to attend a health assessment either at the study centre or in their home. During the health assessment, trained nurses objectively measured participants' weight and height, which were used to calculate BMI.

The CAPI questionnaire did not distinguish between diabetes by type. Therefore, an estimate of the proportion of the population with T2D was derived based on the following assumptions. Individuals were classified as having diabetes if they self-reported a previous doctor-diagnosis. Respondents that did not report doctor-diagnosed diabetes but were currently taking diabetes medication were reclassified as having doctor-diagnosed diabetes. Type 1 diabetes was defined as those who were aged less than 50 years at the time of diabetes diagnosis and reported injecting insulin, but no other anti-hyperglycaemic agents. Individuals reporting a diagnosis of T2D but not fulfilling the criteria for T1D were assumed to have T2D.

Cardio-metabolic treatment targets were selected based on treatment targets used in a cross-sectional analysis of the Diabetes Cycle Of Care programme, and consistent with treatment targets used by the UK National Diabetes Audit: [172, 176] HbA1c ≤58 mmol/mol, TC <5 mmol/litre, and systolic blood pressure ≤140 mmHg and diastolic blood pressure ≤80 mmHg.

Statistical analysis

Survey weights were applied to the analysis to reflect the complex sampling design and to adjust for participation bias. Prevalence estimates are reported as percentages and 95% confidence interval (CI). Prevalence estimates were applied to

the 2021 Irish census projections to determine absolute number of patients potentially eligible for metabolic surgery. Analysis was conducted in Stata v.16 for windows (StataCorp, College Station, TX, USA).

Limitations

Due to the low number of participants with comorbid T2D and obesity, analysis of those with T2D control above treatment targets is subject to considerable uncertainty and should be interpreted with caution.

A limitation common to any analysis based on survey data is that survey respondents have been shown to be systematically healthier when compared with the general population.[513, 514] Although participant responses in TILDA were weighted for age, sex and education to account for differential response rates, a response bias cannot be excluded. Also, while TILDA collects a substantial amount of health data, the use of self-report and medication to define certain diagnoses means that some of the estimates of disease prevalence are open to alternate definitions, which may contribute to inconsistencies between studies.

Missing values were not imputed.

Estimation of the size of the population eligible for surgery

There is no single national data source in Ireland, including adults ≥18 years, recording both T2D status and BMI. Thus, the prevalence of T2D and obesity in adults aged 18 to 49 and ≥50 years, was estimated using the fifth wave of the Health Ireland Survey and the first wave of the TILDA dataset, respectively.

The approach to estimating the prevalence of comorbid T2D and obesity in the TILDA dataset is outlined in the previous section. Data are not available by diabetes type in the Healthy Ireland Survey. It was assumed that 87.9% of reported cases were T2D.[149] However, this may not reflect the ratio of T1D to T2D in adults aged 18 to 49 years, given that the typical age of onset for T2D is middle- to older-age (see section 3.2.3). It was assumed that the population with comorbid T2D and obesity aged 18 to 49 years follow the same BMI distribution as adults ≥50 years (estimated from TILDA) in the absence of age-specific estimates (BMI ≥30 to <35 kg/m$^{2:}$ 54.21% (95% CI: 47.52 to 60.45); BMI ≥35 kg/m^2: 45.79% (95% CI: 39.25 to 52.47).

Based on recommendations from the Second Diabetes Surgery Summit,[7] it was assumed that metabolic surgery would be indicated for all patients with T2D and a BMI ≥35 kg/m^2, and those with T2D and a BMI of ≥30 to <35 kg/m^2 if treatment targets were not met with best medical care. There is no standardized definition of T2D control that is above treatment targets.[160-162] As such, two definitions of T2D control above treatment targets considered potentially applicable to the Irish context were applied to reflect uncertainty. Firstly, UK National Diabetes Audit data for the period 2018 to 2019 suggest that 61.2% of patients did not meet treatment targets, defined as "HbA1c value ≤ 58 mmol/mol, blood pressure ≤140/80 and, for people who fall into the combined prevention of CVD group, is receiving statins".[174] Secondly, using Irish Diabetes Cycle of Care programme data for the period 2014 to 2017, it was estimated that 32.3% of the population with comorbid T2D and obesity enrolled in the programme had a HbA1c >58 mmol/mol.[176] Both estimates were presented.

The absolute number of patients potentially eligible for metabolic surgery was estimated by applying prevalence estimates to the 2021 Irish census population projections.

Table A2.1. International estimates of T2D control above treatment targets

Study	Country or Region	Population	Definition of suboptimal glycaemic control	Year	Results
Ireland					
DECIDE[515] **Murphy** 2020	Ireland (Dublin)	Patients aged between 18 and 75 years with sub-optimally controlled T2D (n=134); 14 general practices	Glycated haemoglobin (HbA1c) ≥70 mmol/mol (8.6%) and/or blood pressure ≥150/95 mmHg	2020	▪ HbA1c ≥70 mmol/mol (8.6%) and BP ≥150/95 mm Hg: ▪ 1.6 patients/practice ▪ HbA1c ≥70 mmol (8.6%) (and/or BP <150/95 mm Hg): ▪ 11.9 patients/practice ▪ BP ≥150/95 mm Hg (but HbA1c <70 mmol/mol): ▪ 6.4 patients/practice
Diabetes Cycle of Care **O'Connor** 2020[176]	Ireland (National)	Patients with T2D registered with the Diabetes Cycle of Care programme (n=3,146)	HbA1c ≤58 mmol/mol, Total cholesterol <5 mmol/litre Blood pressure ≤140/80 mmHg	2014-2017	▪ HbA1c >58 mmol/mol: 29% ▪ Total cholesterol ≥5: 19% ▪ Blood pressure >140/80: 48% **Patients with obesity and T2D:** ▪ HbA1c >58 mmol/mol: 32.3%
Cahill 2010[516]	Galway	Patients with T2D attending 19 consecutive diabetes clinics at Galway University Hospital (n=466)	▪ HbA1c <7% ▪ LDL cholesterol <2.6 mmol/L ▪ blood pressure <130/80 mmHg ▪ use of anti-platelet therapy	2010	▪ HbA1c <7%: 42.7% ▪ LDL-Cholesterol <2.6 mmol/L: 76.2%. ▪ Blood pressure <130/80 mmHg: 42.3% ▪ Combined ADA goals for HbA1c, LDL cholesterol and blood pressure: 15.24%
TILDA **O'Neill** 2017[4]	Ireland (National)	Irish adults aged ≥50 years with T2D and obesity (≥35 kg/m^2)	Patients with T2D and BMI ≥35kg/m^2, who had one or more of the following; previous MI, elevated urine albumin-creatinine ratio, retinopathy, neuropathy or peripheral vascular disease.	2009-11	Obesity and T2D: 2.06% (95%CI:1.70-2.49) Obesity and T2D and any diabetes-related complication: 0.97% (95% CI: 0.73 to 1.28) or ~47% of the population with T2D and obesity

European estimates					
Khunti 2018[517]	Europe (n=10 countries; Belgium, France, Germany, Ireland, Italy, Netherlands, Poland, Spain, Sweden, and the UK)	Meta-analysis of studies reporting on targets for HbA1c, blood pressure, or lipids (LDL-C, HDL-C, or triglycerides)	Proportion of people with T2DM achieving tar-gets recommended by ADA, EASD, or NICE for glycaemic control, blood pressure, or lipid targets.	2006 to 2017	Proportion of patients achieving HbA1c targets:† ▪ Pooled random effects prevalence: 0.50 (95% CI: 0.43 to 0.57) Proportion of patients achieving blood pressure targets: ▪ Pooled random effects prevalence: 0.23 (95% CI: 0.16 to 0.31)
DISCOVER study program **Khunti** 2020; **Patel** 2021[236, 518]	Europe‡	Patients (n = 3,003) aged >18 years with T2D initiating second-line glucose-lowering therapy. Mean time since diagnosis: 5.7 (SD 5.3) years	Poor glycaemic control: HbA1c 64 mmol/mol (>8.0%)	2014 - 2016	▪ HbA1c <7.0%: Approx. 18%§ ▪ HbA1c 7.0% to <8.0: Approx. 36%§ ▪ HbA1c 8.0% to <9.0: Approx. 24%§ ▪ HbA1c ≥9.0: Approx. 22%§ ▪ Systolic blood pressure <140 mmHg: 56% ▪ Statin treatment 42.3% ▪ Non-smoking status: 79.7% ▪ ACE inhibitor/ARB for hypertension/albuminuria: 64.6% ▪ Secondary prevention with aspirin for ASCVD: 52.3% ▪ Optimal comprehensive risk factor control:¶ 14.3%
NHS National Diabetes Audit[174]	England and Wales	Patients with T2D# and obesity (≥30 kg/m^2) not meeting treatment targets§	HbA1c value ≤ 58mmol/mol (7.5%), blood pressure ≤140/80 and, for people who fall into the combined prevention of cardiovascular disease risk group, is receiving statins	2018/ 19	**Percentage not meeting treatment targets:** ▪ T2D and BMI 30 to 34.9 kg/m2: 61.2% ▪ T2D and BMI 35 to 39.9 kg/m2: 65.4% ▪ T2D and BMI ≥40 kg/m2: 69.1%
NHS Scotland[175]	Scotland	Population with T2D in 2020 with a recording of HbA1c in the last 15 months	HbA1c categories: <53 mmol/mol: 53-57 mmol/mol 58-63 mmol/mol	2010/ 2019††	HbA1c <53 mmol/mol: 36.8% HbA1c 53-57 mmol/mol: 14.5% HbA1c 58-63 mmol/mol: 13.4% HbA1c 64-68 mmol/mol: 8.4%

			64-68 mmol/mol 69-75 mmol/mol >75 mmol/mol		HbA1c 69-75 mmol/mol: 7.3% HbA1c >75 mmol/mol: 19.6%
Laustsen 2020[173]	Denmark	Patients with T2D attending an outpatient clinic (n=1,202); minimum duration since diagnosis: 2 years	"Poorly controlled": HbA1c levels ≥ 75 mmol/mol (9.0%) "Tightly controlled": HbA1c levels ≤ 50 mmol/ mol (6.7 %)	2016	**Prevalence of poor control:** 26%
Lolland Falster health study **Bruun-Rasmussen** 2020[519]	Denmark	Adults ≥20 years (n = 10,895)	HbA1c ≥ 60 mmol/mol	2016-2019	**Total population prevalence:** 1.2% (95% CI: 0.5 to 1.9) **Men**: 1.5% (0.5–2.6) **Women:** 0.8% (0–1.7)
DIALOGUE **Schmeider** 2018[520]	Germany	Patients ≥ 18 years with T2D with comorbid hypertension (n=6,691)	Patients were assigned HbA1c targets by their physician: ▪ ≤6.5% (strict) (n= 2,644) ▪ >6.5 to ≤7.0% (intermediate) (n=2,912) ▪ >7.0 to ≤7.5% (lenient) (n=1,135)		53.1% of patients achieved a HbA1c level within, or below their treatment target at 12 months. Percentage reaching target by group: ▪ Strict: 46.2% ▪ Intermediate: 56.8% ▪ Lenient: 59.4%
International evidence					
Bergonsi de Farias 2021[166]	Brazil	T2D patients attending an outpatient endocrinology clinic of a university hospital (n=602)	▪ A1C target of <7%: reasonable goal for most adults ▪ A1C target of <6.5%: patients at lower risk of hypoglycaemia ▪ A1C target of 8%: patients with advanced diabetes complications, a history of severe hypoglycemia, limited life expectancy or extensive comorbid conditions	2013 to 2017	67% patients were not at their target A1C level after individualising goals

MBSAQIP **Mazzei** 2021[521]	United States	Patients with T2D who underwent RYGB or SG (n=40,132) identified from the MBSAQIP databases	poor glycaemic control: HbA1C >53 mmol/mol (7.0%) good glycaemic control: HbA1C ≤53 mmol/mol (≤7.0%)	2017 - 2018	HbA1C >53 mmol/mol (>7%): 47.9% HbA1C >86 mmol/mol (>10%): 9.1%
Jaejin An 2020[522]	United States	Patients ≥20 years with T2D (n=28,315) registered in the Kaiser Permanente Southern California (KPSC) system	Percent of time in suboptimal glycemic control using three A1C thresholds (≥8%, ≥7.5%, ≥7%)		**Up to 2 years post-diagnosis:** ▪ HbA1c 7%: 40% ▪ HbA1c 7.5%: 34% ▪ HbA1c 8%: 30% **6 to 10 years post-diagnosis:** ▪ HbA1c 7%: 61% ▪ HbA1c 7.5%: 48% ▪ HbA1c 8%: 39%
DM-SCAN **Grenier** 2016[523]	Canada	Patients with T2D with or without comorbid CAD seen in primary care (N=5,123)	A1c ≤7.0% BP < 130/80 mmHg LDL-C ≤2.0 mmol/L	2012	**HbA1c** CAD: 48.5%; No CAD: 50.5% **Blood pressure** CAD: 29.1%; No CAD: 35.8% **LDL-Cholesterol** CAD: 66.0%; No CAD: 54.5% **All three treatment targets** CAD: 15.4%; No CAD: 12.0%
Aronson 2016[524]	Canada	Patients with T2D recorded in the LMC Diabetes Registry database (n=10,590)	Good control (Canadian Diabetes Association target): HbA1c ≤53 mmol/mol (7.0%) Minimal control : HbA1c ≥64 mmol/ mol (8.0%) despite specialist care for ≥1 year	2013	>53 mmol/mol (7.0%): 62% ≥75 mmol/mol (9.0%): 16.1%

Key: CAD - coronary artery disease; DM-SCAN - Diabetes Mellitus Status in Canada; HDL-C - high density lipoprotein cholesterol; LDL-C - low density lipoprotein cholesterol.
† Treatment targets differed between studies in the pooled analysis contributing to significant statistical heterogeneity.
‡ Austria, Czech Republic, Denmark, France, Italy, Netherlands, Norway, Poland, Russia, Spain, Sweden and Turkey.
§ Values extracted from graph using WebPlotDigitizer.[525]
¶ Optimal cardiovascular risk factor management was defined as control of all of the following risk factors among eligible patients: (a) systolic BP <140 mmHg (all patients); (b) statin prescription (patients aged ≥40 years or with ASCVD); (c) non-smoking status (all patients); (d) angiotensin-converting enzyme (ACE) inhibitor/angiotensin II receptor blocker (ARB) prescription (patients with hypertension or albuminuria); and (e) daily aspirin (patients with established ASCVD).
# And other diabetes, not including type 1 diabetes.

†† 2019 data shown.

DECIDE[515] **Murphy** 2020	Ireland (Dublin)	Patients aged between 18 and 75 years with sub-optimally controlled T2D (n=134); 14 general practices	Glycated haemoglobin (HbA1c) ≥70 mmol/mol (8.6%) and/or blood pressure ≥150/95 mmHg
Diabetes Cycle of Care **O'Connor** 2020[176]	Ireland (National)	Patients with T2D registered with the Diabetes Cycle of Care programme (n=3,146)	HbA1c ≤58 mmol/mol, Total cholesterol <5 mmol/litre Blood pressure ≤140/80 mmHg
Cahill 2010[516]	Galway	Patients with T2D attending 19 consecutive diabetes clinics at Galway University Hospital (n=466)	▪ HbA1c <7% ▪ LDL cholesterol <2.6 mmol/L ▪ blood pressure <130/80 mmHg ▪ use of anti-platelet therapy

Appendix 3

Appendix A3.1 Literature search strategy

Medline (Ovid)

1. Exp Diabetes Mellitus/
2. Diabetes.mp. OR diabetic.mp. OR type 2 diabetes.mp. OR non-insulin-dependent diabetes.mp. OR hyperglycaemia.mp. OR hyperglycemia.mp.
3. Or 1-2
4. exp Bariatric surgery/
5. Bariatric surgery.mp.
6. (Bariatric adj2 surgery).mp.
7. metabolic surgery.mp.
8. weight loss surgery.mp.
9. obesity surgery.mp.
10. Roux-en-Y.mp. OR RYGB.mp.
11. ((Gastric OR gastrojejunal OR gastro-jejunal OR gastroileal OR gastro-ileal OR duodenojejunal OR duodeno-jejunal OR duodenal-jejunal OR duodenoileal OR duodeno-ileal OR duodenal-ileal OR gastro-intestinal OR gastrointestinal) adj3 (bypass OR diversion OR interposition)).mp.
12. mini gastric bypass.mp. OR one anastomosis gastric bypass.mp. OR OAGB.mp. OR single anastomosis gastric bypass.mp. OR SAGB.mp. OR omega loop gastric bypass.mp.
13. sleeve gastrectomy.mp. OR gastric sleeve.mp.
14. gastric band*.mp. OR intragastric band*.mp. OR gastroplast*.mp. OR vertical band.mp. OR lapband.mp. OR lap-band.mp. OR adjustable band.mp.
15. biliopancreatic diversion.mp. OR bilio-pancreatic diversion OR duodenal switch.mp.
16. Single Anastomosis Duodeno Ileal.mp. OR SADI-S.mp. OR SADIS.mp.
17. Single Anastomosis Sleeve Ileal.mp. OR SASI.mp.
18. Gastric plication.mp.
19. Gastrointestinal liner.mp. OR bypass sleeve.mp. OR bypass liner.mp. OR duodenal mucosal resurfacing.mp.
20. Bariatric endoscopy.mp. OR endobariatric.mp.
21. ((Endoscopy OR endoscopic OR endoluminal) adj3 (bariatric OR metabolic OR sleeve OR gastroplasty)).mp.
22. OR 4-21
23. Randomized Controlled Trials as Topic/
24. exp Clinical Trials as topic/
25. randomized controlled trial.pt. OR controlled clinical trial.pt. OR clinical trial.pt.
26. randomi#ed controlled trial.mp. OR controlled clinical trial.mp. OR RCT.mp. OR trial.mp. OR trials.mp. OR random*.mp.
27. ((multicentre OR multicenter) adj2 (study OR trial)).mp.
28. exp Random Allocation/

29. assign*.mp. OR allocate*.mp. OR allocation.mp.
30. non-random*.mp. OR nonrandom*.mp. OR nRCT.mp. OR non-RCT.mp. OR non-randomised study.mp.
31. Comparative study/
32. ((control* OR compar*) adj3 (group* OR randomised OR randomized)).mp.
33. #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32
34. #3 AND #22 AND #33

Embase

1. 'Diabetes Mellitus'/exp
2. Diabetes:ab,ti,kw OR diabetic:ab,ti OR 'type 2 diabetes':ab,ti,kw OR 'non-insulin-dependent diabetes':ab,ti,kw OR hyperglycaemia:ab,ti,kw OR hyperglycemia:ab,ti,kw
3. OR 1-2
4. 'Bariatric surgery'/exp
5. 'bariatric surgery':ab,ti,kw
6. (bariatric NEAR/2 surgery):ab,ti,kw
7. 'metabolic surgery':ab,ti,kw
8. 'weight loss surgery':ab,ti,kw
9. 'obesity surgery':ab,ti,kw
10. 'Roux-en-Y gastric bypass'/exp OR 'Roux-en-Y':ab,ti,kw OR RYGB:ab,ti,kw
11. ((Gastric OR gastrojejunal OR 'gastro-jejunal' OR gastroileal OR 'gastro-ileal' OR duodenojejunal OR 'duodeno-jejunal' OR 'duodenal-jejunal' OR duodenoileal OR 'duodeno-ileal' OR 'duodenal-ileal' OR 'gastro-intestinal' OR gastrointestinal) NEAR/3 (bypass OR diversion OR interposition)):ab,ti,kw
12. 'mini gastric bypass':ab,ti,kw OR 'one anastomosis gastric bypass':ab,ti,kw OR OAGB:ab,ti,kw OR 'single anastomosis gastric bypass':ab,ti,kw OR SAGB OR 'omega loop gastric bypass':ab,ti,kw
13. 'sleeve gastrectomy'/exp OR 'sleeve gastrectomy':ab,ti,kw OR 'gastric sleeve':ab,ti,kw
14. 'gastric band*':ab,ti,kw OR 'intragastric band':ab,ti,kw OR 'gastroplasty':ab,ti,kw OR 'vertical band':ab,ti,kw OR lapband:ab,ti,kw OR lap-band:ab,ti,kw OR 'adjustable band':ab,ti,kw
15. 'Biliopancreatic bypass'/exp OR 'biliopancreatic diversion':ab,ti,kw OR 'bilio-pancreatic diversion':ab,ti,kw OR 'duodenal switch':ab,ti,kw
16. 'Single Anastomosis Duodeno Ileal':ab,ti,kw OR SADI-S:ab,ti,kw OR SADIS:ab,ti,kw
17. 'Single Anastomosis Sleeve Ileal':ab,ti,kw OR SASI:ab,ti,kw
18. 'Gastric plication':ab,ti,kw
19. 'Gastrointestinal liner':ab,ti,kw OR 'bypass sleeve':ab,ti,kw OR 'bypass liner':ab,ti,kw OR 'duodenal mucosal resurfacing':ab,ti,kw
20. 'Bariatric endoscopy':ab,ti,kw OR 'endobariatric':ab,ti,kw
21. ((Endoscopy OR endoscopic OR endoluminal) NEAR/3 (bariatric OR metabolic OR sleeve OR gastroplasty)):ab,ti,kw

22. OR 4-20
23. 'Clinical Trial'/exp
24. 'Randomized Controlled Trial'/exp
25. 'controlled clinical trial'/exp
26. 'Randomi#ed controlled trial':ab,ti,kw OR RCT:ab,ti,kw OR 'trial':ab,ti,kw OR 'trials':ab,ti,kw OR random*:ab,ti,kw
27. ((multicentre OR multicenter) NEAR/2 (study OR trial)):ab,ti,kw
28. assign*:ab,ti,kw OR allocate*:ab,ti,kw OR allocation:ab,ti,kw
29. 'non-random*':ab,ti,kw OR nonrandom*:ab,ti,kw OR nRCT:ab,ti,kw or 'non-RCT':ab,ti,kw OR 'non-randomi#ed study':ab,ti,kw
30. 'Comparative study'/exp
31. 'Intervention study'/exp
32. ((control* OR compar*) NEAR/3 (group* OR randomised OR randomized)):ab,ti,kw
33. #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31
34. #2 AND #21 AND #32
35.

Cochrane CENTRAL

1. MeSH descriptor: [Diabetes Mellitus] explode all trees
2. Diabetes:ti,ab,kw
3. diabetic:ti,ab,kw
4. MeSH descriptor: [hyperglycemia] explode all trees
5. #1 OR #2 OR #3 OR #4
6. MeSH descriptor: [Bariatric Surgery] explode all trees
7. "Bariatric Surgery":ti,ab,kw
8. (Bariatric NEAR/2 surgery):ti,ab,kw
9. "Obesity surgery":ti,ab,kw
10. "Metabolic surgery":ti,ab,kw
11. MeSH descriptor: [Anastomosis, Roux-en-Y]
12. ((gastric OR gastrojejunal OR gastro-jejunal OR gastroileal OR gastro-ileal OR duodenojejunal OR duodeno-jejunal OR duodenal-jejunal OR duodenoileal OR duodeno-ileal OR duodenal-ileal OR gastrointestinal OR gastro-intestinal) NEAR/3 (bypass OR diversion OR interposition)):ti,ab,kw
13. "gastric bypass":ti,ab,kw
14. "mini gastric bypass":ti,ab,kw
15. "one anastomosis gastric bypass":ti,ab,kw
16. OAGB:ti,ab,kw
17. "single anastomosis gastric bypass":ti,ab,kw
18. SAGB:ti,ab,kw
19. "omega loop gastric bypass":ti,ab,kw
20. "sleeve gastrectomy":ti,ab,kw
21. "gastric sleeve":ti,ab,kw

22. “gastric band*”:ti,ab,kw
23. “intragastric band*”:ti,ab,kw
24. gastroplast*:ti,ab,kw
25. “vertical band”:ti,ab,kw
26. lapband:ti,ab,kw
27. lap-band:ti,ab,kw
28. “adjustable band”:ti,ab,kw
29. MeSH descriptor: [Biliopancreatic Diversion]
30. “biliopancreatic diversion”:ti,ab,kw
31. “duodenal switch”:ti,ab,kw
32. “Single Anastomosis Duodeno Ileal”:ti,ab,kw
33. SADI-S:ti,ab,kw
34. SADIS:ti,ab,kw
35. “Single Anastomosis Sleeve Ileal”:ab,ti,kw
36. “Gastric plication’”:ab,ti,kw
37. “Gastrointestinal liner”:ab,ti,kw
38. “bypass sleeve”:ab,ti,kw
39. “bypass liner”:ab,ti,kw
40. “duodenal mucosal resurfacing”:ab,ti,kw
41. ((Endoscopy OR endoscopic OR endoluminal) NEAR/3 (bariatric OR metabolic OR sleeve OR gastroplasty)):ab,ti,kw
42. #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41
43. #5 AND #42

Appendix A3.2 List of excluded studies

Conference abstract / Insufficient information

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14. Benes M, Spicak J, Drastich P, Hucl T. Interim results of a multi-center, prospective, controlled trial of the duodenal-jejunal bypass liner for the treatment of type 2 diabetes

in obese patients: are there any factors predicting a sub-optimal effect? Gastroenterology. 2015;148(4 SUPPL. 1):S901.
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Appendix A3.3. GRADE tables

Roux-en-Y gastric bypass compared to best medical care for type 2 diabetes and obesity

Patient or population: type 2 diabetes and obesity
Setting: not defined
Intervention: Roux-en-Y gastric bypass
Comparison: best medical care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with best medical care	Risk with Roux-en-Y gastric bypass				
T2D remission assessed with: HbA1c <48 mmol/mol follow-up: 2 years	2 per 100	47 per 100 (10 to 100)	RR 30.79 (6.22 to 152.50)	193 (3 RCTs)	⨁⨁⨁◯ Moderate[a]	An additional 47 participants per 100 randomised to RYGB were in T2D remission relative to best medical care at medium term follow-up.
T2D remission assessed with: HbA1c <48 mmol/mol follow-up: 5 years	3 per 100	25 per 100 (8 to 74)	RR 7.88 (2.64 to 23.50)	274 (4 RCTs)	⨁⨁◯◯ Low[a,b]	An additional 25 per 100 participants randomised to RYGB group were in T2D remission at 5 years relative to best medical care.
T2D remission assessed with: HbA1c <48 mmol/mol follow-up: 10 years	6 per 100	25 per 100 (3 to 100)	RR 4.50 (0.58 to 34.97)	38 (1 RCT)	⨁⨁◯◯ Low[c]	An additional 19 of participants randomised to RYGB were in T2D remission relative to best medical care at 10 years follow-up.
Glycaemic control assessed with: HbA1c follow-up: 2 years	-	SMD 0.70 SD lower (1.07 lower to 0.33 lower)	-	328 (5 RCTs)	⨁⨁⨁◯ Moderate[d]	RYGB was associated with a clinically significant reduction in HbA1c compared with best medical care at two years' follow-up, although there was some uncertainty regarding the magnitude of the effect.

Roux-en-Y gastric bypass compared to best medical care for type 2 diabetes and obesity

Patient or population: type 2 diabetes and obesity
Setting: not defined
Intervention: Roux-en-Y gastric bypass
Comparison: best medical care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with best medical care	Risk with Roux-en-Y gastric bypass				
Glycaemic control assessed with: HbA1c follow-up: 5 years	-	SMD 0.73 SD lower (1.08 lower to 0.37 lower)	-	274 (4 RCTs)	⨁⨁⨁◯ Moderate[d]	HbA1c values were consistently lower in participants randomised to RYGB when compared with best medical care at long-term follow-up, although there was some uncertainty regarding the magnitude of the effect.
Glycaemic control assessed with: HbA1c follow-up: 10 years	-	SMD 0.78 SD lower (1.48 lower to 0.08 lower)	-	35 (1 RCT)	⨁⨁⨁◯ Moderate[e]	HbA1c values were lower in participants randomised to RYGB when compared with best medical care at ten years follow-up based on a limited evidence.
30-day mortality follow-up: 30 days	0 per 100	0 per 100 (0 to 0)	not estimable	532 (6 RCTs)	⨁⨁◯◯ Low[f]	There was no evidence of a difference in the mortality rate between RYGB and best medical care, although trials were not powered to detect differences in rare serious adverse events.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
Note: GRADE does not automatically apply a continuity correction for studies with zero events in one or more arms. Where zero events were reported in the comparator group, estimation of the absolute risk relative to the comparison group was not possible. The risk in the comparison group reflects the random or fixed effect weight estimated using R. Minor variation in methods for calculation of absolute risk using GRADE and R may produce minor discrepancies (e.g. studies are not weighted in GRADE estimates of absolute effect).

CI: confidence interval; RR: risk ratio; SMD: standardised mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded by one level for unclear risk of bias across multiple domains in all studies.
b. Downgraded by one level for imprecision related to the fragility of the effect estimate due to the low number of events and small sample sizes.
c. Downgraded by two levels overall for imprecision. 95% confidence interval include both clinically significant benefits and no effect. Unclear risk of bias related to loss-to-follow-up was not considered serious enough to downgrade further as a single criterion.
d. Downgraded by one level due to some concerns regarding unclear risk of bias and inconsistency. Inconsistency related to difference in the magnitude rather than the direction of effect and was not considered serious enough to downgrade the evidence as a single criterion.
e. Downgraded by two levels for unclear risk of bias relating to loss to follow-up and imprecision: 95% confidence interval includes both clinically significant and unclear benefits.
f. Downgraded by two levels for imprecision due to the absence of events in either arm.

Sleeve gastrectomy compared to best medical care for type 2 diabetes and obesity

Patient or population: type 2 diabetes and obesity
Setting: not defined
Intervention: Sleeve gastrectomy
Comparison: best medical care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with best medical care	Risk with Sleeve gastrectomy				
T2D remission assessed with: HbA1c <48 mmol/mol follow-up: 3 years	1 per 100	29 per 100 (2 to 100)	RR 23.78 (1.46 to 386.69)	89 (1 RCT)	⨁⨁⨁◯ Moderate[a]	An additional 29 per 100 participants randomised to SG were in T2D remission compared with best medical care at 3 years follow-up based on limited evidence.
T2D remission assessed with: HbA1c<48 mmol/mol follow-up: 5 years	1 per 100	24 per 100 (1 to 100)	RR 18.69 (1.14 to 307.22)	85 (1 RCT)	⨁⨁◯◯ Low[b,c]	An additional 23 participants per 100 randomised to SG were in T2D remission compared with best medical care at 3 years follow-up based on limited evidence.
Glycaemic control assessed with: HbA1c follow-up: 3 years	-	SMD 0.82 SD lower (1.26 lower to 0.39 lower)	-	89 (1 RCT)	⨁⨁⨁◯ Moderate[b]	Participants randomised to SG had clinically significant reductions in HbA1c levels at 3 years follow-up compared with best medical care based on limited evidence.
Glycaemic control assessed with: HbA1c follow-up: 5 years	-	SMD 0.82 SD lower (1.27 lower to 0.38 lower)	-	85 (1 RCT)	⨁⨁⨁◯ Moderate[b]	Participants randomised to SG had clinically significant reductions in HbA1c levels at 5 years follow-up compared with best medical care based on limited evidence.
30-day mortality follow-up: 30 days	0 per 100	0 per 100 (0 to 0)	not estimable	92 (1 RCT)	⨁⨁◯◯ Low[d]	There was no evidence of a difference in the mortality rate between SG and best medical care, although trials were not powered to detect differences in rare serious adverse events.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
Note: GRADE does not automatically apply a continuity correction for studies with zero events in one or more arms. Where zero events were reported in the comparator group, estimation of the absolute risk relative to the comparison group was not possible. The risk in the comparison group reflects the random or fixed effect weight estimated using R. Minor variation in methods for calculation of absolute risk using GRADE and R may produce minor discrepancies (e.g. studies are not weighted in GRADE estimates of absolute effect).
CI: confidence interval; RR: risk ratio; SMD: standardised mean difference

Sleeve gastrectomy compared to best medical care for type 2 diabetes and obesity

Patient or population: type 2 diabetes and obesity
Setting: not defined
Intervention: Sleeve gastrectomy
Comparison: best medical care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with best medical care	Risk with Sleeve gastrectomy				

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded by one level due to unclear risk of bias related to differential loss to follow-up and potential for imprecision related to the low number of events.
b. Downgraded by one level due to unclear risk of bias related to differential loss to follow-up.
c. Downgraded by one level due to imprecision: 95% confidence intervals includes both clinically significant and unclear clinical benefits.
d. Downgraded by two levels for imprecision due to the absence of events in either arm and small sample size.

Roux-en-Y gastric bypass compared to sleeve gastrectomy for type 2 diabetes and obesity

Patient or population: type 2 diabetes and obesity
Setting: not defined
Intervention: Roux-en-Y gastric bypass
Comparison: sleeve gastrectomy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with sleeve gastrectomy	Risk with Roux-en-Y gastric bypass				
T2D remission assessed with: HbA1c <48 mmol/mol follow-up: 3 years	51 per 100	63 per 100 (50 to 80)	RR 1.24 (0.98 to 1.58)	152 (2 RCTs)	⨁⨁◯◯ Low[a,b]	There was no evidence of a clinically significant difference in T2D remission between RYGB and SG at three years' follow-up.
T2D remission assessed with: HbA1c <48 mmol/mol follow-up: 5 years	23 per 100	31 per 100 (16 to 60)	RR 1.31 (0.67 to 2.55)	96 (1 RCT)	⨁⨁⨁◯ Moderate[b,c]	There was no evidence of a clinically significant difference in T2D remission between RYGB and SG at five years' follow-up.
Glycaemic control assessed with: HbA1c follow-up: 3 years	-	SMD 0.12 SD lower (0.44 lower to 0.2 higher)	-	152 (2 RCTs)	⨁⨁◯◯ Low[a,b]	The difference in HbA1c between RYGB and SG at 3 years' follow-up was not clinically significant.
Glycaemic control assessed with: HbA1c follow-up: 5 years	-	SMD 0 SD (0.4 lower to 0.4 higher)	-	96 (1 RCT)	⨁⨁⨁◯ Moderate[c,d]	The difference in HbA1c between RYGB and SG at five years' follow-up was not clinically significant.
30-day mortality follow-up: 30 days	0 per 100	0 per 100 (0 to 0)	not estimable	421 (6 RCTs)	⨁⨁◯◯ Low[e]	There was no evidence of a difference in the mortality rate for RYGB compared with SG, although trials were not powered to detect rare serious adverse events.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; RR: risk ratio; SMD: standardised mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded by one level for risk of bias.
b. Downgraded by one level for imprecision: 95% CI included no difference in effect and important clinical differences in favour of RYGB.
c. Unclear risk of bias across several domains was not considered serious enough to downgrade the evidence as a single criterion.
d. Downgraded by one level for imprecision: 95% CI included important clinical benefits in favour of RYGB or SG.
e. Downgraded by two levels for imprecision due to the absence of events in either arm and small sample sizes.

One anastomosis gastric bypass compared to sleeve gastrectomy for type 2 diabetes and obesity

Patient or population: type 2 diabetes and obesity
Setting: not defined
Intervention: One anastomosis gastric bypass
Comparison: sleeve gastrectomy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with sleeve gastrectomy	Risk with One anastomosis gastric bypass				
T2D remission assessed with: HbA1c <48 mmol/mol follow-up: 1 year	47 per 100	93 per 100 (63 to 100)	RR 2.00 (1.35 to 2.97)	60 (1 RCT)	⨁⨁⨁◯ Moderate[a]	T2D remission was two times more likely in the LOAGB group relative to LSG at one year follow-up in one RCT.
T2D remission assessed with: HbA1C <48 mmol/mol follow-up: 5 years	30 per 100	60 per 100 (32 to 100)	RR 2.00 (1.08 to 3.72)	60 (1 RCT)	⨁⨁⨁◯ Moderate[b]	T2D remission was two times more likely in the LOAGB group relative to LSG at five years' follow-up in one RCT.
Glycaemic control assessed with: HbA1c follow-up: 1 year	-	SMD 0.7 SD lower (1.22 lower to 0.18 lower)	-	60 (1 RCT)	⨁⨁⨁◯ Moderate[c]	HbA1c was lower in participants randomised to LOAGB relative to LSG at one year, however the difference may not be clinically significant.
Glycaemic control assessed with: HbA1c follow-up: 5 years	-	SMD 0.49 SD lower (1.01 lower to 0.02 higher)	-	60 (1 RCT)	⨁⨁◯◯ Low[b,d]	HbA1c was lower in participants randomised to LOAGB relative to LSG at five years, however the difference may not be clinically significant.
30-day mortality follow-up: 30 days	0 per 100	0 per 100 (0 to 0)	not estimable	60 (1 RCT)	⨁⨁◯◯ Low[e]	There was no evidence of a difference in the mortality rate for LOAGB relative to LSG, although the trial was not powered to detect rare serious adverse events.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; RR: risk ratio; SMD: standardised mean difference

One anastomosis gastric bypass compared to sleeve gastrectomy for type 2 diabetes and obesity

Patient or population: type 2 diabetes and obesity
Setting: not defined
Intervention: One anastomosis gastric bypass
Comparison: sleeve gastrectomy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with sleeve gastrectomy	Risk with One anastomosis gastric bypass				

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded by one level overall for unclear risk of bias and imprecision. The effect estimate was based on few events.
b. Downgraded by one level for risk of bias related to loss to follow-up. 20% loss to follow-up in both arms. Methods for multiple imputation of results were poorly reported.
c. Downgraded by one level overall for unclear risk of bias and imprecision. 95% CI include effect estimates that may not be clinically significant.
d. Downgraded by one level for imprecision. 95% CI includes no effect and clinically important differences.
e. Downgraded by two levels overall. Results were downgraded for imprecision due to the absence of events in either arm and small sample sizes. Concerns regarding unclear risk of bias.

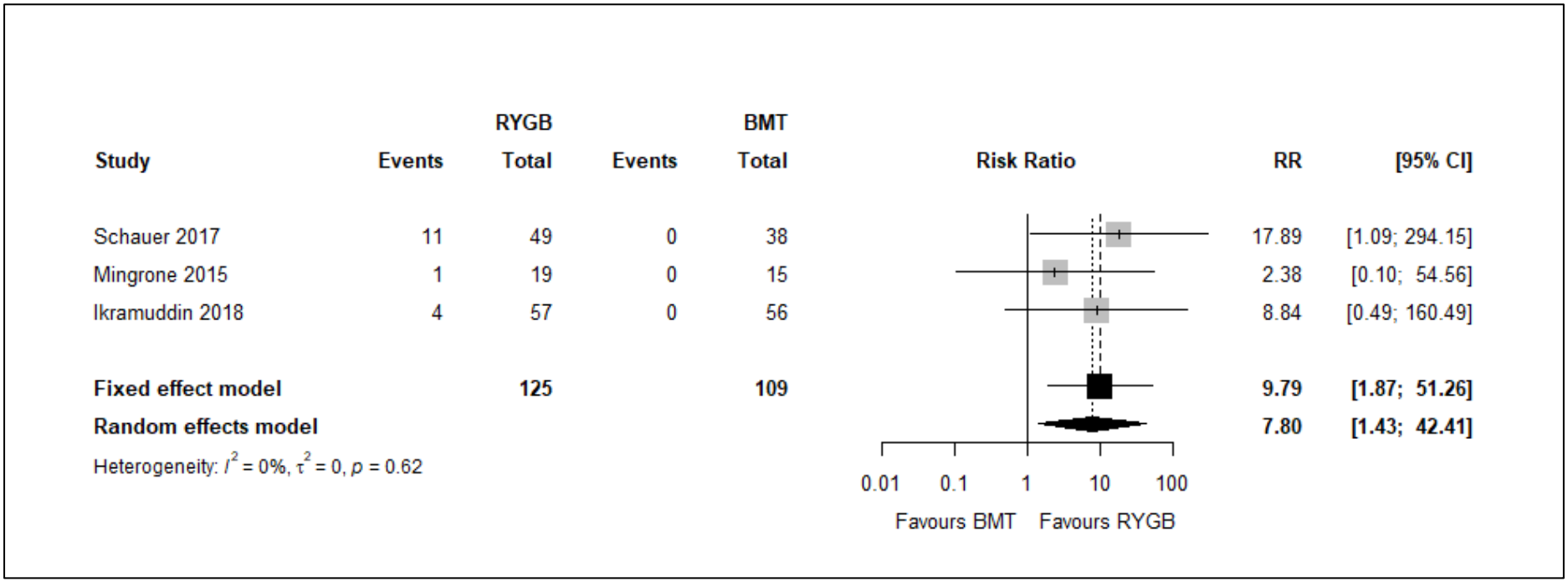
Appendix A3.4. Additional results for T2D remission

Table A3.1 Effect of metabolic surgery compared with best medical management on T2D remission (HbA1c <6%)†

Comparison	Number of RCTs	Author, year	Surgery (n)	Comparator (n)	Risk ratio (95% CI)	P value‡	I^2 (95% CI)	Risk difference (95% CI)	P value‡	I^2 (95% CI)
One year follow-up										
RYGB v BMC	2	Cummings 2016; Schauer 2012	65	58	19.51 (3.78 to 100.60)	**0.0004**	0.0%	0.45 (0.33 to 0.58)	**<0.0001**	0.0%
SG v BMC	1	Schauer 2012	49	41	22.68 (1.39 to 370.25)	**0.0285**	NA	0.27 (0.14 to 0.39)	**<0.0001**	NA
Mix of surgeries v BMC	1	Parikh 2014	20	24	32.14 (2.03 to 509.08)	**0.0138**	NA	0.65 (0.44 to 0.86)	**<0.0001**	NA
Two years follow-up										
RYGB v BMC	1	Ikramuddin 2018 (2 years)	57	56	18.67 (1.11 to 313.33)	**0.0419**	NA	0.16 (0.06 to 0.26)	**0.0016**	NA
LAGB v BMC	1	Dixon 2008	30	30	5.50 (2.15 to 14.04)	**0.0004**	NA	0.60 (0.40 to 0.80)	**<0.0001**	NA
Three years follow-up										
RYGB v BMC	2	Schauer 2014; Ikramuddin 2018 (3 years)	105	96	22.29 (3.04 to 163.46)	0.0023	0.0%	0.22 (0.15 to 0.30)	**<0.0001**	87.9 (53.3 to 96.6)
SG v BMC	1	Schauer 2014	49	40	17.22 (1.04 to 285.12)	**0.0469**	NA	0.20 (0.09 to 0.32)	**0.0007**	NA
Five years follow-up										
RYGB v BMC	3	Schauer 2017; Mingrone 2015; Ikramuddin 2018	125	109	9.79 (1.87 to 51.26)	**0.0069**	0.0% (0.0 to89.6)	0.12 (0.06 to 0.19)	**<0.0001**	64.7 (0.0 to 89.9)
SG v BMC	1	Schauer 2017	47	38	12.19 (0.72 to 206.80)	0.0835	NA	0.15 (0.04 to 0.26)	**0.0072**	NA
BPD v BMC	1	Mingrone 2015	19	15	0.79 (0.02 to 37.84)	0.915	NA	0.00 (-0.11 to 0.11)	1.000	NA

† HbA1c <6% without anti-hyperglycaemic medication in accordance with the previous American Diabetes Association (ADA) definition of complete T2D remission.[526]

Figure A3.1. Effect of RYGB compared with best medical management on T2D remission at five years follow-up†



† HbA1c <6% without antihyperglycaemic medication in accordance with the previous American Diabetes Association (ADA) definition of complete T2D remission.[526]

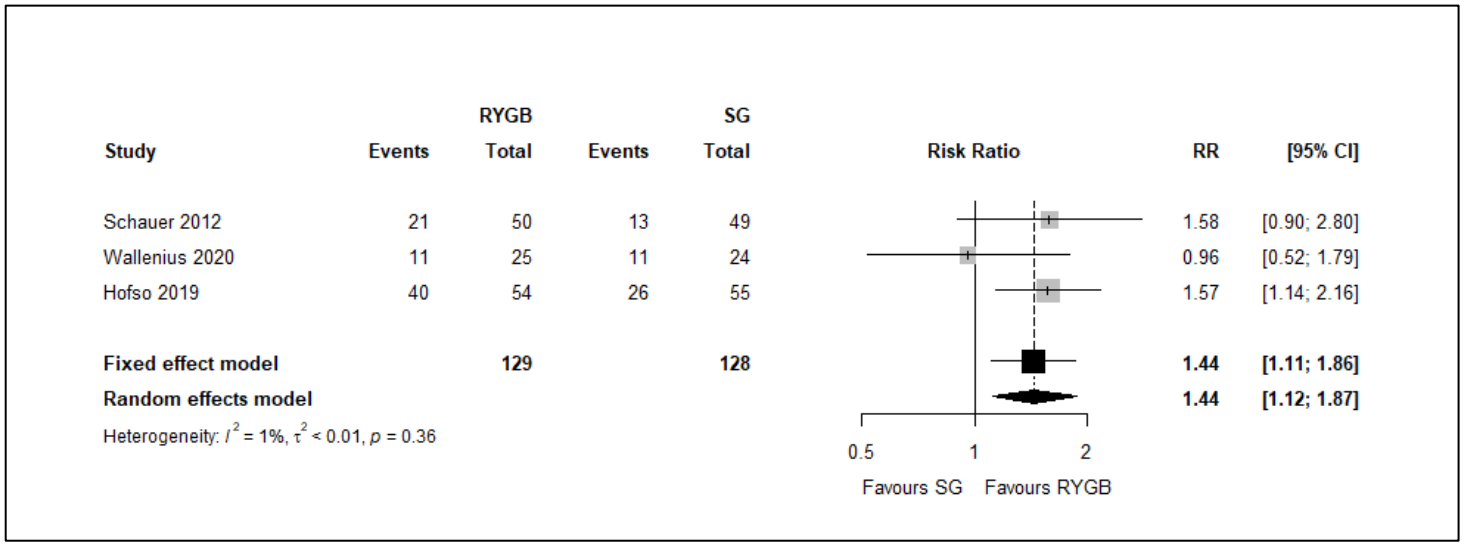
Table A3.2. Effect of metabolic surgery compared with other metabolic surgeries on T2D remission†

Comparison	Number of RCTs	Author, year	Surgery (n)	Comparator (n)	Risk ratio (95% CI)	P value‡	I^2 (95% CI)	Risk difference (95%CI)	P value‡	I^2 (95% CI)
One year follow-up										
RYGB v SG	3	Schauer 2012; Wallenius 2020; Hofso 2019	129	128	1.44 (1.11 to 1.86)	**0.0062**	0.8 (0.0 to 89.7)	0.17 (0.05 to 0.29)	**0.0041**	32.7 (0.0 to 93.0)
SR-LRYGB v LSG	1	Murphy 2018	56	53	1.06 (0.73 to 1.53)	0.7760	NA	0.03 (-0.16 to 0.22)	0.7757	NA
mRYGB v SG	1	Casajoana 2017	15	14	1.40 (0.83 to 2.35)	0.2042	NA	0.23 (-0.10 to 0.56)	0.1732	NA
mRYGB v GCP	1	Casajoana 2017	15	15	4.00 (1.41 to 11.35)	**0.0092**	NA	0.60 (0.31 to 0.89)	**<0.0001**	NA
SG v GCP	1	Casajoana 2017	14	15	2.86 (0.94 to 8.66)	0.0636	NA	0.37 (0.04 to 0.70)	**0.0269**	NA
Two years follow-up										
RYGB v SG	2	Tang 2016; Wallenius 2020	63	56	0.80 (0.54 to 1.17)	0.2492	0.0	-0.11 (-0.28 to 0.07)	0.2455	0.0
Three years follow-up										
RYGB v SG	2	Schauer 2014; Yang 2015	75	77	1.29 (0.96 to 1.72)	0.0874	61.5 (0.0 to 91.1)	0.12 (-0.01 to 0.25)	0.0805	0.0

Five years follow-up										
RYGB v SG	1	Schauer 2017	49	47	1.51 (0.64 to 3.56)	0.3492	NA	0.08 (-0.08 to 0.23)	0.3392	NA
BPD V RYGB	1	Mingrone 2015	19	19	7.00 (0.95 to 51.54)	0.0561	NA	0.31 (0.08 to 0.55)	**0.0096**	NA
mRYGB v SG	1	Casajoana 2017	14	14	2.33 (0.75 to 7.23)	0.1422	NA	0.29 (-0.05 to 0.62)	0.0984	NA
mRYGB v GCP	1	Casajoana 2017	14	14	7.00 (0.99 to 49.69)	0.0517	NA	0.43 (0.13 to 0.72)	**0.0044**	NA
SG v GCP	1	Casajoana 2017	14	14	3.00 (0.35 to 25.46)	0.314	NA	0.14 (-0.11 to 0.40)	0.2699	NA

† HbA1c <6% without antihyperglycaemic medication in accordance with the previous American Diabetes Association (ADA) definition of complete T2D remission.[526]

Figure A4.2. Effect of RYGB compared with SG on T2D remission at one year follow-up†



† HbA1c <6% without antihyperglycaemic medication in accordance with the previous American Diabetes Association (ADA) definition of complete T2D remission.[526]

Any T2D remission

Table A3.3. Definitions of T2D remission used for "any T2D remission"†

Study, year	Definition of T2D remission
Azevedo 2018†	HbA1c level <6.0%
Casajoana 2017; 2021	HbA1c < 6.5% and fasting glucose <100 mg/dL (<5.6 mmol/L) with no diabetes medication for 1 year
Cohen 2020 (MOMS) †	HbA1c level ≤6.0% [<42 mmol/mol]
Courcoulas 2014; 2015, 2020 (TRIABETES)	Partial or complete remission: ▪ Partial remission: the absence of any medications HbA1c level <6.5% and FPG ≤125 mg/dL ▪ Complete remission: absence of medications with HbA1c <5.7% and FPG ≤100 mg/dL
Cummings 2016 (CROSSROADS)	HbA1c <6.5% [<47.5 mmol/mol], off all diabetes medicines
Dixon 2008†	FPG levels less than 126 mg/dL in addition to HbA1c values less than 6.2% without the use of oral hypoglycemics or insulin
Ding 2015; Simonson 2019† (SLIMM-T2D)	Ding 2015: HbA1c <6.5% and a fasting plasma glucose <7.0 mmol/L (126 mg/dL) and off medications Simonson 2019: HbA1c <42.1 mmol/mol (<6.0%)
Halperin 2014; Simonson 2018† (SLIMM-T2D)	HbA1c <42.1 mmol/mol (<6.0%)
Hofso 2019; 2021 (OSEBERG) †	HbA1c of <6·0% (42 mmol/mol) without the use of glucose-lowering medication
Ikramuddin 2013†; 2015; 2016; 2018 (Diabetes Surgery Study)	Ikramuddin 2013:§ HbA1c <6·0% (<42 mmol/mol) Ikramuddin 2018: Full or partial remission: ▪ Full remission: HbA1c level of less than 6.0% at the 4- and 5-year visits and no use of antihyperglycemic medication at either visit ▪ Partial remission: HbA1c level of 6.0%with 6.5% at the same time points
Katsogiannos 2019 (Bariglykos)	NA
Keidar 2013†	normal fasting glucose and HbA1c
Lee 2011; 2014	FPG < 126 mg/dL and HbA1c <6.5% without medication

Liang 2013¶	Unclear
Mingrone 2012; 2015, 2021	fasting glucose level of <100 mg per deciliter [5.6 mmol per liter] and a glycated hemoglobin level of <6.5% in the absence of pharmacologic therapy
Murphy 2018	HbA1c <6.5% (48 mmol/mol) without diabetes medication
Parikh 2014	no longer meeting the ADA criteria for T2DM, without the use of diabetes medications
Picu 2020 (CREDOR) †	HbA1c ≤6%
Ren 2015†	HbA1c <6%
Schauer 2012†; 2015; 2017 (STAMPEDE)	Schauer 2012: HbA1c < 6.0% Schauer 2014; 2017: HbA1c ≤6.5% without diabetes medications
Tang 2016	FPG concentration of ≤6.9 mmol/L or less and a HbA1c concentration of ≤6.5% (47.5 mmol/mol) without active pharmacological treatment for at least 1 year
Wallenius 2020†	HbA1c <6.0% (42 mmol/mol)
Yan 2021	NA
Yang 2021	HbA1c ≤6.5 % without medications

Key: ADA – American Diabetes Association; FPG – fasting plasma glucose; HbA1c – glycated Haemoglobin; NA – not applicable.
† HbA1c <6% with anti-hyperglycaemic medication is considered sufficiently equivalent to HbA1c <6.5% without anti-hyperglycaemic medication based on consultation with clinical experts. Unless it was explicitly stated in the definition of T2D remission that participants no longer required anti-hyperglycaemic medication for T2D management at HbA1c <6%, it was assumed that some participants may still be taking medication.
‡ Conservative definition of T2D remission based on current guidance. Alternative definitions were not reported.
§ Analyses based on multiple imputation were reported for 2 to 5 years follow-up in Ikramuddin 2018. Data for the outcome T2D remission at 1 year follow-up were extracted from Ikramuddin 2013.
¶ Excluded from the analyses as the cut-point used to diagnose T2D remission was not reported.

Table A3.4. Effect of metabolic surgery compared with best medical management on any T2D remission†

Comparison	Number of RCTs	Author, year	Surgery (n)	Comparator (n)	Risk ratio (95% CI)	P value‡	I^2 (95% CI)	Risk difference (95% CI)	P value‡	I^2 (95% CI)
One year follow-up										
RYGB v BMC	5	Courcoulas 2020 (1 year); Cummings 2016; Simonson 2018, Ikramuddin 2018 (1 year); Schauer 2012	165	157	5.06 (2.86 to 8.95)	**<0.0001**	0.0 (0.0 to 79.2)	0.38 (0.29 to 0.46)	**<0.0001**	1.5% (0.0 to 79.5)
AGB v BMC	2	Courcoulas 2020 (1 year); Simonson 2019 (1 year)	40	45	8.79 (1.12 to 69.12)	0.0388§	0.0%	0.17 (0.05 to 0.29)	0.0054§	74.1 (0.0 to 94.2)
SG v BMC	2	Iosif 2019; Schauer 2012	68	58	4.30 (2.07 to 8.91)	**<0.0001**	24.6	0.40 (0.26 to 0.53)	**<0.0001§**	93.8 (80.2 to 98.1)
Mix of surgeries v BMC	1	Parikh 2014	20	24	32.14 (2.03 – 509.08)	**0.0138**	NA	0.65 (0.44 to 0.86)	**<0.0001**	NA
Two years' follow-up										
RYGB v BMC	5	Cohen 2020; Courcoulas 2020 (2 years); Simonson 2018; Ikramuddin 2018 (2 years); Mingrone 2012	167	164	9.33 (1.58 to 55.08)	**0.0137**	70.3% (24.3 – 88.3)	0.35 (0.15 to 0.56)	**0.0006**	85.3 (67.4 to 93.3)

AGB v BMC	3	Dixon 2008; Simonson 2019 (2 years); Courcoulas 2020 (2 years)	69	72	5.65 (2.46 to 12.94)	**<0.0001**	0.0% (0.0 to 89.6)	0.36 (0.24 to 0.47)	**<0.0001§**	88.6 (68.5 to 95.9)
BPD v BMC	1	Mingrone 2012	20	20	39.00 (2.52 to 604.71)	**0.0088**	NA	0.95 (0.82 to 1.08)	**<0.0001**	NA
SG-TB v BMC	1	Azevedo 2018	10	10	9.00 (1.39 – 58.44)	**0.0213**	NA	0.80 (0.54 to 1.06)	**<0.0001**	NA
Three years' follow-up										
RYGB v BMC	4	Courcoulas 2020 (3 years); Simonson 2018; Ikramuddin 2018 (3 years); Schauer 2014	144	135	17.44 (4.31 to 72.98)	**<0.0001**	0.0% (0.0 – 84.7)	0.29 (0.13 to 0.45)	**0.0003**	76.9 (37.1 to 91.5)
AGB v BMC	2	Courcoulas 2015; Simonson 2019	39	42	6.06 (1.07 to 34.35)	**0.0420§**		0.18 (0.05 to 0.31)	**0.0077§**	
SG v BMC	1	Schauer 2014	49	40	23.78 (1.46 to 386.69)	**0.0259**	NA	0.29 (0.16 to 0.42)	**<0.0001**	NA
Five years' follow-up										
RYGB v BMC	4	Courcoulas 2020; Ikramuddin 2018; Mingrone 2015; Schauer 2017	145	129	6.20 (1.96 to 19.60)	**0.0019**	1.9% (0.0 to 85.0)	0.24 (0.06 to 0.42)	**0.0082**	82.3 (54.3 to 93.1)
AGB V BMC	1	Courcoulas 2020	21	20	8.59	0.1405	NA	0.19	**0.0389**	NA

					(0.49 to 150.00)			(0.01 to 0.37)		
SG V BMC	1	Schauer 2017	47	38	18.69 (1.14 to 307.22)	**0.0404**	NA	0.23 (0.11 to 0.36)	**0.0003**	NA
BPD V BMC	1	Mingrone 2015	19	15	20.00 (1.28 – 312.60)	**0.0327**	NA	0.63 (0.40 to 0.86)	**<0.0001**	NA
Ten years' follow-up										
RYGB v BMC	1	Mingrone 2021	20	18	4.50 (0.58 to 34.97)	0.1505	NA	0.19 (-0.02 to 0.41)	0.0794	NA
BPD V BMC	1	Mingrone 2021	20	18	9.00 (1.27 – 63.54)	**0.0276**	NA	0.44 (0.20 to 0.69)	**0.0003**	NA

† "Any T2D remission" was based on a ranking system of T2D definitions: 1 - HbA1c <6.5% without pharmacological therapy (updated definition); 2 - HbA1c <6% with or without pharmacological therapy; 3 - HbA1c <6% without pharmacological therapy (previously full remission).
‡ P <0.05 is considered statistically significant. Bold values denote statistical significance.
§ Tests for statistical significance yield different results under fixed or random effects meta-analysis due to the presence of significant statistical heterogeneity.

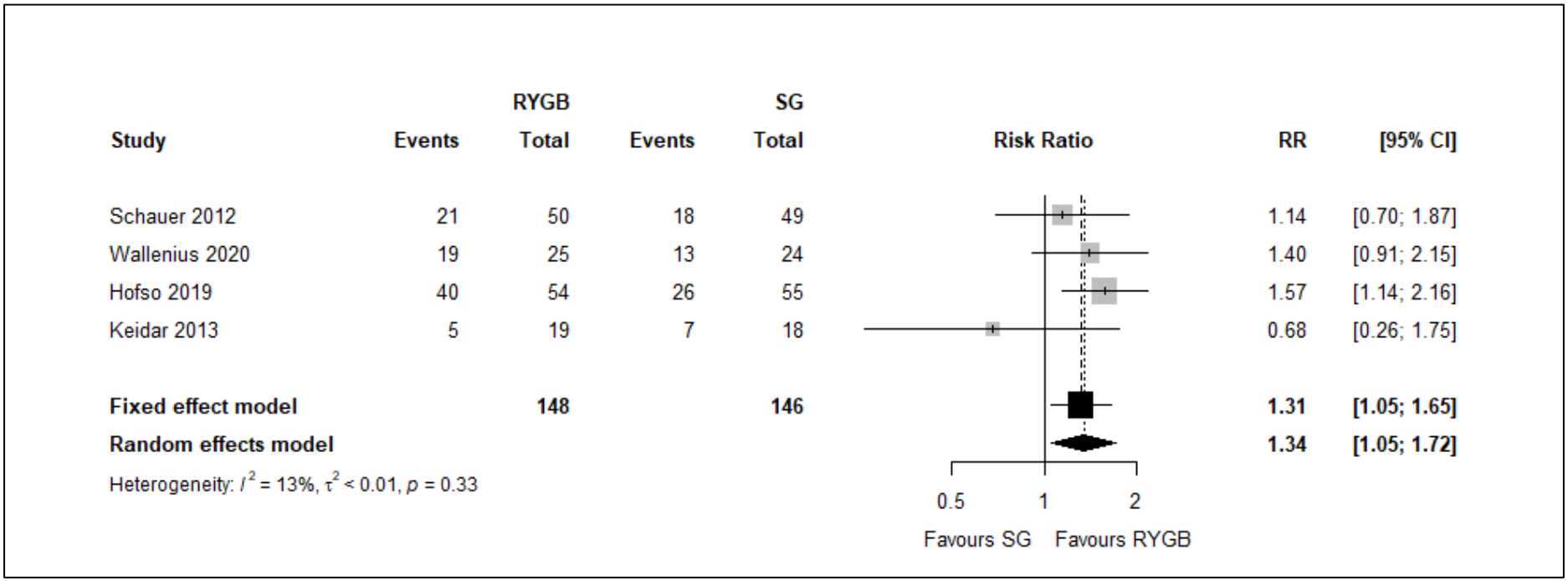
Table A3.5 Effect of metabolic surgery compared with other metabolic surgeries on any T2D remission†

Comparison	Number of RCTs	Author, year	Surgery (n)	Comparator (n)	Risk ratio (95% CI)	P value‡	I^2 (95% CI)	Risk difference (95% CI)	P value‡	I^2 (95% CI)
One year follow-up										
RYGB v SG	4	Schauer 2012; Wallenius 2020; Hofso 2019; Keidar 2013	148	146	1.34 (1.05 to 1.72)	**0.0174**	12.6% (0.0 to 86.6)	0.12 (-0.04 to 0.28)	0.1359	51.5 (0.0 to 84)
RYGB v AGB	1	Courcoulas 2020 (1 year)	24	22	1.83 (0.83 to 4.04)	0.1331	NA	0.23 (-0.05 to 0.50)	0.1030	NA
OAGB v SG	1	Lee 2011	30	30	2.00 (1.35 to 2.97)	**0.0006**	NA	0.47 (0.27 to 0.67)	**<0.0001**	NA
SR-RYGB v SG	1	Murphy 2018	56	53	1.05 (0.83 to 1.31)	0.6973	NA	0.03 (-0.13 to 0.20)	0.6967	NA
Small pouch RYGB v Large pouch RYGB	1	Ren 2015	36	33	1.19 (0.61 to 2.34)	0.6110	NA	0.06 (-0.16 to 0.28)	0.6078	NA
mRYGB v SG	1	Casajoana 2017	15	15	1.63 (1.08 to 2.47)	**0.0207**	NA	0.40 (0.14 to 0.66)	**0.0021**	NA
mRYGB v GCP	1	Casajoana 2017	15	15	1.82 (1.14 to 2.91)	**0.0120**	NA	0.47 (0.21 to 0.73)	**0.0004**	NA
SG v GCP	1	Casajoana 2017	15	15	1.13 (0.60 to 2.11)	0.7133	NA	0.07 (-0.29 to 0.42)	0.7119	NA
Two years' follow-up										
RYGB v SG	2	Tang 2016; Wallenius 2020	63	56	- 0.91 (0.71 to 1.17)	0.4621	67.9 (0.0 to 92.8)	-0.06 (-0.23 to -.10)	0.4490	69.2 (0.0 to 93.1)
RYGB v AGB	1	Courcoulas 2020 (2 year)	24	22	1.58 (0.69 to 3.62)	0.2845	NA	0.16 (-0.13 to 0.46)	0.2690	NA
RYGB v BPD	1	Mingrone 2012	20	19	0.79	0.0888	NA	-0.20	0.0650	NA

					(0.60 to 1.04)			(-0.41 to 0.013)		
Three years' follow-up										
RYGB v SG	2	Schauer 2014; Yang 2015	75	77	1.24 (0.98 to 1.58)	0.0791	81.3 (20.4 to 95.6)	0.12 (-0.01 to 0.25)	0.0712	37.7
RYGB v AGB	1	Courcoulas 2020 (3 years)	20	21	1.40 (0.59 to 3.32)	0.4450	NA	0.11 (-0.17 to 0.44)	0.4380	NA
Five years' follow-up										
RYGB v SG	1	Schauer 2017	49	47	1.31 (0.67 to 2.55)	0.4303	NA	0.07 (-0.11 to 0.25)	0.4246	NA
RYGB v AGB	1	Courcoulas 2020	20	21	1.58 (0.52 to 4.77)	0.4213	NA	0.11 (-0.15 to 0.37)	0.4123	NA
RYGB v BPD	1	Mingrone 2015	19	19	0.58 (0.30 to 1.15)	0.1211	NA	-0.26 (-0.57 to 0.04)	0.0927	NA
OAGB v SG	1	Lee 2015	30	30	2.00 (1.08 to 3.72)	**0.0284**	NA	0.30 (0.06 to 0.54)	**0.0143**	NA
mRYGB v SG	1	Casajoana 2021	15	15	2.80 (1.35 to 5.80)	**0.0056**	NA	0.60 (0.33 to 0.87)	**<0.0001**	NA
mRYGB v GCP	1	Casajoana 2021	15	15	7.00 (1.91 to 25.62)	**0.0033**	NA	0.80 (0.59 to 1.01)	**<0.0001**	NA
SG v GCP	1	Casajoana 2021	15	15	2.50 (0.57 to 10.93)	0.2235	NA	0.20 (-0.09 to 0.49)	0.1826	NA
Ten years' follow-up										
RYGB v BPD	1	Mingrone 2021	20	20	0.50 (0.21 to 1.20)	0.1212	NA	-0.25 (-0.54 to 0.04)	0.0910	NA

† "Any T2D remission" was based on a ranking system of T2D definitions: 1 - HbA1c <6.5% without pharmacological therapy (updated definition); 2 - HbA1c <6% with or without pharmacological therapy; 3 - HbA1c <6% without pharmacological therapy (previously full remission).
‡ P <0.05 is considered statistically significant. Bold values denote statistical significance.
§ Pooled estimate based on the random effects model.
¶ Pooled estimate based on the fixed effects model.

Figure A3.3 Effect of RYGB versus SG on T2D remission at one year follow-up†



Appendix A3.5 Additional results for change in HbA1c

Table A3.6. Standardised mean difference in change in HbA1c from baseline for metabolic surgery compared with best medical care

Comparison	Number of RCTs	Author, year	Surgery (n)	Comparator (n)	SMD	(95% CI)	P value†	I^2	(95% CI)
One year follow-up									
RYGB v BMC	6	Cummings 2016; Halperin 2014; Schauer 2012; Courcoulas 2014; Ikramuddin 2013; Liang 2013	192	187	-0.84	(-1.14 to -0.53)	**<0.0001**	47.0%	(0.0 to 79.0)
AGB v BMC	2	Ding 2015; Courcoulas 2014	39	42	-0.35	(-0.79 to -0.09)	0.1205	0.0%	NA
SG v BMC	2	Picu 2020; Schauer 2012	68	56	-1.12	(-1.50 to -0.73)	**<0.0001**	79.6%	(12.2 to 95.3)
Mix of surgeries v BMC	1	Parikh 2014	20	24	-0.96	(-1.59 to -0.33)	**0.0029**	NA	NA
Two years' follow-up									
RYGB v BMC	5	Cohen 2020; Simonson 2018; Courcoulas 2020; Mingrone 2012; Ikramuddin 2015	166	162	-0.70	(-1.07 to -0.33)	**0.0002**	59.0	(0.0 to 84.7)
LAGB v BMC	3	Dixon 2008; Simonson 2019; Courcoulas 2020	69	72	-0.73	(-1.08 to -0.39)	**<0.0001**	44.4	(0.0 to 83.4)
BPD v BMC	1	Mingrone 2012	19	18	-3.46	(-4.52 to -2.41)	**<0.0001**	NA	NA
SG-TB v BMC	1	Azevedo 2018	10	10	-1.82	(-2.90 to -0.74)	**0.0009**	NA	NA
Three years' follow-up									
RYGB v BMC	4	Simonson 2018; Schauer 2015; Courcoulas 2015; Ikramuddin 2016	144	135	-0.99	(-1.24 to -0.74)	**<0.0001**	0.0	(0.0 to 84.7)

AGB v BMC	2	Simonson 2019; Courcoulas 2015	39	42	-0.67	(-1.12 to -0.22 to -0.86)	**0.0037**	0.0	NA
SG v BMC	1	Schauer 2014	49	40	-0.82	(-1.26 to -0.39)	**0.0002**	NA	NA
Five years' follow-up									
RYGB v BMC	4	Schauer 2017; Courcoulas 2020; Ikramuddin 2018; Mingrone 2015	145	129	-0.73	(-1.08 to -0.37)	**<0.0001**	46.4	(0.0 to 82.2)
AGB v BMC	1	Courcoulas 2020	21	20	-0.78	(-1.42 to -0.15)	**0.0162**	NA	NA
SG v BMC	1	Schauer 2017	47	38	-0.82	(-1.27 to -0.38)	**0.0003**	NA	NA
BPD v BMC	1	Mingrone 2015	19	15	-0.58	(-1.28 to 0.11)	0.0982	NA	NA
Ten years' follow-up									
RYGB v BMC	1	Mingrone 2021	20	15	-0.78	(-1.48 to -0.08)	**0.0283**	NA	NA
BPD v BMC	1	Mingrone 2021	20	15	-1.13	(-1.86 to -0.41)	**0.0022**	NA	NA

† P <0.05 is considered statistically significant. Bold values denote statistical significance.
‡ Tests for statistical significance yield different results under fixed or random effects meta-analysis due to the presence of significant statistical heterogeneity.

Table A3.7. Standardised mean difference in change from baseline in HbA1c for metabolic surgery compared with other metabolic surgeries

Comparison	Number of RCTs	Author, year	Surgery (n)	Comparator (n)	SMD	(95% CI)	P value†	I^2	(95% CI)
One year follow-up									
RYGB v SG	4	Schauer 2012; Hofso 2019; Wallenius 2020; Keidar 2013	148	146	0.01	(-0.22 to 0.24)	0.9458	0.0%	(0.0 to 84.7)
LGBP v LSG	1	Yan 2021	77	80	-0.03	(-0.34 to 0.29)	0.8746	NA	NA
RYGB v AGB	1	Courcoulas 2020 (1 year)	20	21	-0.66	(-1.29 to -0.03)	**0.0414**	NA	NA
LOAGB v LSG	1	Lee 2011	30	30	-0.70	(-1.22 to -0.18)	**0.0085**	NA	NA
Small pouch RYGB v large pouch RYGB	1	Ren 2015	36	33	-0.63	(-1.11 to -0.14)	**0.0109**	NA	NA

mRYGB v SG	1	Casajoana 2017	15	14	-0.27	(-1.01 to 0.46)	0.4651	NA	NA
mRYGB v GCP	1	Casajoana 2017	15	15	-0.37	(-1.10 to 0.35)	0.3129	NA	NA
SG v GCP	1	Casajoana 2017	14	15	-0.14	(-0.87 to 0.59)	0.7092	NA	NA
Two years' follow-up									
RYGB v SG	2	Tang 2016; Wallenius 2020	63	58	0.18	(-0.18 to 0.53)	0.3367	0.0%	NA
RYGB v AGB	1	Courcoulas 2020	20	21	0.02	(-0.59 to 0.63)	0.9504	NA	NA
BPD v RYGB	1	Mingrone 2012	19	19	-1.07	(-1.76 to -0.39)	**0.0021**	NA	NA
Three years follow-up									
RYGB v SG	2	Schauer 2014; Yang 2015	75	77	-0.12	(-0.44 to 0.20)	0.4698	0.0%	NA
RYGB v AGB	1	Courcoulas 2020 (3 years)	20	21	-0.41	(-1.03 to 0.21)	0.197	NA	NA
Five years' follow-up									
RYGB v SG	1	Schauer 2017	49	47	0.00	(-0.40 to 0.40)	1.000	NA	NA
RYGB v AGB	1	Courcoulas 2020	20	21	-0.49	(-1.12 to 0.13)	0.1204	NA	NA
BPD v RYGB	1	Mingrone 2015	19	19	-0.30	(-0.94 to 0.34)	0.3654	NA	NA
LOAGB v LSG	1	Lee 2014	30	30	-0.49	(-1.01 to 0.02)	0.0609	NA	NA
mRYGB v SG	1	Casajoana 2021	14	14	-0.47	(-1.22 to 0.28)	0.2208	NA	NA
mRYGB v GCP	1	Casajoana 2021	14	14	-0.39	(-1.14 to 0.36)	0.311	NA	NA
SG v GCP	1	Casajoana 2021	14	14	0.03	(-0.71 to 0.77)	0.9415	NA	NA
Ten years' follow-up									
BPD v RYGB	1	Mingrone 2021	20	20	-0.31	(-0.93 to 0.32)	0.3359	NA	NA

† P <0.05 is considered statistically significant. Bold values denote statistical significance.
‡ Tests for statistical significance yield different results under fixed or random effects meta-analysis due to the presence of significant statistical heterogeneity.

Appendix A3.6 Additional results for change in BMI

Table A3.8. Standardised mean difference in change from baseline in BMI for metabolic surgery compared with best medical care

Comparison	Number of RCTs	Author, year	Surgery (n)	Comparator (n)	SMD	(95% CI)	P value†	I^2	(95% CI)
One year follow-up									
RYGB v BMC	6	Katsogiannos 2019; Courcoulas 2014; Liang 2013; Schauer 2012; Ikramuddin 2013; Halperin 2014	190	176	-2.24	(-3.00 to -1.48)	**<0.0001**	86.5	(72.9 to 93.3)
AGB v BMC	2	Ding 2015; Courcoulas 2014	39	42	-1.16	(-1.64 to -0.69)	**<0.0001**	0.0%	NA
SG v BMC	2	Picu 2020; Schauer 2012	68	56	-2.23	(-2.69 to -1.77)	**<0.0001**	68.0%	(0.0 to 92.8)
SG-TB v BMC	1	Azevedo 2018	10	10	-2.36	(-3.56 to -1.16)	**0.0001**	NA	NA
Mix of surgeries v BMC	1	Parikh 2014	20	24	-2.84	(-3.71 to -1.98)	**<0.0001**	NA	NA
Two years' follow-up									
RYGB v BMC	5	Mingrone 2012; Courcoulas 2020; Ikramuddin 2015; Cohen 2020; Simonson 2018	166	162	-2.31	(-3.15 to -1.47)	**<0.0001**	87.7	(73.7 to 94.2)
AGB v BMC	2	Simonson2019; Courcoulas 2020	39	42	-1.07	(-1.54 to -0.60)	**<0.0001**	0.0%	NA
BPD v BMC	1	Mingrone 2012	19	18	-3.33	(-4.36 to -2.30)	**<0.0001**	NA	NA
Three years' follow-up									

RYGB v BMC	4	Courcoulas 2015; Schauer 2014; Ikramuddin 2016; Simonson 2018	144	135	-1.78	(-2.59 to -0.98)	**0.0002**	86.4	(66.9 to 94.4)
AGB v BMC	2	Simonson 2019; Courcoulas 2015	39	42	-0.87	(-1.33 to -0.41)	**0.0002**		0.0%
SG v BMC	1	Schauer 2014	49	40	-1.67	(-2.15 to -1.18)	**<0.0001**	NA	NA
Five years' follow-up									
RYGB v BMC	4	Mingrone 2015; Courcoulas 2020; Schauer 2017; ikramuddin 2018	145	129	-1.63	(-2.29 to -0.96)	**<0.0001**	80.1	(47.5 to 92.5)
AGB v BMC	1	Courcoulas 2020	21	20	-0.88	(-1.53 to -0.24)	**0.0072**	NA	NA
SG v BMC	1	Schauer 2017	47	38	-1.26	(-1.73 to -0.79)	**<0.0001**	NA	NA
BPD v BMC	1	Mingrone 2015	19	15	-1.97	(-2.81 to -1.13)	**<0.0001**	NA	NA
Ten years' follow-up									
RYGB v BMC	1	Mingrone 2021	20	15	-2.28	(-3.15 to -1.40)	**<0.0001**	NA	NA
BPD v BMC	1	Mingrone 2021	20	15	-2.10	(-2.95 to -1.25)	**<0.0001**	NA	NA

† P <0.05 is considered statistically significant. Bold values denote statistical significance.

Table A3.9. Standardised mean difference (SMD) in change from baseline in BMI for metabolic surgery compared with other metabolic surgeries

Comparison	Number of RCTs	Author, year	Surgery (n)	Comparator (n)	SMD	(95% CI)	P value†	I^2	(95% CI)
One year follow-up									
RYGB v SG	4	Wallenius 2020; Keidar 2013; Hofso 2019; Schauer 2012	148	146	-0.46	(-0.94 to 0.02)	0.0609‡	74.0%	(27.3 to 90.7)
LGBP v LSG	1	Yan 2021	77	80	0.10	(-0.21 to 0.41)	0.5303	NA	NA
RYGB v AGB	1	Courcoulas 2020 (1 year)	20	21	-1.48	(-2.18 to -0.78)	**<0.0001**	NA	NA
LOAGB v LSG	1	Lee 2011	30	30	-0.24	(-0.75 to 0.27)	0.3577	NA	NA

SR-LRYGB v LSG	1	Murphy 2018	56	53	-0.52	(-0.90 to -0.13)	**0.0082**	NA	NA
Small pouch RYGB v large pouch RYGB	1	Ren 2015	36	33	-0.44	(-0.92 to -0.04)	0.0733	NA	NA
Two years' follow-up									
RYGB v SG	2	Tang 2016; Wallenius 2020	63	58	-0.20	(-0.56 to 0.16)	0.2659	54.3%	(0.0 to 88.8)
RYGB v AGB	1	Courcoulas 2020 (2 years)	20	21	-1.12	(-1.79 to -0.46)	**0.0009**	NA	NA
BPD v RYGB	1	Mingrone 2012	19	19	-0.05	(-0.69 to 0.58)	0.8657	NA	NA
Three years' follow-up									
RYGB v SG	2	Schauer 2014; Yang 2015	75	77	-0.68	(-1.01 to -0.35)	**<0.0001**	0.0%	NA
RYGB v AGB	1	Courcoulas 2020 (3 years)	20	21	-1.14	(-1.80 to -0.47)	**0.0008**	NA	NA
Five years' follow-up									
RYGB v SG	1	Schauer 2017	49	47	-0.37	(-0.78 to 0.03)	0.0688	NA	NA
RYGB v AGB	1	Courcoulas 2020	20	21	-1.29	(-1.97 to -0.61)	**0.0002**	NA	NA
BPD v RYGB	1	Mingrone 2015	19	19	-0.29	(-0.93 to 0.35)	0.3770	NA	NA
LOAGB v LSG	1	Lee 2014	30	30	-0.28	(-0.79 to 0.23)	0.2756	NA	NA
mRYGB v SG	1	Casajoana 2021	14	14	-0.86	(-1.64 to -0.08)	**0.0306**	NA	NA
mRYGB v GCP	1	Casajoana 2021	14	14	-1.24	(-2.06 to -0.42)	**0.003**	NA	NA
SG v GCP	1	Casajoana 2021	14	14	-0.23	(-0.98 to 0.51)	0.5390	NA	NA
Ten years' follow-up									
BPD v RYGB	1	Mingrone 2021	20	20	-0.14	(-0.77 to 0.48)	0.6486	NA	NA

† P <0.05 is considered statistically significant. Bold values denote statistical significance.
‡ Tests for statistical significance yield different results under fixed or random effects meta-analysis due to the presence of significant statistical heterogeneity.

Appendix A3.7 Additional results for change in blood pressure

Table A3.10. Standardised mean difference in change from baseline in systolic blood pressure for metabolic surgery compared with best medical care

Comparison	Number of RCTs	Author, year	Surgery (n)	Comparator (n)	SMD	(95% CI)	P value†	I^2	(95% CI)
One year follow-up									
RYGB v BMC	7	Katsogiannos 2019; Cummings 2016; Courcoulas 2020 (1 year);Simonson 2018 (1 year); Schauer 2012; Ikramuddin 2018 (1 year); Liang 2013	205	193	-0.37	(-0.64 to -0.10)	**0.0071**	38.8%	(0.0 to 74.3)
AGB v BMC	2	Simonson 2019 (1 year); Courcoulas 2020(1 year)	39	42	0.38	(-0.06 to 0.83)	0.0896	23.5%	NA
SG v BMC	2	Picu 2020; Schauer 2012	68	56	-0.01	(-0.36 to 0.35)	0.9651	0.0%	NA
Mix of surgeries v BMC	1	Parikh 2014	20	24	-0.15	(-0.74 to 0.45)	0.6278	NA	NA
Two years' follow-up									
RYGB v BMC	5	Courcoulas 2020 (2 years); Simonson 2018 (2 years); Mingrone 2012; Cohen 2020; Ikramuddin 2019 (2years)	166	162	-0.33	(-0.74 to 0.07)	0.1041	66.4%	(12.5 to 87.1)
AGB v BMC	3	Dixon 2008; Courcoulas 2020 (2 years); Simonson 2019 (2 years)	69	72	-0.24	(-0.57 to 0.09)	0.1555	0.0%	(0.0 to 89.6)
BPD v BMC	1	Mingrone 2012	19	18	-0.26	(-0.91 to 0.39)	0.4269	NA	NA
Three years' follow-up									

RYGB v BMC	4	Courcoulas 2020 (3 years); Simonson 2018 93 years); Schauer 2014; Ikramuddin 2018 (3 years)	144	135	-0.23	(-0.53 to 0.07)	0.137	33.4	(0.0 to 76.5)
AGB v BMC	2	Simonson 2019; Courcoulas 2020 (3 years)	39	42	0.02	(-0.41 to 0.46)	0.9221	0.0%	NA
SG v BMC	1	Schauer 2014	49	40	-0.23	(-0.65 to 0.19)	0.277	NA	NA
Five years' follow-up									
RYGB v BMC	4	Courcoulas 2020; Mingrone 2015; Schauer 2017; Ikramuddin 2018	145	129	-0.10	(-0.47 to 0.28)	0.6179	54.7%	(0.0 to 85.0)
AGB v BMC	1	Courcoulas 2020	21	20	0.08	(-0.53 to 0.69)	0.8026	NA	NA
SG v BMC	1	Schauer 2017	47	38	-0.21	(-0.64 to 0.22)	0.3366	NA	NA
BPD v BMC	1	Mingrone 2015	19	15	-0.03	(-0.70 to 0.65)	0.9356	NA	NA
Ten year follow-up									
RYGB v BMC	1	Mingrone 2021	20	20	0.21	(-0.46 to 0.88)	0.5443	NA	NA
BPD v BMC	1	Mingrone 2021	20	20	-0.19	(-0.86 to 0.48)	0.5840	NA	NA

† P <0.05 is considered statistically significant. Bold values denote statistical significance.

Table A3.11. Standardised mean difference in change from baseline in systolic blood pressure for metabolic surgery compared with other metabolic surgeries

Comparison	Number of RCTs	Author, year	Surgery (n)	Comparator (n)	SMD	(95% CI)	P value†	I^2	(95% CI)
One year follow-up									
RYGB v SG	3	Hofso 2019; Wallenius 2020; Schauer 2012	129	128	-0.09	(-0.34 to 0.15)	0.4612	75.6%	(19.6 to 92.6)
RYGB v AGB	1	Courcoulas 2020 (1 year)	20	21	-0.61	(-1.23 to 0.02)	0.0583	NA	NA
LOAGB v LSG	1	Lee 2011	30	30	-0.33	(-0.84 to 0.18)	0.2011	NA	NA
LSR-RYGB v LSG	1	Murphy 2018	56	53	0.07	(-0.31 to 0.45)	0.7170	NA	NA

Two years' follow-up									
RYGB v SG	1	Wallenius 2020	25	22	-0.58	(-1.17 to 0.01)	0.0513	NA	NA
RYGB v AGB	1	Courcoulas 2020 (2 years)	20	21	-0.75	(-1.38 to -0.11)	**0.0214**	NA	NA
BPD v RYGB	1	Mingrone 2012	19	19	-0.52	(-1.17 to 0.13)	0.1149	NA	NA
Three years' follow-up									
RYGB v SG	1	Schauer 2014	48	49	0.28	(-0.12 to 0.68)	0.1758	NA	NA
RYGB v AGB	1	Courcoulas 2020 (3 years)	20	21	-0.82	(-1.47 to -0.18)	**0.0116**	NA	NA
Five years' follow-up									
RYGB v SG	1	Schauer 2017	49	47	0.23	(-0.17 to 0.63)	0.2636	NA	NA
RYGB v AGB	1	Courcoulas 2020	20	21	-0.93	(-1.58 to -0.29)	**0.0048**	NA	NA
BPD v RYGB	1	Mingrone 2015	19	19	-0.46	(-1.11 to 0.18)	0.1608	NA	NA
LOAGB v LSG	1	Lee 2014	30	30	-0.63	(-1.14 to -0.11)	0.0182	NA	NA
Ten years' follow-up									
BPD v RYGB	1	Mingrone 2021	20	20	-0.49	(-1.12 to 0.14)	0.1290	NA	NA

† P <0.05 is considered statistically significant. Bold values denote statistical significance.

Table A3.12. Standardised mean difference in change from baseline in diastolic blood pressure for metabolic surgery compared with best medical care

Comparison	Number of RCTs	Author, year	Surgery (n)	Comparator (n)	SMD	(95% CI)	P value†	I^2	(95% CI)
One year follow-up									
RYGB v BMC	5	Katsogiannos 2019; Courcoulas 2020 (1 year);Simonson 2018 (1 year); Schauer 2012; Ikramuddin 2018 (1 year)	159	142	-0.20	(-0.43 to 0.03)	0.0816	0.0%	(0.0 to 79.2)
AGB v BMC	2	Courcoulas 2020 (1 year); Simonson 2019 (1 year)	39	42	0.20	(-0.24 to 0.63)	0.3819	0.0%	NA
SG v BMC	2	Picu 2020; Schauer 2012	68	56	0.14	(-0.22 to 0.49)	0.4527	0.0%	NA
Mix of surgeries v BMC	1	Parikh 2014	20	24	0.03	(-0.57 to 0.62)	0.9332	NA	NA
Two years' follow-up									
RYGB v BMC	5	Courcoulas 2020 (2 years); Simonson 2018 (2 years); Mingrone 2012; Cohen 2020; Ikramuddin 2018 (2 years)	166	162	-0.33	(-0.55 to -0.11)	**0.0031**	0.0%	(0.0 to 79.2)
AGB v BMC	3	Dixon 2008; Courcoulas 2020 (2 years); Simonson 2019 (2 years)	69	72	-0.10	(-0.43 to 0.23)	0.5592	9.6%	(0.0 to 90.6))
BPD v BMC	1	Mingrone 2012	19	18	-0.56	(-1.22 to 0.10)	0.0938	NA	NA
Three years' follow-up									
RYGB v BMC	4	Courcoulas 2020 (3 years); Simonson 2019; Schauer 2014; Ikramuddin 2018 (3 years)	144	135	-0.04	(-0.37 to 0.29)	0.8067	44.5%	(0.0 to 81.5)

-	2	Simonson 2019; Courcoulas 2020 (3 years)	39	42	0.08	(-0.36 to 0.53)	0.7143	82.0%	(24.2 to 95.7)
SG v BMC	1	Schauer 2014	49	40	0.02	(-0.40 to 0.43)	0.9395	NA	NA
Five years' follow-up									
RYGB v BMC	4	Courcoulas 2020; Mingrone 2015; Schauer 2017; Ikrauddin 2018	145	129	-0.16	(-0.41 to 0.10)	0.2265	9.1%	(0.0 to 86.1)
LAGB v BMC	1	Courcoulas 2020	21	20	0.19	(-0.42 to 0.81)	0.5348	NA	NA
SG v BMC	1	Schauer 2017	47	38	-0.29	(-0.72 to 0.14)	0.1862	NA	NA
BPD v BMC	1	Mingrone 2015	19	15	0.06	(-0.62 to 0.73)	0.8689	NA	NA
Ten years' follow-up									
RYGB v BMC	1	Mingrone 2021	20	15	0.17	(-0.50 to 0.84)	0.6281	NA	NA
BPD v BMC	1	Mingrone 2021	20	15	-0.29	(-0.96 to 0.39)	0.4016	NA	NA

† P <0.05 is considered statistically significant. Bold values denote statistical significance.
‡ Tests for statistical significance yield different results under fixed or random effects meta-analysis due to the presence of significant statistical heterogeneity.

Table A3.13. Standardised mean difference in change from baseline in diastolic blood pressure for metabolic surgery compared with other metabolic surgeries

Comparison	Number of RCTs	Author, year	Surgery (n)	Comparator (n)	SMD	(95% CI)	P value†	I^2	(95% CI)
One year follow-up									
RYGB v SG	3	Hofso 2019; Wallenius 20; Schauer 2012	129	128	-0.24	(-0.49 to 0.01)	0.0569	65.5%	(0.0 to 90.1)
RYGB v AGB	1	Courcoulas 2020 (1 year)	20	21	-0.58	(-1.21 to 0.04)	0.0683	NA	NA
LOAGB v LSG	1	Lee 2011	30	30	0.14	(-0.36 to 0.65)	0.5784	NA	NA
LSR-RYGB v LSG	1	Murphy 2018	56	53	-0.08	(-0.46 to 0.29)	0.6578	NA	NA
Two years' follow-up									

RYGB v SG	1	Wallenius 2020	25	22	-0.84	(-1.44 to -0.24)	**0.0062**	NA	NA
RYGB v AGB	1	Courcoulas 2020 (2 years)	20	21	-0.70	(-1.33 to -0.06)	**0.0308**	NA	NA
BPD v RYGB	1	Mingrone 2012	19	19	-0.61	(-1.27 to 0.04)	0.0655	NA	NA
Three years' follow-up									
RYGB v SG	1	Schauer 2014	48	49	0.17	(-0.23 to 0.57)	0.4128	NA	NA
RYGB v AGB	1	Courcoulas 2020 (3 years)	20	21	-0.98	(-1.63 to -0.32)	**0.0033**	NA	NA
Five years' follow-up									
RYGB v SG	1	Schauer 2017	49	47	0.17	(-0.23 to 0.57)	0.4144	NA	NA
RYGB v AGB	1	Courcoulas 2020	20	21	-0.79	(-1.43 to -0.15)	**0.015**	NA	NA
BPD v RYGB	1	Mingrone 2015	19	19	-0.32	(-0.96 to 0.32)	0.3343	NA	NA
LOAGB v LSG	1	Lee 2014	30	30	-0.79	(-1.31 to -0.26)	**0.0035**	NA	NA
Ten years' follow-up									
BPD v RYGB	1	Mingrone 2021	20	20	-0.55	(-1.19 to 0.08)	0.0858	NA	NA

† P <0.05 is considered statistically significant. Bold values denote statistical significance.

Appendix A3.8 Additional results for change in lipid profiles

Table A3.14. Standardised mean difference in change from baseline in total cholesterol for metabolic surgery compared with best medical care

Comparison	Number of RCTs	Author, year	Surgery (n)	Comparator (n)	SMD	(95% CI)	P value†	I^2	(95% CI)
One year follow-up									
RYGB v BMC	5	Simonson2018 (1 year); Schauer 2012; Courcoulas 2020 (1 year); Katsogiannos 2019; Liang 2013; Ikramuddin 2018 (1 year)	190	176	-0.32	(-0.69 to 0.05)	0.09	63.6%	(11.8 to 84.9)
LAGB v BMC	2	Simonson 2019 (1 year); Courcoulas 2020 (1 year)	39	42	-0.03	(-0.47 to 0.41)	0.883	5.8%	NA
SG v BMC	2	Picu 2020; Schauer 2012	68	56	0.18	(-0.18 to 0.53)	0.3291	0.0%	NA
Mix of surgeries v BMC	1	Parikh 2014	20	24	0.54	(-0.06 to 1.15)	0.0794	NA	NA
Two years' follow-up									
RYGB v BMC	5	Cohen 2020; Simonson 2018 (2 years); Courcoulas 2020 (2 years); Mingrone 2012; Ikramuddin 2018 (2 years)	166	162	0.12	(-0.18 to 0.41)	0.4367	38.2	(0.0 to 77.1)
LAGB v BMC	3	Dixon 2008; Simonson 2019 (2 years); Courcoulas 2020 (2 years)	69	72	0.18	(-0.15 to 0.51)	0.283	0.0%	(0.0 to 89.6)
BPD v BMC	1	Mingrone 2012	19	18	-2.75	(-3.67 to -1.82)	**<0.0001**	NA	NA
SG-TB v BMC	1	Azevedo 2018	10	10	-0.96	(-1.9 to -0.02)	**0.0442**	NA	NA

Three years' follow-up									
RYGB v BMC	3	Simonson 2018; Courcoulas 2020 (3 years); Ikramuddin 2018 (3 years)	96	95	-0.16	(-0.45 to 0.122)	0.2616	47.6%	(0.0 to 84.7)
AGB v BMC	2	Simonson 2019; Courcoulas 2020 (3 years)	39	42	0.22	(-0.22 to 0.65)	0.3337	0.0%	NA
Five years' follow-up									
RYGB v BMC	3	Courcoulas 2020; Mingrone 2015; Ikramuddin 2018	96	91	0.04	(-0.25 to 0.34)	0.7625	79.6	(35.2 to 93.6)
LAGB v BMC	1	Courcoulas 2020	21	20	0.27	(-0.34 to 0.89)	0.3840	NA	NA
BPD v BMC	1	Mingrone 2015	19	15	-0.76	(-1.47 to -0.06)	**0.0333**	NA	NA
Ten years' follow-up									
RYGB v BMC	1	Mingrone 2021	20	20	1.14	(0.41 to 1.87)	**0.0021**	NA	NA
BPD v BMC	1	Mingrone 2021	20	20	-0.62	(-1.31 to 0.07)	0.0764	NA	NA

† P <0.05 is considered statistically significant. Bold values denote statistical significance.
‡ Tests for statistical significance yield different results under fixed or random effects meta-analysis due to the presence of significant statistical heterogeneity.

Table A3.15. Standardised mean difference in change from baseline in total cholesterol for metabolic surgery compared with other metabolic surgeries

Comparison	Number of RCTs	Author, year	Surgery (n)	Comparator (n)	SMD	(95% CI)	P value†	I^2	(95% CI)
One year follow-up									
RYGB v SG	3	Schauer 2012; Hofso 2019; Wallenius 2020;	129	128	0.27	(0.02 to 0.52)	**0.034**‡	89.2	(70.6 to 96.0)
LGBP v BMC	1	Yan 2021	77	80	-0.01	(-0.32 to 0.31)	0.9732	NA	NA

RYGB v AGB	1	Courcoulas 2020 (1 year)	20	21	-0.61	(-1.24 to 0.02)	0.0574	NA	NA
LOAGB v LSG	1	Lee 2011	30	30	-0.16	(-0.66 to 0.35)	0.5415	NA	NA
LSR-RYGB v LSG	1	Murphy 2018	56	53	-0.67	(-1.06 to -0.29)	**0.0006**	NA	NA
Two years' follow-up									
RYGB v SG	2	Tang 2016; Wallenius 2020	63	56	-0.34	(-0.70 to 0.03)	0.0689	31.7 %	NA
RYGB v AGB	1	Courcoulas 2020 (2 years)	20	21	-0.01	(-0.62 to 0.60)	0.9712	NA	NA
BPD v RYGB	1	Mingrone 2012	19	19	-2.00	(-2.79 to -1.21)	**<0.0001**	NA	NA
Three years' follow-up									
RYGB v SG	1	Yang 2015	27	28	0.22	(-0.31 to 0.75)	0.4258	NA	NA
RYGB v AGB	1	Courcoulas 2020 (3 years)	20	21	-0.46	(-1.08 to 0.16)	0.1488	NA	NA
Five years' follow-up									
RYGB v AGB	1	Courcoulas 2020	20	21	-0.12	(-0.74 to 0.49)	0.6939	NA	NA
BPD v RYGB	1	Mingrone 2015	19	19	-1.67	(-2.42 to -0.92)	**<0.0001**	NA	NA
LOAGB v LSG	1	Lee 2014	30	30	-0.09	(-0.6 to 0.42)	0.7290	NA	NA
Ten years' follow-up									
BPD v RYGB	1	Mingrone 2021	20	20	-1.72	(-2.46 to -0.99)	**<0.0001**	NA	NA

† P <0.05 is considered statistically significant. Bold values denote statistical significance.
‡ Tests for statistical significance yield different results under fixed or random effects meta-analysis due to the presence of significant statistical heterogeneity.

Table A3.16. Standardised mean difference in change from baseline in LDL-cholesterol for metabolic surgery compared with best medical care

Comparison	Number of RCTs	Author, year	Surgery (n)	Comparator (n)	SMD	(95% CI)	P value†	I^2	(95% CI)
One year follow-up									
RYGB v BMC	6	Simsonson 2018 (1 year); Ikramuddin 2018 (1 year); Schauer 2012; Courcoulas 2020 (1 year); Katsogiannos 2019; Liang 2013	190	176	-0.30	(-0.67 to 0.06)	0.1053	63.5	(11.6 to 84.9)
LAGB v BMC	2	Simonson 2019(1 year); Courcoulas 2020 (1 year)	39	42	-0.11	(-0.55 to 0.34)	0.6381	66.6%	(0.0 to 92.4)
SG v BMC	2	Picu 2020; Schauer 2012	68	56	0.07	(-0.28 to 0.43)	0.6925	0.0%	NA
Mix of surgeries v BMC	1	Parikh 2014	20	24	0.60	(0.003 to 1.21)	0.0512	NA	NA
Two years' follow-up									
RYGB v BMC	5	Cohen 2020; Simonson 2018 (2 years); Ikramuddin 2018 (2 years); Courcoulas 2020 (2 years); Mingrone 2012	166	162	0.01	(-0.26 to 0.29)	0.9255	31.0%	(0.0 to 73.5)
LAGB v BMC	2	Simonson 2019 (2 years); Courcoulas 2020 (2 years)	39	42	0.18	(-0.25 to 0.62)	0.4117	0.0%	NA

BPD v BMC	1	Mingrone 2012	19	15	-2.78	(-3.71 to-1.85)	**<0.0001**	NA	NA
SG-TB v BMC	1	Azevedo 2018	10	10	-0.36	(-1.25 to 0.52)	0.4218	NA	NA
Three years' follow-up									
RYGB v BMC	4	Simonson 2018 (3 years); Ikramuddin 2018 (3 years); Schauer 2014; Courcoulas 2020 (3 years)	144	135	0.07	(-0.27 to 0.42)	0.684	49.1	(0.0 to 83.1)
LAGB v BMC	2	Simonson 2019 (3 years); Courcoulas 2020 (3 years)	39	42	0.22	(-0.22 to 0.66)	0.337	29.2%	NA
SG v BMC	1	Schauer 2014	49	40	0.27	(-0.15 to 0.69)	0.2027	NA	NA
Five years' follow-up									
RYGB v BMC	4	Ikramuddin 2018; Schauer 2017; Courcoulas 2020; Mingrone 2015	145	129	0.18	(-0.26 to 0.63)	0.4195	67.0%	(3.7 to 88.7)
AGB v BMC	1	Courcoulas 2020	21	20	0.28	(-0.33 to 0.90)	0.3676	NA	NA
SG v BMC	1	Schauer 2017	47	38	0.25	(-0.18 to 0.68)	0.2589	NA	NA
BPD v BMC	1	Mingrone 2015	19	15	-0.74	(-1.44 to -0.04)	**0.0392**	NA	NA
Ten years' follow-up									
RYGB v BMC	1	Mingrone 2021	20	15	0.98	(0.26 to 1.69)	**0.0072**	NA	NA
BPD v BMC	1	Mingrone 2021	20	15	-0.66	(-1.34 to 0.03)	0.0623	NA	NA

† P <0.05 is considered statistically significant. Bold values denote statistical significance.

‡ Tests for statistical significance yield different results under fixed or random effects meta-analysis due to the presence of significant statistical heterogeneity.

Table A3.17. Standardised mean difference in change from baseline in LDL-cholesterol for metabolic surgery compared with other metabolic surgeries

Comparison	Number of RCTs	Author, year	Surgery (n)	Comparator (n)	SMD	(95% CI)	P value†	I^2	(95% CI)
One year follow-up									
RYGB v SG	3	Schauer 2012; Hofso 2019; Wallenius 2020	129	128	-0.41	(-0.66 to -0.16)	**0.0012**	72.7	(7.9 to 91.9)
LGBP v BMC	1	Yan 2021	77	80	-0.10	(-0.41 to 0.22)	0.5395	NA	NA
RYGB v AGB	1	Courcoulas 2020 (1 year)	20	21	-0.58	(-1.20 to 0.05)	0.0708	NA	NA
LOAGB v LSG	1	Lee 2011	30	30	-0.60	(-1.12 to -0.08)	**0.0228**	NA	NA
LSR-RYGB v LSG	1	Murphy 2018	56	53	-0.75	(-1.14 to -0.36)	**0.0002**	NA	NA
Two years' follow-up									
RYGB v SG	2	Tang 2016; Wallenius 2020	63	56	-0.16	(-0.52 to 0.20)	0.3847	0.0	NA
RYGB v AGB	1	Courcoulas 2020 (2 years)	20	21	-0.12	(-0.73 to 0.50)	0.7131	NA	NA
BPD v RYGB	1	Mingrone 2012	19	19	-1.66	(-2.41 to -0.91)	**<0.0001**	NA	NA
Three years' follow-up									
RYGB v SG	2	Schauer 2014; Yang 2015	75	77	-0.09	(-0.41 to 0.23)	(0.5930	14.6	NA
RYGB v AGB	1	Courcoulas 2020(3 years)	20	21	-0.48	(-1.10 to 0.15)	0.1329	NA	NA
Five years' follow-up									
RYGB v SG	1	Schauer 2017	49	47	-0.08	(-0.48 to 0.32)	0.6910	NA	NA
RYGB v AGB	1	Courcoulas 2020	20	21	-0.04	(-0.66 to 0.57)	0.8885	NA	NA
BPD v RYGB	1	Mingrone 2015	19	19	-1.53	(-2.26 to -0.80)	**<0.0001**	NA	NA
LOAGB v LSG	1	Lee 2014	30	30	-0.43	(-0.94 to 0.09)	0.1033	NA	NA
Ten years' follow-up									
BPD v RYGB	1	Mingrone 2021	20	20	-1.68	(-2.41 to -0.95)	**<0.0001**	NA	NA

† P <0.05 is considered statistically significant. Bold values denote statistical significance.
‡ Tests for statistical significance yield different results under fixed or random effects meta-analysis due to the presence of significant statistical heterogeneity.

Table A3.18. Standardised mean difference in change from baseline in HDL-cholesterol for metabolic surgery compared with best medical care

Comparison	Number of RCTs	Author, year	Surgery (n)	Comparator (n)	SMD	(95% CI)	P value†	I^2	(95% CI)
One year follow-up									
RYGB v BMC	7	Cummings 2016; Simonson 2018 (1 year); Schauer 2012; Courcoulas 2020 (1 year); Katsogiannos 2019; Liang 2013; Ikramuddin 2018 (1 year)	205	193	0.74	(0.52 to 0.95)	**<0.0001**	5.2%	(0.0 to 72.3
LAGB v BMC	2	Ding 2018; Courcoulas 2020 (1 year)	39	42	0.41	(-0.04 to 0.85)	0.072	0.0%	NA
SG v BMC	2	Picu 2020; Schauer 2012	68	56	0.92	(0.54 to 1.30)	**<0.0001**	55.9%	(0.0 to 89.3)
Mix of surgeries v BMC	1	Parikh 2014	20	24	-0.15	(-0.75 to 0.44)	0.6181	NA	NA
Two years' follow-up									
RYGB v BMC	5	Cohen 2020; Simonson 2018; Courcoulas 2020 (2 years); Mingrone 2012; Ikramuddin 2015	166	162	0.91	(0.49 to 1.32)	**<0.0001**	65.1%	(8.6 to 86.7)
LAGB v BMC	3	Dixon 2008; Simonson 2019; Courcoulas 2020 (2 years)	69	72	0.98	(0.63 to 1.33)	**<0.0001**	31.9%	(0.0 to 92.9)
BPD v BMC	1	Mingrone 2012	19	18	0.44	(-0.21 to 1.09)	0.1865	NA	NA
SG-TB v BMC	1	Azevedo 2018	10	10	0.99	(0.05 to 1.93)	**0.0397**	NA	NA
Three years' follow-up									
RYGB v BMC	4	Simonson 2018; Schauer 2014; Courcoulas 2020 (3 years); Ikramuddin 2016	144	135	0.89	(0.48 to 1.30)	**<0.0001**	59.4%	(0.0 to 86.5)
LAGB v BMC	2	Simonson 2019; Courcoulas 2020 (3 years)	39	42	0.79	(0.33 to 1.24)	**0.0007**	0.0%	NA
SG v BMC	1	Schauer 2014	49	40	1.12	(0.67 to 1.57)	**<0.0001**	NA	NA

Five years' follow-up									
RYGB v BMC	4	Schauer 2017; Courcoulas 2020; Mingrone 2015; Ikramuddin 2018	145	129	0.78	(0.43 to 1.14)	**<0.0001**	45.0%	(0.0 to 81.7)
LAGB v BMC	1	Courcoulas 2020	21	20	0.36	(-0.25 to 0.98)	0.2490	NA	NA
SG v BMC	1	Schauer 2017	47	38	0.61	(0.17 to 1.04)	**0.0066**	NA	NA
BPD v BMC	1	Mingrone 2015	19	15	0.51	(-0.18 to 1.19)	0.1502	NA	NA
Ten years' follow-up									
RYGB v BMC	1	Mingrone 2021	20	15	0.37	(-0.30 to 1.05)	0.2800	NA	NA
BPD v BMC	1	Mingrone 2021	20	25	0.49	(-0.19 to 1.17)	0.1593	NA	NA

† P <0.05 is considered statistically significant. Bold values denote statistical significance.

Table A3.19. Standardised mean difference in change from baseline in HDL-cholesterol for metabolic surgery compared with other metabolic surgeries

Comparison	Number of RCTs	Author, year	Surgery (n)	Comparator (n)	SMD	(95% CI)	P value‡	I^2	(95% CI)
One year follow-up									
RYGB v SG	3	Schauer 2012; Hofso 2019; Wallenius 2020	129	128	-0.08	(-0.32 to 0.17)	0.5426	2.5%	(0.0 to 89.9)
LGBP v LSG	1	Yan 2021	77	80	-0.04	(-0.35 to 0.28)	0.8211	NA	NA
RYGB v AGB	1	Courcoulas 2020 (1 year)	20	21	0.69	(0.05 to 1.32)	**0.0335**	NA	NA
LOAGB v LSG	1	Lee 2011	30	30	-0.14	(-0.64 to 0.37)	0.6009	NA	NA
LSR-RYGB v LSG	1	Murphy 2019	56	53	-0.12	(-0.50 to 0.25)	0.5219	NA	NA
Two years' follow-up									
RYGB v SG	2	Tang 2016; Wallenius 2020	63	56	0.08	(-0.28 to 0.44)	0.6732	0.0	NA
RYGB v AGB	1	Courcoulas 2020 (2 years)	20	21	0.58	(-0.04 to 1.21)	0.0681	NA	NA
BPD v RYGB	1	Mingrone 2012	19	19	-0.84	(-1.50 to -0.17)	**0.0136**	NA	NA
Three years' follow-up									

RYGB v SG	2	Schauer 2014; Yang 2015	75	77	0.21	(-0.11 to 0.53)	0.1952	70.8	0.0 to 93.4
RYGB v AGB	1	Courcoulas 2020 (3 years)	20	21	0.44	(-0.19 to 1.06)	0.1690	NA	NA
Five years' follow-up									
RYGB v SG	1	Schauer 2017	49	47	0.08	(-0.32 to 0.48)	0.7030	NA	NA
RYGB v AGB	1	Courcoulas 2020	20	21	0.53	(-0.09 to 1.16)	0.0949	NA	NA
BPD v RYGB	1	Mingrone 2015	19	19	-0.76	(-1.42 to -0.10)	**0.0242**	NA	NA
LOAGB v LSG	1	Lee 2014	30	30	-0.56	(-1.08 to -0.05)	**0.0327**	NA	NA
Ten years follow-up									
BPD v RYGB	1	Mingrone 2021	20	20	0.00	(-0.62 to 0.62)	1.00	NA	NA

† P <0.05 is considered statistically significant. Bold values denote statistical significance.
‡ Tests for statistical significance yield different results under fixed or random effects meta-analysis due to the presence of significant statistical heterogeneity.

Table A3.20. Standardised mean difference in change from baseline in triglycerides for metabolic surgery compared with best medical care

Comparison	Number of RCTs	Author, year	Surgery (n)	Comparator (n)	SMD	(95% CI)	P value†	I^2	(95% CI)
One year follow-up									
RYGB v BMC	7	Cummings 2016; Halperin2014; Schauer 2012; Courcoulas 2020 (1 year); Katsogiannnos 2019; Liang 2013; Ikramuddin 2018 (1 year)	205	193	-0.65	(-1.00 to -0.31)	**0.0002**	60.4%	(9.3 to 82.7)
AGB v BMC	2	Ding 2015; Courcoulas 2020 (1 year)	39	42	-0.33	(-0.78 to 0.12)	0.1487	80.0%	(14.2 to 95.4)
SG v BMC	2	Picu 2020; Schauer 2012	68	56	-0.37	(-0.73 to -0.02)	**0.0409**	0.0%	
Mix of surgeries v BMC		Parikh 2014	20	24	-0.34	(-0.94 to 0.26)	0.2664	NA	NA
Two years' follow-up									
RYGB v BMC	5	Cohen 2020; Simonson 2018; Courcoulas 2020 (2 years); Mingrone 2012; Ikramuddin 2018 (2 year)	166	162	-0.48	(-0.80 to -0.17)	**0.0026**	45.3%	(0.0 to 79.9)
AGB v BMC	2	Dixon 2008; Simonson 20019; Courcoulas 2020 (2 years)	69	72	-0.40	(-0.74 to -0.06)	**0.0193**	0.0%	(0.0 to 89.6)
BPD v BMC	1	Mingrone 2012	19	18	-2.86	(-3.81 to -1.92)	**<0.0001**	NA	NA
SG-TB v BMC	1	Azevedo 2018	10	10	-0.83	(-1.76 to 0.09)	0.0766	NA	NA
Three years' follow-up									
RYGB v BMC	4	Simonson 2018; Schauer 2014; Courcoulas 2020	144	135	-0.52	(-0.76 to -0.28)	**<0.0001**	0.0%	(0.0 to 84.7)

		(3 years); Ikramuddin 2018 (3 years)							
AGB v BMC	2	Simonson 2019; Courcoulas 2020 (3 years)	39	42	-0.30	(-0.74 to 0.14)	0.1856	0.0%	NA
SG v BMC	1	Schauer 2014	49	40	-0.34	(-0.76 to 0.09)	0.1185	NA	NA
Five years' follow-up									
RYGB v BMC	4	Schauer 2017; Courcoulas 2020; Mingrone 2015; Ikramuddin 2018	145	129	-0.34	(-0.81 to 0.13)	0.1526	69.7%	(12.8 to 89.5)
AGB v BMC	1	Courcoulas 2020	21	20	-0.54	(-1.17 to 0.08)	0.0890	NA	NA
SG v BMC	1	Schauer 2017	47	38	-0.49	(-0.93 to -0.06)	**0.0260**		
BPD v BMC	1	Mingrone 2015	19	15	-0.65	(-1.35 to 0.05)	0.0676	NA	NA
Ten years' follow-up									
RYGB v BMC	1	Mingrone 2021	20	15	0.44	(-0.23 to 1.12)	0.1991	NA	NA
BPD v BMC	1	Mingrone 2021	20	15	-0.62	(-1.31 to 0.07)	0.0765	NA	NA

† P <0.05 is considered statistically significant. Bold values denote statistical significance.
‡ Tests for statistical significance yield different results under fixed or random effects meta-analysis due to the presence of significant statistical heterogeneity.

Table A3.21. Standardised mean difference in change from baseline in triglycerides for metabolic surgery compared with other metabolic surgeries

Comparison	Number of RCTs	Author, year	Surgery (n)	Comparator (n)	SMD	(95% CI)	P value†	I^2	(95% CI)
One year follow-up									
RYGB v SG	3	Schauer 2012; Hofso 2019; Wallenius 2020	129	128	-0.12	(-0.36 to 0.13)	0.3495	5.5%	(0.0 to 90.2)
LGBP v BMC	1	Yan 2021	77	80	-0.13	(-0.45 to 0.18)	0.4064	NA	NA
RYGB v AGB	1	Courcoulas 2020 (1 year)	20	21	-0.48	(-1.11 to 0.14)	0.1279	NA	NA
LOAGB v LSG	1	Lee 2011	30	30	0.16	(-0.35 to 0.67)	0.5354	NA	NA
LSR-RYGB v LSG	1	Murphy 2018	56	53	-0.08	(-0.45 to 0.30)	0.6886	NA	NA

Two years' follow-up									
RYGB v SG	2	Tang 2016; Wallenius 2020	63	56	0.03	(-0.34 to 0.39)	0.8898	0.0	NA
RYGB v AGB	1	Courcoulas 2020 (2 years)	20	21	-0.30	(-0.91 to 0.32)	0.3457	NA	NA
BPD v RYGB	1	Mingrone 2012	19	19	-1.11	(-1.80 to -0.42)	**0.0016**	NA	NA
Three years' follow-up									
RYGB v SG	2	Schauer 2014; Yang 2015	75	77	-0.11	(-0.43 to 0.21)	0.4853	0.0	NA
RYGB v AGB	1	Courcoulas 2020 (3 years)	20	21	-0.59	(-1.22 to 0.04)	0.0644	NA	NA
Five years' follow-up									
RYGB v SG	1	Schauer 2017	49	47	-0.06	(-0.46 to 0.34)	0.7793	NA	NA
RYGB v AGB	1	Courcoulas 2020	20	21	-0.54	(-1.17 to 0.08)	0.0874	NA	NA
BPD v RYGB	1	Mingrone 2015	19	19	-0.92	(-1.59 to -0.25)	**0.0073**	NA	NA
LOAGB v LSG	1	Lee 2014	30	30	0.18	(-0.33 to 0.69)	0.4880	NA	NA
Ten years' follow-up									
BPD v RYGB	1	Mingrone 2021	20	20	-0.97	(-1.63 to -0.31)	**0.0038**	NA	NA

† P <0.05 is considered statistically significant. Bold values denote statistical significance.

‡ Tests for statistical significance yield different results under fixed or random effects meta-analysis due to the presence of significant statistical heterogeneity.

Appendix A3.9 Cardiovascular medication use

Table A3.22. Risk differences for T2D medication usage by intervention and comparator combination†‡

Comparison	Intervention/comparator combination			
	RYGB vs BMC	SG vs BMC	LAGB vs BMC	RYGB vs SG
Lipid-lowering agents				
Baseline	RD = 0.13 (95% CI: 0.01 to 0.25, **p = 0.037**, n = 2)	RD = -0.05 (95% CI: =0.22 to 0.11, p = 0.521, n = 1)	RD = 0.13 (95% CI: -0.10 to 0.37, p = 0.269, n = 1)	RD = 0.08 (95% CI: -0.07 to 0.24, p = 0.274, n = 1)
First follow-up	RD = -0.38 (95% CI: -0.49 to -0.26, **p <0.001**, n = 2)	RD = -0.53 (95% CI: -0.70 to -0.38, **p < 0.001**, n = 1)	RD = -0.13 (95% CI: -0.34 to 0.08, p = 0.224, n = 1)	RD = -0.12 (95% CI: -0.31 to 0.06, p = 0.192, n = 1)
All follow-up	No change over time (p = 0.640, n = 4)	Decreasing risk difference over time (**p = 0.005**, n = 3)	Only single time point available	No change over time (p = 767, n = 3)
Anti-hypertensive agents				
Baseline	RD = 0.02 (95% CI: -0.15 to 0.20, p = 0.788, n = 1)	RD = -0.08 (95% CI: -0.27 to 0.10, p = 0.383, n = 1)	RD = 0.17 (95% CI: -0.08 to 0.41, p = 0.184, n = 1)	RD = 0.11 (95% CI: -0.07 to 0.28, p = 0.231, n = 1)
First follow-up	RD = -0.44 (95% CI: -0.63 to -0.26, **p < 0.001**, n = 1)	RD = -0.50 (95% CI: -0.68 to -0.32, **p < 0.001**, n = 1)	RD = -0.37 (95% CI: -0.61 to -0.13, **p = 0.003**, n = 1)	RD = 0.06 (95% CI: -0.12 to 0.24, p = 0.506, n = 1)
All follow-up	Only single time point available	Only single time point available	Only single time point available	Only single time point available

Key: BMC – best medical care; CI – confidence interval; (L)AGB – (laparoscopic) adjustable gastric banding; (L)RYGB – (laparoscopic) Roux-en-Y gastric bypass; (L)SG – (laparoscopic) sleeve gastrectomy; RD – risk difference; T2D - type 2 diabetes.
† A negative value means a reduced risk of medication usage for the intervention relative to the comparator. A positive value means an increased risk of medication usage for the intervention relative to the comparator. Fixed effect meta-analysis was used when fewer than three RCTs were available.
‡ P <0.05 is considered statistically significant. Bold values denote statistical significance.

Appendix A3.10 T2D-related complications

Nephropathy

Table A3.23. Risk ratio for the effect of metabolic surgery versus best medical care in proteinuria and chronic kidney disease

Comparison	Number of RCTs	Follow-up	Author, year	Surgery (n)	Comparator (n)	RR	(95% CI)	P value[†]
No albuminuria								
RYGB v BMC	1	5	Schauer 2017	47	37	0.98	(0.71 to 1.36)	0.928
SG v BMC	1	5	Schauer 2017	45	37	1.20	(0.90 to 1.59)	0.212
RYGB v SG	1	5	Schauer 2017	47	45	0.82	(0.63 to 1.07)	0.146
New-onset albuminuria								
RYGB v BMC	1	5	Schauer 2017	47	37	0.45	(0.14 to 1.42)	0.174
SG v BMC	1	5	Schauer 2017	45	37	0.23	(0.05 to 1.06)	0.060
RYGB v SG	1	5	Schauer 2017	47	45	1.91	(0.37 to 9.95)	0.448
Albumin to creatinine ratio >30 mg/mmol								
LRYGB v BMC	1	5	Mingrone 2015	19	15	0.09	(0.01 to 1.52)	0.094
		10	Mingrone 2021	20	15	0.75	(0.05 to 11.05)	0.845
BPD v BMC	1	5	Mingrone 2015	19	15	0.09	(0.01 to 1.52)	0.094
		10	Mingrone 2021	20	15	0.75	(0.05 to 11.05)	0.845
LRYGB v BPD	1	5	Mingrone 2015	19	19	1.00	(0.02 to 47.91)	1.00
		10	Mingrone 2021	20	20	1.00	(0.07 to 14.90)	1.00
Proteinuria >0.5 g/24 h								
RYGB v BMC	1	5	Mingrone 2015	19	15	0.79	(0.05 to 11.61)	0.873
BPD v BMC	1	5	Mingrone 2015	19	15	0.26	(0.01 to 6.06)	0.413
RYGB v BMC	1	5	Mingrone 2015	19	19	3.00	(0.13 to 69.21)	0.503
Albuminuria remission[‡]								
RYGB v BMC	2	2	Cohen 2020	51	49	1.51	(1.13 to 2.00)	**0.005**

		3	Schauer 2014	13	4	2.46	(0.43 to 14.18)	0.318
		5	Schauer 2017	13	3	0.92	(0.37 to 2.29)	0.873
SG v BMC	1	3	Schauer 2014	10	4	3.20	(0.57 to 17.97)	0.188
RYGB v SG	1	3	Schauer 2014	13	10	0.77	(0.45 to 1.31)	0.337
SG v BMC	1	5	Schauer 2017	8	3	0.94	(0.36 to 2.46)	0.904
RYGB v SG	1	5	Schauer 2017	13	8	0.98	(0.50 to 1.96)	0.968
Chronic kidney disease remission§								
RYGB v BMC	1	2	Cohen 2020	51	49	1.70	(1.24 to 2.33)	**0.001**

† P <0.05 is considered statistically significant. Bold values denote statistical significance.
‡ Albumin to creatinine ratio <30 mg/g of creatinine.
§ American Diabetes Association composite criteria, defined as urinary albumin to creatinine ratio less than 30mg/g of creatinine and eGFR greater than 60mL/min/1.73m^2.

Table A3.24. Mean difference in change from baseline in markers of kidney function for metabolic surgery compared with best medical care

Comparison	Number of RCTs	Follow-up	Author, year	Surgery (n)	Comparator (n)	MD	(95% CI)	P value†
Albumin/creatinine ratio								
RYGB v BMC	1	3	Schauer 2014	48	40	-10.5	(-17.15 to -3.85)	**0.002**
		5	Schauer 2017	47	37	-9.53	(-16.68 to -2.38)	**0.009**
SG v BMC	1	3	Schauer 2014	49	40	-6.00	(-8.93 to -3.07)	**<0.0001**
		5	Schauer 2017	45	37	-11.50	(-16.95 to -6.05)	**<0.0001**
RYGB v SG	1	3	Schauer 2014	48	49	-4.50	(-11.29 to 2.29)	0.194
		5	Schauer 2017	47	45	1.97	(-4.33 to 8.27)	0.540
Serum creatinine								
RYGB v BMC	1	3	Schauer 2014	48	40	0.03	(-0.03 to 0.09)	0.337
		5	Schauer 2017	47	37	0.08	(0.02 to 0.14)	**0.015**
SG v BMC	1	3	Schauer 2014	49	40	0.02	(-0.02 to 0.06)	0.376
		5	Schauer 2017	45	37	0.06	(0.001 to 0.12)	**0.046**
RYGB v SG	1	3	Schauer 2014	48	49	0.01	(-0.05 to 0.07)	0.737

		5	Schauer 2017	47	45	0.02	(-0.04 to 0.08)	0.5097
Glomerular filtration rate								
RYGB v BMC	2	3	Schauer 2014	48	40	-2.66	(-7.23 to 1.91)	0.254
		5	Schauer 2017	47	37	-5.04	(-9.88 to -0.20)	**0.041**
		10	Mingrone 2021	20	15	14.40	(2.86 to 25.94)	**0.014**
SG v BMC	1	3	Schauer 2014	49	40	-1.40	(-4.25 to 1.45)	0.335
		5	Schauer 2017	45	37	-4.50	(-9.20 to 0.20)	0.060
BPD v BMC	1	10	Mingrone 2021	20	15	-2.10	(-12.62 to 8.42)	0.696
RYGB v SG	1	3	Schauer 2014	48	49	-1.26	(-5.95 to 3.43)	0.598
		5	Schauer 2017	47	45	-0.54	-5.25 to 4.17)	0.822
RYGB v BPD	1	10	Mingrone 2021	20	20	16.50	(7.58 to 25.42)	**0.0003**

† P <0.05 is considered statistically significant. Bold values denote statistical significance.

Retinopathy

Table A3.25 Risk ratio for the effect of metabolic surgery versus best medical care on development or progression of retinopathy

Comparison	Number of RCTs	Follow-up	Author, year	Surgery (n)	Comparator (n)	RR	(95% CI)	P value†
No retinopathy								
RYGB v BMC	1	2	Cohen 2020	51	49	1.01	(0.80 to 1.28)	0.934
Non-proliferative diabetic retinopathy								
RYGB v BMC	1	2	Cohen 2020	51	49	1.01	(0.48 to 2.15)	0.974
Proliferative diabetic retinopathy								
RYGB v BMC	1	2	Cohen 2020	51	49	0.81	(0.14 to 4.62)	0.828
Any retinopathy								
RYGB v BMC	2	3	Schauer 2014	50	43	2.58	(0.11 to 61.82)	0.569
		5	Schauer 2017	42	25	1.79	(0.39 to 8.18)	0.464
		5	Mingrone 2015	19	15	0.26	(0.01 to 6.06)	0.413
		10	Mingrone 2021	20	15	0.25	(0.01 to 5.78)	0.395
SG v BMC	2	3	Schauer 2014	49	43	4.39	(0.22 to 89.05)	0.340
		5	Schauer 2017	36	25	1.39	(0.28 to 7.01)	0.704
BPD v BMC	2	5	Mingrone 2015	19	15	0.26	(0.01 to 6.06)	0.413
		10	Mingrone 2021	20	15	0.25	(0.01 to 5.78)	0.395
RYGB v SG	2	3	Schauer 2014	50	49	0.49	(0.05 to 5.23)	0.566
		5	Schauer 2017	42	36	1.29	(0.39 to 4.20)	0.691
RYGB v BPD	2	5	Mingrone 2015	19	19	1.00	(0.02 to 47.91)	1.000
		10	Mingrone 2021	20	20	1.00	(0.02 to 48.03)	1.000

† P <0.05 is considered statistically significant. Bold values denote statistical significance.

Neuropathy

Table A3.26. Risk ratio for the effect of metabolic surgery versus best medical care on neuropathy

Comparison	Number of RCTs	Follow-up	Author, year	Surgery (n)	Comparator (n)	RR	(95% CI)	P value†
LRYGB v BMC	2	2	Cohen 2020	51	49	0.80	(0.39 to 1.69)	0.564
		5	Mingrone 2015	19	15	0.16	(0.01 to 3.07)	0.226
		10	Mingrone 2021	20	15	0.15	(0.02 to 2.93)	0.213
BPD v BMC	1	5	Mingrone 2015	19	15	0.16	(0.01 to 3.07)	0.2256
		10	Mingrone 2021	20	15	0.15	(0.01 to 2.93)	0.213
LRYGB v BPD	1	5	Mingrone 2015	19	19	1.00	(0.02 to 47.91)	1.000
		10	Mingrone 2021	20	20	1.00	(0.02 to 48.03)	1.000

† P <0.05 is considered statistically significant. Bold values denote statistical significance.

Appendix A3.11 Adverse events

Technical complications of bariatric / metabolic surgery:[250] †

- bleeding problems including intra-abdominal, gastrointestinal, and staple-line bleeding
- anastomotic leak
- gastric fistula
- bowel stricture
- anastomotic ulceration
- internal hernia
- gastric band problems
- port problems
- venous thromboembolism
- septcaemia
- admission to ICU for ventilation
- Other post-operative complications/serious adverse events requiring prolonged hospitalisation or re-admission*

† Other complications not listed in the core outcome set were included if they required intervention (for example, IV treatment for dehydration) or were associasted with prolonged hospitalisation, re-admission or reoperation.

Table A3.27. Incidence of severe hypoglycaemia† (all comparisons)

Comparison	Number of RCTs	Author, year	Surgery (person-years)	Comparator (person-years)	IRR	(95% CI)	P value‡
LRYGB v BMC	6	Halperin 2014; Cummings 2016; Ikramuddin 2013; Schauer 2017; Mingrone 2021; Cohen 2020	628	550	1.76	(0.57 to 5.47)	NS
LAGB v BMC	1	Simonson 2019	54	66	1.22	(0.024 to 61.60)	NS
LSG v BMC	1	Schauer 2017	325	215	0.91	(0.02 to 46.11)	NS
BPD v BMC	1	Mingrone 2021	200	150	0.75	(0.01 to 37.80)	NS
LRYGB v LSG	1	Hofso 2019	54	55	1.46	(0.55 to 3.82)	NS
LRYGB v LSG	1	Schauer 2017	245	235	2.88	(0.12 to 70.64)	NS
LRYGB v BPD	1	Mingrone 2021	200	200	15.00	(0.86 to 262.63)	NS

Key: NS – not statistically significant.
† As defined by study authors. At medium- to long-term follow-up RCTs reported all hypoglycaemic events occurring during the study period. Where studies reported at multiple time points, only the data from the longest available follow-up are presented.
‡ P <0.05 is considered statistically significant.

Table A3.28. Incidence of any hypoglycaemia† (all comparisons)

Comparison	Number of RCTs	Author, year	Surgery (person-years)	Comparator (person-years)	Risk ratio	(95% CI)	P value‡
LAGB v BMC	1	Dixon 2008	58	52	0.90	(0.06 to 14.33)	0.9385
LSG v BMC	1	Schauer 2017	235	215	0.94	(0.60 to 1.46)	0.7774
LRYGB v BMC	4	Schauer 2012; Ikramuddin 2013; Cummings 2016; Cohen 2020	409	381	1.05	(0.47 to 2.38)	0.9044
LRYGB v LSG	1	Schauer 2017	245	235	0.77	(0.48 to 1.22)	0.2642

† At medium- to long-term follow-up RCTs reported all hypoglycaemic events occurring during the study period. Where studies reported at multiple time points, only the data from the longest available follow-up are presented.
‡ P <0.05 is considered statistically significant.

Table A3.29. Absolute risk difference of early (≤30 days) mortality for metabolic surgery versus best medical care

Comparison	Number of RCTs	Author, year	Surgery (n)	Comparator (n)	Risk difference	(95% CI)	P value†	I^2	(95% CI)
RYGB v BMC	6	Cohen 2020; Courcoulas 2014; Cummings 2016; Halperin 2014; Ikramuddin 2013; Liang 2013; Mingrone 2012; Schauer 2012	269	263	0	(-0.02 to 0.02)	1.000	0.0%	(0.0 to 67.6)
LAGB v BMC	1	Courcoulas 2014	22	23	0	(-0.08 to 0.08)	1.000	NA	NA
SG v BMC	1	Schauer 2012	49	43	0	(-0.04 to 0.04)	1.000	NA	NA
BPD v BMC	1	Mingrone 2012	19	18	0	(-0.10 to 0.10)	1.000	NA	NA
SG-TB v BMC	1	Azevedo 2018	10	10	0	(-0.17 to 0.17)	1.000	NA	NA
Mix of surgeries v BMC	1	Parikh 2014	20	24	0	(-0.09 t0 0.09)	1.000	NA	NA

† P <0.05 is considered statistically significant.

Table A3.30. Absolute risk difference of early (≤30 days) mortality for metabolic surgery versus best medical care

Comparison	Number of RCTs	Author, year	Surgery (n)	Comparator (n)	Risk difference	(95% CI)	P value†	I^2	(95% CI)
RYGB v SG	6	Hofso 2019; Keidar 2013; Schauer 2012; Tang 2016; Wallenius 2020; Yang 2019	213	208	0	(-0.02 to 0.02)	1.000	0.0%	(0.0 to 74.6)
RYGB v LAGB	1	Courcoulas 2014	24	22	0	(-0.08 to 0.08)	1.000	NA	NA
RYGB v BPD	1	Schauer 2012	19	19	0	(-0.1 to 0.1)	1.000	NA	NA
LOAGB v LSG	1	Lee 2011	30	30	0	(-0.06 to 0.06)	1.000	NA	NA
LSR-RYGB v LSG	1	Murphy 2018	56	53	0	(-0.04 to 0.04)	1.000	NA	NA
mRYGB v SG	1	Casajoana 2017	15	14	0	(-0.12 to 0.12)	1.000	NA	NA
mRYGB v GCP	1	Casajoana 2017	15	15	0	(-0.12 to 0.12)	1.000	NA	NA
SG v GCP	1	Casajoana 2017	14	15	0	(-0.12 to 0.12)	1.000	NA	NA

† P <0.05 is considered statistically significant.

Table A3.31. Absolute risk difference of late (>30 days) mortality for metabolic surgery versus best medical care

Comparison	Number of RCTs	Author, year	Surgery (n)	Comparator (n)	Risk difference	(95% CI)	P value†	I^2	(95% CI)
One year follow-up									
RYGB v BMC	6	Courcoulas 2014; Cummings 2016; Halperin 2014; Ikramuddin 2013; Liang 2013; Schauer 2012	192	190	0	(-0.02 to 0.02)	1.000	0.0%	(0.0 to 74.6)
AGB v BMC	2	Courcoulas 2014; Ding 2015	39	42	0	(-0.06 to 0.06)	1.000	0.0%	
SG v BMC	1	Schauer 2012	49	43	0	(-0.04 to 0.04)	1.000	NA	NA
Mix of surgeries v BMC	1	Parikh 2014	20	24	0	(-0.17 to 0.17)	1.000	NA	NA
Two years' follow-up									
RYGB v BMC	3	Cohen 2020; Ikramuddin 2015; Mingrone 2012	125	120	-0.0082	(-0.04 to 0.02)	0.6058	0.0%	(0.0 to 89.6)
BPD v BMC	1	Mingrone 2012	19	18	0	(-0.1 to 0.1)	1.000	NA	NA
SG-TB v BMC	1	Azevedo 2018	10	10	0	(-0.17 to 0.17)	1.000	NA	NA
Three years' follow-up									
RYGB v BMC	4	Courcoulas 2015; Simonson 2018; Ikramuddin 2016; Schauer 2014	141	113	0	(-0.03 to 0.03)	1.000	0.0%	(0.0 to 84.7)
AGB v BMC	2	Courcoulas 2015; Simonson 2019	39	42	-0.02	(-0.10 to 0.05)	0.5655	0.0%	NA
SG v BMC	1	Schauer 2014	49	43	0	(-0.04 to 0.04)	1	NA	NA
Five years' follow-up									
RYGB v BMC	5	Courcoulas 2020; Ikramuddin 2018; Mingrone 2015; Schauer 2017	151	123	-0.001	(-0.04 to 0.02)	0.6003	0.0%	(0.0 to 84.7)
AGB v BMC	1	Courcoulas 2020	20	14	0	(-0.1 to 0.11)	1.000	NA	NA

SG v BMC	1	Schauer 2017	49	43	-0.023	(-0.08 to 0.04)	0.4497	NA	NA
BPD v BMC	1	Mingrone 2015	19	15	-0.067	(-0.23 to 0.09)	0.4093	NA	NA
Ten years' follow-up									
RYGB v BMC	1	Mingrone 2021	20	15	-0.067	(-0.22 to 0.09)	0.4053	NA	NA
BPD v BMC	1	Mingrone 2021	20	15	-0.067	(-0.23 to 0.09)	0.4093	NA	NA

† P <0.05 is considered statistically significant.

Table A3.32. Absolute risk difference of late (>30 days) mortality between metabolic surgeries

Comparison	Number of RCTs	Author, year	Surgery (n)	Comparator (n)	RD	(95% CI)	P value†	I^2	(95% CI)
One year follow-up									
RYGB v SG	3	Schauer 2012; Hofso 2019; Keidar 2013	122	121	0	(-0.03 to 0.03)	1.000	0.0%	(0.0 to 89.6)
RYGB v AGB	1	Courcoulas 2014	20	21	0	(-0.09 to 0.09)	1.000	NA	NA
LOAGB v LSG	1	Lee 2011	30	30	0	(-0.06 to 0.06)	1.000	NA	NA
SR-LRYGB v LSG	1	Murphy 2018	56	53	0	(-0.04 to 0.04)	1.000	NA	NA
mRYGB v SG	1	Casajoana 2017	15	14	0	(-0.12 to 0.12)	1.000	NA	NA
mRYGB v GCP	1	Casajoana 2017	15	15	0	(-0.12 to 0.12)	1.000	NA	NA
SG v GCP	1	Casajoana 2017	14	15	0	(-0.12 to 0.12)	1.000	NA	NA
Two years' follow-up									
RYGB v SG	2	Tang 2016; Wallenius 2020	63	56	0	(-0.04 to 0.04)	1.000	0.0	NA
BPD v RYGB	1	Mingrone 2012	19	19	0	(-0.1 to 0.1)	1.000	NA	NA
Three years' follow-up									
RYGB v SG	2	Schauer 2014; Yang 2015	77	77	0	(-0.03 to 0.03)	1.000	0.0	NA
RYGB v AGB	1	Courcoulas 2015	20	21	0	(-0.09 to 0.09)	1.000	NA	NA
Five years' follow-up									
RYGB v SG	1	Schauer 2017	50	49	0	(-0.07 to 0.07)	1.000	NA	NA

RYGB v AGB	1	Courcoulas 2020	20	21	0	(-0.09 to 0.09)	1.000	NA	NA
BPD v RYGB	1	Mingrone 2015	19	19	0	(-0.1 to 0.1)	1.000	NA	NA
LOAGB v LSG	1	Lee 2014	24	24	0.0417	(-0.07 to 0.15)	0.4498	NA	NA
mRYGB v SG	1	Casajoana 2021	14	14	0	(-0.13 to 0.13)	1.000	NA	NA
mRYGB v GCP	1	Casajoana 2021	14	14	0	(-0.13 to 0.13)	1.000	NA	NA
SG v GCP	1	Casajoana 2021	14	14	0	(-0.13 to 0.13)	1.000	NA	NA
Ten years' follow-up									
BPD v RYGB	1	Mingrone 2021	20	20	0	(-0.1 to 0.1)	1.000	NA	NA

† P <0.05 is considered statistically significant.

Table A3.33. Reoperation/re-intervention rates in included RCTs by procedure

Author, year	Follow-up		n	LAGB	SG	SG+TB	GCP	RYGB	mRYGB	SR-RYGB	OAGB	BPD	Description
Azevedo 2018	2	SG+TB	10			1							Cholecystectomy
Casajoana 2017; 2021	5	mRYGB	14						1				Reversal due to diarrhea and hypoproteinemia
		SG	14		0								NA
		GCP	14				2						Converted to SADI-S due to weight regain and T2D targets not being met(n=1); hemoperitoneum treated with laparoscopic surgery(n=1)
Courcoulas 2014; 2015; 2020	5	RYGB	16					1					Reoperation
		LAGB	20	2									Reoperation(n=1); port malposition(n=1)
Cohen 2020	2	RYGB	46					2					Endoscopic interventions: anastomotic stricture (Clavien-Dindo grade IIIb) (n=1); gastric pouch leak [day 2; Clavien-Dindo grade IIIa]) (n=1)
Cummings 2016	1	RYGB	15					0					NA
Ding 2015; **Simonson** 2019	3	LAGB	18	1									Conversion to RYGB at 22 months for insufficient weight loss
Dixon 2008	2	LAGB	29	3									Gastric pouch enlargement with laparoscopic revision surgery to replace LAGB (n=2); removal of LAGB due to regurgitation (n=1)
Halperin 2014; **Simonson** 2018	3	RYGB	19					7					Cholecystectomy (n=2); lysis of adhesions (n=3); marginal ulceration (n=2)
Hofso 2019	1	SG	54		1								Intra-abdominal bleeding
		RYGB	53					0					NA
Ikramuddin 2013; 2015; 2016;2018[†]	5	RYGB	62					2					Lower extremity amputation following sepsis as a result of anastomotic leak (n=1)[‡]; re-intervention due to anastomotic leak (n=1)
Lee 2011;2014	5	OAGB	24								1		Conversion to RYGB due to reflux eosophagitis
		SG	24		4								Conversion to RYGB (n=4): T2D treatment targets not being met (n=2), insufficient

													weight loss (n=1) and reflux esophagitis (n=1)
Liang 2013	1	RYGB	31					0					NA
Mingrone 2012; 2015; 2021	10	BPD	20									1	Incisional hernia
		RYGB	20					1					Intestinal obstruction
Murphy 2018	1	SR-RYGB	56							5			Jejunal perforation after endoscopic dilatation of a stricture following an earlier subclinical anastomotic leak (n = 1); laparotomy for mesenteric bleeding (n = 1); removal of silastic ring for vomiting (n = 1); perforated stomal ulcer (n = 1); drainage of wound abscess (n = 1)
		SG	53		3								Cholecystectomy (n = 1); revision to SR-LRYGB for sleeve stricture (n = 1); wound debridement for infection (n = 1)
Schauer 2012; 2014; 2017	5	RYGB	50					3					Blood clot evacuation (n=1); assessment of nausea and vomiting (n=1); cholecystectomy (n=1)
		SG	49		2								Gastric leak (n=1); conversion to RYGB due to recurrent gastric fistula (n=1)
Wallenius 2020	2	RYGB	25					0					NA
		SG	22		1								Staple line leak (requiring 5 day hospital stay)
Yang 2015	3	SG	28		0								NA
		RYGB	27					0					NA
Total number of re-operations				6	11	1	2	16	1	5	1	1	
Total number of re-operations/10,000 person years				276	165	500	286	120	143	893	83	50	

Key: BMC – best medical care; BPD – biliopancreatic diversion; GCP – greater curvature plication; (L)AGB – (laparoscopic) adjustable gastric banding; (L)RYGB – (laparoscopic) Roux-en-Y gastric bypass; (L)SAGB – (laparoscopic) single anastomosis gastric bypass/one anastomosis gastric bypass/mini gastric bypass; (L)SG – (laparoscopic) sleeve gastrectomy; (L)SG+TB – (laparoscopic) sleeve gastrectomy with transit bipartition; MI – myocardial infarction; NA – not applicable; SADI-S - Single anastomosis duodeno-ileal bypass with sleeve gastrectomy; SR-LRYGB – silastic ring (laparoscopic) Roux-en-Y gastric bypass; T2D – type 2 diabetes.
† Population size was adjusted in line with crossover during the RCT.
‡ Number of re-intervention surgeries not stated but at least one is assumed.

Table A3.34. Risk of gastroesophageal reflux after metabolic surgery versus best medical care

Comparison	Number of RCTs	Author, year	Surgery (n)	Comparator (n)	RR	(95% CI)	P value†
One year follow-up							
RYGB v BMC	1	Ikramuddin 2018 (1 year)	64	45	0.14	(0.01 to 2.88)	0.203
Two years' follow-up							
RYGB v BMC	2	Cohen 2020	46	46	1.00	(0.06 to 15.51)	1.000
		Ikramuddin 2018 (2 years)	64	45	4.94	(0.26 to 93.30)	0.291
AGB v BMC	1	Dixon 2008	29	26	2.69	(0.11 to 63.35)	0.549
Three years' follow-up							
RYGB v BMC	1	Ikramuddin 2018 (3 years)	64	45	0.70	(0.01 to 34.79)	0.869
Five years' follow-up							
RYGB v BMC	1	Ikramuddin 2018 (5 years)	64	45	0.70	(0.01 to 34.79)	0.869
SG v BMC	1	Schauer 2017	49	43	1.27	(0.60 to 2.67)	0.544
RYGB v BMC	1	Schauer 2017	50	43	0.48	(0.17 to 1.32)	0.154

† P <0.05 is considered statistically significant. Bold values denote statistical significance.

Table A3.35. Risk of gastroesophageal reflux after metabolic surgery versus other metabolic surgeries

Comparison	Number of RCTs	Author, year	Surgery (n)	Comparator (n)	RR	(95% CI)	P value†
One year follow-up							
mRYGB v SG	1	Casajoana 2017	15	14	0.93	(0.02 to 43.94)	0.975
mRYGB v GCP	1	Casajoana 2017	15	15	0.33	(0.01 to 7.57)	0.500
SG v GCP	1	Casajoana 2017	14	15	0.36	(0.02 to 8.07)	0.527
Three years' follow-up							
SG v RYGB	1	Yang 2015	28	27	4.82	(0.24 to 96.02)	0.307
Five years' follow-up							
SG v RYGB	1	Schauer 2017	49	50	2.65	(1.02 to 6.88)	**0.044**
LOAGB v LSG	1	Lee 2014	24	24	3.00	(0.13 to 70.10)	0.505

† P <0.05 is considered statistically significant. Bold values denote statistical significance.

Table A3.36. Risk of dumping syndrome after metabolic surgery

Comparison	Number of RCTs	Author, year	Surgery (n)	Comparator (n)	RR	(95% CI)	P value†
Two years follow-up							
RYGB v BMC	1	Cohen 2020	46	46	19.00	(1.14 to 317.06)	**0.040**
Five years' follow-up							
RYGB v BMC	1	Schauer 2017	50	43	7.75	(0.43 to 139.99)	0.166
SG v BMC	1	Schauer 2017	49	43	2.64	(0.11 to 63.06)	0.561
RYGB v SG	1	Schauer 2017	50	49	3.92	(0.45 to 33.84)	0.216

† P <0.05 is considered statistically significant.

Table A3.37. Risk of gallstones after metabolic surgery versus best medical care

Comparison	Number of RCTs	Author, year	Surgery (n)	Comparator (n)	RR	(95% CI)	P value†
One year follow-up							
RYGB v BMC	1	Ikramuddin 2018 (1 year)	64	45	0.70	(0.01 to 34.79)	0.869
Two years' follow-up							
SG-TB v BMC	1	Azevedo 2018	10	10	3.00	(0.14 to 65.55)	0.495
RYGB v BMC	2	Cohen 2020	46	46	9.00	(0.50 to 162.49)	0.137
		Ikramuddin 2018 (2 years)	64	45	2.12	(0.09 to 50.79)	0.657
Three years' follow-up							
RYGB v BMC	2	Simonson 2018	19	19	5.00	(0.26 to 97.54)	0.292
		Ikramuddin 2018 (3 years)	64	45	0.24	(0.01 to 5.64)	0.378
Five years' follow-up							
RYGB v BMC	3	Ikramuddin 2018 (5 years)	66	45	0.24	(0.01 to 5.64)	0.378
		Schauer 2017	50	43	2.58	(0.11 to 61.82)	0.569
		Courcoulas 2020	16	14	0.88	(0.06 to 12.73)	0.929
SG v BMC	1	Schauer 2017	49	43	2.64	(0.11 to 63.06)	0.561
LAGB v BMC	1	Courcoulas 2020	20	14	0.24	(0.01 to 5.39)	0.372

† P <0.05 is considered statistically significant.

Table A3.38. Risk of gallstones after metabolic surgery versus other metabolic surgeries

Comparison	Number of RCTs	Author, year	Surgery (n)	Comparator (n)	RR	(95% CI)	P value†
One year follow-up							
SG v RYGB	1	Hofso 2019	54	53	0.98	(0.06 to 15.29)	0.990
LSR-RYGB v LSG	1	Murphy 2018	56	53	0.32	(0.01 to 7.58)	0.487
Five years' follow-up							
SG v RYGB	1	Schauer 2017	49	50	1.02	(0.07 to 15.86)	0.990
RYGB v LAGB	1	Courcoulas 2020	16	20	3.73	(0.16 to 85.63)	0.418

† P <0.05 is considered statistically significant.

Table A3.39. Nutritional deficiencies

Comparison	Author, year	Follow-up	Surgery (n)	Comparator (n)	RR	(95% CI)	P value[†]
Anaemia							
SG-TB v BMC	Azevedo 2018	2	10	10	3.00	(0.14 to 65.55)	0.495
RYGB v BMC	Schauer 2012	1	50	43	1.72	(0.46 to 6.47)	0.430
	Cohen 2020	2	46	46	2.00	(0.53 to 7.52)	0.309
	Schauer 2014	3	50	43	1.15	(0.43 to 3.05)	0.796
	Schauer 2017	5	50	43	1.72	(0.76 to 3.87)	0.191
	Courcoulas 2020	5	16	14	2.64	(0.12 to 59.82)	0.554
LAGB v BMC	Courcoulas 2020	5	20	14	0.71	(0.01 to 33.64)	0.870
SG v BMC	Schauer 2012	1	49	43	1.76	(0.47 to 6.60)	0.412
	Schauer 2014	3	49	43	2.19	(0.93 to 5.15)	0.071
	Schauer 2017	5	49	43	3.01	(1.44 to 6.28)	**0.003**
RYGB v LAGB	Courcoulas 2020	5	16	60	3.73	(0.16 to 85.63)	0.418
SG v RYGB	Schauer 2012	1	49	50	1.02	(0.35 to 2.95)	0.973
	Schauer 2014	3	49	50	1.91	(0.89 to 4.10)	0.095
	Schauer 2017	5	49	50	1.75	(1.03 to 2.97)	**0.038**
	Yang 2015	3	27	28	0.32	(0.01 to 7.56)	0.491
Iron-deficiency anaemia							
RYGB v BMC	Ikramuddin 2013[‡]	1	57	57	27.00	(1.64 to 443.54)	**0.021**
	Mingrone 2015	5	19	15	5.56	(0.31 to 99.84)	0.247
	Mingrone 2021	10	20	15	3.78	(0.20 to 73.24)	0.386
BPD v BMC	Mingrone 2015	5	19	15	8.74	(0.52 to 146.29)	0.132
	Mingrone 2021	10	20	15	5.29	(0.29 to 95.13)	0.261
BPD v RYGB	Mingrone 2012	2	19	19	1.00	(0.16 to 6.39)	1.000
	Mingrone 2015	5	19	19	1.67	(0.46 to 6.01)	0.443
	Mingrone 2021	10	20	20	1.50	(0.28 to 8.04)	0.649
Vitamin B deficiency							

RYGB v BMC	Cohen 2020	2	46	46	8.00	(1.04 to 61.42)	**0.045**
	Ikramuddin 2013	1	57	57	5.50	(1.28 to 23.71)	**0.022**
Vitamin A deficiency							
BPD v BMC	Mingrone 2015	5	19	15	2.38	(0.10 to 54.57)	0.599
	Mingrone 2021	10	20	15	3.78	(0.20 to 73.24)	0.386
RYGB v BMC	Mingrone 2015	5	19	15	1.00	(0.02 to 47.91)	1.000
	Mingrone 2021	10	20	15	1.00	(0.02 to 47.91)	1.000
BPD v RYGB	Mingrone 2015	5	19	19	3.00	(0.13 to 69.21)	0.503
	Mingrone 2021	10	20	20	5.00	(0.26 to 97.86)	0.293
Vitamin D deficiency							
RYGB v BMC	Cohen 2020	2	46	46	3.00	(0.13 to 71.76)	0.508
	Ikramuddin 2013	1	57	57	0.80	(0.23 to 2.83)	0.742
Hypokalaemia							
RYGB v BMC	Schauer 2012	1	50	43	1.72	(0.16 to 18.32)	0.666
SG v BMC	Schauer 2012	1	49	43	1.76	(0.16 to 18.69)	0.654
RYGB v SG	Schauer 2012	1	50	49	0.98	(0.14 to 6.68)	0.985

† P <0.05 is considered statistically significant. Bold values denote statistical significance.
‡ Clinically significant and serious adverse events (SAE) were reported for years 1 and 2. For years 3 to 5 only SAEs were reported (nutritional deficiencies were not captured). Not all participants were tested for nutritional deficiencies at the 2 year follow-up, therefore data for nutritional deficiencies is based on 1 year follow-up (RYGB n=57; BMC n=57).

Table A3.40. Cases of osteopenia, osteoporosis and fracture in included RCTs

Author, year	Follow-up (years)	Intervention; Comparator	Participants (n)	Osteopenia (LS)	Osteopenia (FN)	Any osteopenia	Osteoporosis (LS)	Osteoporosis (FN)	Any Osteoporosis	Fracture
Guerrero-Pérez 2020† (Casajoana 2017; 2021)	5	mRYGB	14	11 (78.6%)	7 (50%)		1(7%)	0		0
		SG	12	4 (33.3%)	3 (25%)		0	0		0
		GCP	13	6 (50%)	3 (25%)		1(8%)	1(8%)		0
Courcoulas 2014; 2015; 2020	5	RYGB	16							2 (13%)
		LAGB	20							0
		BMC	14							0
Cohen 2020	2	RYGB	46						2 (4%)	
		BMC	46						0	
Hofso 2019	1	LSG	48							1
		LRYGB	44							0
Ikramuddin 2015‡	2	LRYGB	59							5
		BMC	60							1
Mingrone 2021§	10	BPD	20			6 (30%)			3 (15%)	
		RYGB	20			2 (10%)			0	
		BMC	15			0			0	
Schauer 2012; 2014; 2017	5	RYGB	50							4
		SG	49							3
		BMC	43							4

Key: BMC – best medical care; BPD – biliopancreatic diverson; FN – femoral neck; GCP – greater curvature plication; (L)AGB – (laparoscopic) adjustable gastric banding; (L)RYGB – (laparoscopic) Roux-en-Y gastric bypass; (L)SG –(laparoscopic) sleeve gastrectomy; LS - lumbar spine; mRYGB – metabolic Roux-en-Y gastric bypass.
† World Health Organization (WHO) criteria were used to defined osteoporosis (T-score below -2.5) and osteopenia (T-score between -1.0 and -2.5).
‡ Extracted from 2-year follow-up publication. Reporting in subsequent years includes fall with injury (with or without fracture) and could not be disaggregated.
§ Osteopenia defined by bone mineral density T score measured by dual-energy x-ray absorptiometry. Osteoporosis defined by BMD T score –2.5.

Table A3.41. Cardiovascular events across included RCTs

Author, year	Follow-up (years)	Intervention; Comparator	Participants (n)	Cardiovascular event(s)	Description
Courcoulas 2014; 2015; 2020	5	RYGB	20	1	Cardiovascular event with coronary stent placement >3 years post-surgery
		LAGB	21	0	NA
		BMC	20	0	NA
Ding 2015; **Simonson** 2019	3	LAGB	18	0	NA
		BMC	22	2	IHD leading to CABG with subsequent cardiovascular death >1 year after randomization; IHD with 8 coronary revascularization procedures
Dixon 2008	2	LAGB	29	0	NA
		BMC	26	1	Angina and transient cerebral ischemic episode requiring hospital admission
Halperin 2014; **Simonson** 2018	3	RYGB	19	1	IHD leading to CABG <1 year post-surgery
		BMC	19	1	Cardiac arrest with resuscitation
Hofso 2019	1	LSG	54	1	Myocardial infarction
		LRYGB	53	0	NA
Ikramuddin 2013; 2015; 2016; 2018†	5	LRYGB	62	1	Myocardial infarction 3 years post-surgery
		BMC	45	1	Heart failure 2 years after randomisation
Lee 2011; 2014	5	LSAGB	24	2	Fatal MI 54 months post-surgery; acute myocardial ischemia with stenting
		LSG	24	1	Stroke
Mingrone 2012; 2015; 2021	10	BPD	20	0	NA
		RYGB	20	0	NA
		BMC	15	2	Fatal MI 2-5 years after randomization; myocardial infraction 5-10 years after randomisation
Schauer 2012; 2014; 2017	5	RYGB	50	0	NA
		SG	49	1	Stroke

		BMC	43	1	Fatal MI >3 years after randomisation
Total				**16**	

Key: BMC – best medical care; BPD – biliopancreatic diversion; CABG – coronary artery bypass graft; HbA1c – glycated haemoglobin; IHD – ischaemic heart disease; (L)AGB – (laparoscopic) adjustable gastric banding; (L)RYGB – (laparoscopic) Roux-en-Y gastric bypass; (L)SAGB – (laparoscopic) single anastomosis gastric bypass/one anastomosis gastric bypass/mini gastric bypass; (L)SG –(laparoscopic) sleeve gastrectomy; MI – myocardial infarction; NA – not applicable.
† Population size was adjusted in line with crossover during the RCT.

Appendix 4

Appendix A4.1 Search strategy

Table A4.1. Medline (Ovid) search strategy

#	Query	Results
1	exp Diabetes Mellitus/	435,008
2	(Diabetes or diabetes mellitus or diabetic or Type 2 diabetes mellitus or type 2 diabetes or T2D or T2DM or non-insulin-dependent diabetes).mp.	717,894
3	(Diabetes complications or diabetic complications or microvascular complications or macrovascular complications or retinopathy or neuropathy or nephropathy).mp.	228,281
4	(obesity-related comorbidit* or obesity-related co-morbidit* or obesity-associated comorbidit* or obesity-associated co-morbidit* or obesity-related disease* or obesity-associated disease* or obesity-related complication* or obesity-associated complication* or obesity-related condition* or obesity-associated condition* or obesity-related adverse outcome* or obesity-related adverse event* or co-morbid* or comorbid*).mp.	264,837
5	Comorbidity/	112,183
6	1 or 2 or 3 or 4 or 5	1,049,358
7	exp Bariatric surgery/	26,590
8	Bariatric surgery.mp.	20,754
9	metabolic surgery.mp.	1,079
10	weight loss surgery.mp.	904
11	obesity surgery.mp.	1,122
12	(Roux-en-Y or RYGB).mp.	13,387
13	(gastric bypass or gastrojejunal bypass or gastro-jejunal bypass or gastroileal bypass or gastro-ileal bypass or duodenojejunal bypass or duodeno-jejunal bypass or duodenoileal bypass).mp.	14,734
14	(mini gastric bypass or MGB or one anastomosis gastric bypass or OAGB or single anastomosis gastric bypass or SAGB or omega loop gastric bypass).mp.	1,847
15	(sleeve gastrectomy or gastric sleeve or VSG or SG).mp.	16,950
16	(gastric band* or intragastric band* or gastroplast* or vertical band or lapband or lap-band or adjustable band or AGB).mp.	7,721
17	(biliopancreatic diversion or bilio-pancreatic diversion or duodenal switch or BPD-DS).mp.	1,862
18	(Single Anastomosis Duodeno-Ileal Bypass with Sleeve Gastrectomy or SADI-S or SADIS).mp.	71
19	(Single Anastomosis Sleeve Ileal Bypass with Sleeve Gastrectomy or SASI).mp.	99
20	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19	55,221
21	Economics/	27,280
22	"costs and cost analysis"/	49,219
23	Cost allocation/	2,008
24	Cost-benefit analysis/	83,035
25	Cost control/	21,552
26	Cost savings/	12,076

27	Cost of illness/	28,087
28	Cost sharing/	2,575
29	"deductibles and coinsurance"/	1,771
30	Medical savings accounts/	538
31	Health care costs/	40,596
32	Direct service costs/	1,198
33	Drug costs/	16,360
34	Employer health costs/	1,093
35	Hospital costs/	11,322
36	Health expenditures/	20,905
37	Capital expenditures/	1,994
38	Value of life/	5,730
39	exp economics, hospital/	24,904
40	exp economics, medical/	14,237
41	Economics, nursing/	4,002
42	Economics, pharmaceutical/	2,969
43	exp "fees and charges"/	30,554
44	exp budgets/	13,781
45	(low adj cost).mp.	63,270
46	(high adj cost).mp.	15,566
47	(health?care adj cost$).mp.	12,620
48	(fiscal or funding or financial or finance).tw.	155,707
49	(cost adj estimate$).mp.	2,384
50	(cost adj variable).mp.	46
51	(unit adj cost$).mp.	2,647
52	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.	320,694
53	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52	767,724
54	6 and 20 and 53	464

Table A4.2. Embase search strategy

No.	Query	Results
#1	'diabetes mellitus'/exp	1038771
#2	diabetes:ab,ti OR 'diabetes mellitus':ab,ti OR diabetic:ab,ti OR 'type 2 diabetes mellitus':ab,ti OR 'type 2 diabetes':ab,ti OR t2d:ab,ti OR t2dm:ab,ti OR 'non-insulin-dependent diabetes':ab,ti	979810
#3	'diabetes complications':ab,ti OR 'diabetic complication*':ab,ti OR 'microvascular complication*':ab,ti OR 'microvascular disease*':ab,ti OR 'macrovascular complication*':ab,ti OR 'macrovascular disease*':ab,ti OR retinopathy:ab,ti OR neuropathy:ab,ti OR nephropathy:ab,ti	253909
#4	'obesity-related comorbidit*':ab,ti OR 'obesity-related co-morbidit*':ab,ti OR 'obesity-associated comorbidit*':ab,ti OR 'obesity-associated co-morbidit*':ab,ti OR 'obesity-related disease*':ab,ti OR 'obesity-associated disease*':ab,ti OR 'obesity-related complication*':ab,ti OR 'obesity-associated complication*':ab,ti OR 'obesity-related condition*':ab,ti OR 'obesity-associated condition*':ab,ti OR	447593

	'obesity-related adverse outcome*':ab,ti OR 'obesity-related adverse event*':ab,ti OR 'co-morbid*':ab,ti OR 'comorbid*':ab,ti OR 'comorbidity'/exp	
#5	'diabetes mellitus'/exp OR (diabetes:ab,ti OR 'diabetes mellitus':ab,ti OR diabetic:ab,ti OR 'type 2 diabetes mellitus':ab,ti OR 'type 2 diabetes':ab,ti OR t2d:ab,ti OR t2dm:ab,ti OR 'non-insulin-dependent diabetes':ab,ti) OR ('diabetes complications':ab,ti OR 'diabetic complication*':ab,ti OR 'microvascular complication*':ab,ti OR 'microvascular disease*':ab,ti OR 'macrovascular complication*':ab,ti OR 'macrovascular disease*':ab,ti OR retinopathy:ab,ti OR neuropathy:ab,ti OR nephropathy:ab,ti) OR ('obesity-related comorbidit*':ab,ti OR 'obesity-related co-morbidit*':ab,ti OR 'obesity-associated comorbidit*':ab,ti OR 'obesity-associated co-morbidit*':ab,ti OR 'obesity-related disease*':ab,ti OR 'obesity-associated disease*':ab,ti OR 'obesity-related complication*':ab,ti OR 'obesity-associated complication*':ab,ti OR 'obesity-related condition*':ab,ti OR 'obesity-associated condition*':ab,ti OR 'obesity-related adverse outcome*':ab,ti OR 'obesity-related adverse event*':ab,ti OR 'co-morbid*':ab,ti OR 'comorbid*':ab,ti OR 'comorbidity'/exp)	1703614
#6	'bariatric surgery'/exp	46133
#7	'bariatric surgery':ab,ti	30948
#8	'metabolic surgery':ab,ti	1614
#9	'weight loss surgery':ab,ti	1433
#10	'obesity surgery':ab,ti	1621
#11	'roux-en-y gastric bypass'/exp OR 'roux-en-y':ab,ti OR rygb:ab,ti	22950
#12	'gastric bypass surgery'/exp OR 'gastric bypass':ab,ti OR 'gastrojejunal bypass':ab,ti OR 'gastro-jejunal bypass':ab,ti OR 'gastroileal bypass':ab,ti OR 'gastro-ileal bypass':ab,ti OR 'duodenojejunal bypass':ab,ti OR 'duodeno-jejunal bypass':ab,ti OR 'duodenoileal bypass':ab,ti	28648
#13	'mini gastric bypass':ab,ti OR mgb:ab,ti OR 'one anastomosis gastric bypass':ab,ti OR oagb:ab,ti OR 'single anastomosis gastric bypass':ab,ti OR sagb OR 'omega loop gastric bypass':ab,ti	3222
#14	'sleeve gastrectomy'/exp OR 'sleeve gastrectomy':ab,ti OR 'gastric sleeve':ab,ti OR vsg:ab,ti OR sg:ab,ti	31408
#15	'gastric band':ab,ti OR 'intragastric band':ab,ti OR 'gastroplasty':ab,ti OR 'vertical band':ab,ti OR lapband:ab,ti OR 'lap band':ab,ti OR 'adjustable band':ab,ti OR agb:ab,ti	6800
#16	'biliopancreatic bypass'/exp OR 'biliopancreatic diversion':ab,ti OR 'bilio-pancreatic diversion':ab,ti OR 'duodenal switch':ab,ti OR 'bpd ds':ab,ti OR bpd:ab,ti	17485
#17	'single anastomosis duodeno–ileal bypass with sleeve gastrectomy':ab,ti OR 'sadi s':ab,ti OR sadis:ab,ti	177
#18	'single anastomosis sleeve ileal bypass with sleeve gastrectomy':ab,ti OR sasi:ab,ti	169
#19	'bariatric surgery'/exp OR 'bariatric surgery':ab,ti OR 'metabolic surgery':ab,ti OR 'weight loss surgery':ab,ti OR 'obesity surgery':ab,ti OR ('roux-en-y gastric bypass'/exp OR 'roux-en-y':ab,ti OR rygb:ab,ti) OR ('gastric bypass surgery'/exp OR 'gastric bypass':ab,ti OR 'gastrojejunal bypass':ab,ti OR 'gastro-jejunal bypass':ab,ti OR 'gastroileal bypass':ab,ti OR 'gastro-ileal bypass':ab,ti OR 'duodenojejunal bypass':ab,ti OR 'duodeno-jejunal bypass':ab,ti OR	99090

	'duodenoileal bypass':ab,ti) OR ('mini gastric bypass':ab,ti OR mgb:ab,ti OR 'one anastomosis gastric bypass':ab,ti OR oagb:ab,ti OR 'single anastomosis gastric bypass':ab,ti OR sagb OR 'omega loop gastric bypass':ab,ti) OR ('sleeve gastrectomy'/exp OR 'sleeve gastrectomy':ab,ti OR 'gastric sleeve':ab,ti OR vsg:ab,ti OR sg:ab,ti) OR ('gastric band':ab,ti OR 'intragastric band':ab,ti OR 'gastroplasty':ab,ti OR 'vertical band':ab,ti OR lapband:ab,ti OR 'lap band':ab,ti OR 'adjustable band':ab,ti OR agb:ab,ti) OR ('biliopancreatic bypass'/exp OR 'biliopancreatic diversion':ab,ti OR 'bilio-pancreatic diversion':ab,ti OR 'duodenal switch':ab,ti OR 'bpd ds':ab,ti OR bpd:ab,ti) OR ('single anastomosis duodeno–ileal bypass with sleeve gastrectomy':ab,ti OR 'sadi s':ab,ti OR sadis:ab,ti) OR ('single anastomosis stomach–ileal bypass with sleeve gastrectomy':ab,ti OR sasi:ab,ti)	
#20	'socioeconomics'/exp	405474
#21	'cost benefit analysis'/exp	85775
#22	'cost effectiveness analysis'/exp	156063
#23	'cost of illness'/exp	19520
#24	'cost control'/exp	69582
#25	'economic aspect'/exp	1756973
#26	'financial management'/exp	452444
#27	'health care cost'/exp	299612
#28	'health care financing'/exp	13385
#29	'health economics'/exp	888789
#30	'hospital cost'/exp	39845
#31	fiscal:ti,ab,de OR financial:ti,ab,de OR finance:ti,ab,de OR funding:ti,ab,de	333465
#32	'cost minimization analysis'/exp	3583
#33	cost NEXT/1 estimate$	3579
#34	cost NEXT/1 variable$	279
#35	unit NEXT/1 cost$	4695
#36	'socioeconomics'/exp OR 'cost benefit analysis'/exp OR 'cost effectiveness analysis'/exp OR 'cost of illness'/exp OR 'cost control'/exp OR 'economic aspect'/exp OR 'financial management'/exp OR 'health care cost'/exp OR 'health care financing'/exp OR 'health economics'/exp OR 'hospital cost'/exp OR (fiscal:ti,ab,de OR financial:ti,ab,de OR finance:ti,ab,de OR funding:ti,ab,de) OR 'cost minimization analysis'/exp OR cost NEXT/1 estimate$ OR cost NEXT/1 variable$ OR unit NEXT/1 cost$	1847542
#37	('diabetes mellitus'/exp OR (diabetes:ab,ti OR 'diabetes mellitus':ab,ti OR diabetic:ab,ti OR 'type 2 diabetes mellitus':ab,ti OR 'type 2 diabetes':ab,ti OR t2d:ab,ti OR t2dm:ab,ti OR 'non-insulin-dependent diabetes':ab,ti) OR ('diabetes complications':ab,ti OR 'diabetic complication*':ab,ti OR 'microvascular complication*':ab,ti OR 'microvascular disease*':ab,ti OR 'macrovascular complication*':ab,ti OR 'macrovascular disease*':ab,ti OR retinopathy:ab,ti OR neuropathy:ab,ti OR nephropathy:ab,ti) OR ('obesity-related comorbidit*':ab,ti OR 'obesity-related co-morbidit*':ab,ti OR 'obesity-associated comorbidit*':ab,ti OR 'obesity-associated co-morbidit*':ab,ti OR 'obesity-related disease*':ab,ti OR 'obesity-associated disease*':ab,ti OR 'obesity-related complication*':ab,ti OR 'obesity-associated complication*':ab,ti OR 'obesity-related condition*':ab,ti OR 'obesity-associated condition*':ab,ti OR	2021

	'obesity-related adverse outcome*':ab,ti OR 'obesity-related adverse event*':ab,ti OR 'co-morbid*':ab,ti OR 'comorbid*':ab,ti OR 'comorbidity'/exp)) AND ('bariatric surgery'/exp OR 'bariatric surgery':ab,ti OR 'metabolic surgery':ab,ti OR 'weight loss surgery':ab,ti OR 'obesity surgery':ab,ti OR ('roux-en-y gastric bypass'/exp OR 'roux-en-y':ab,ti OR rygb:ab,ti) OR ('gastric bypass surgery'/exp OR 'gastric bypass':ab,ti OR 'gastrojejunal bypass':ab,ti OR 'gastro-jejunal bypass':ab,ti OR 'gastroileal bypass':ab,ti OR 'gastro-ileal bypass':ab,ti OR 'duodenojejunal bypass':ab,ti OR 'duodeno-jejunal bypass':ab,ti OR 'duodenoileal bypass':ab,ti) OR ('mini gastric bypass':ab,ti OR mgb:ab,ti OR 'one anastomosis gastric bypass':ab,ti OR oagb:ab,ti OR 'single anastomosis gastric bypass':ab,ti OR sagb OR 'omega loop gastric bypass':ab,ti) OR ('sleeve gastrectomy'/exp OR 'sleeve gastrectomy':ab,ti OR 'gastric sleeve':ab,ti OR vsg:ab,ti OR sg:ab,ti) OR ('gastric band':ab,ti OR 'intragastric band':ab,ti OR 'gastroplasty':ab,ti OR 'vertical band':ab,ti OR lapband:ab,ti OR 'lap band':ab,ti OR 'adjustable band':ab,ti OR agb:ab,ti) OR ('biliopancreatic bypass'/exp OR 'biliopancreatic diversion':ab,ti OR 'bilio-pancreatic diversion':ab,ti OR 'duodenal switch':ab,ti OR 'bpd ds':ab,ti OR bpd:ab,ti) OR ('single anastomosis duodeno–ileal bypass with sleeve gastrectomy':ab,ti OR 'sadi s':ab,ti OR sadis:ab,ti) OR ('single anastomosis stomach–ileal bypass with sleeve gastrectomy':ab,ti OR sasi:ab,ti)) AND ('socioeconomics'/exp OR 'cost benefit analysis'/exp OR 'cost effectiveness analysis'/exp OR 'cost of illness'/exp OR 'cost control'/exp OR 'economic aspect'/exp OR 'financial management'/exp OR 'health care cost'/exp OR 'health care financing'/exp OR 'health economics'/exp OR 'hospital cost'/exp OR (fiscal:ti,ab,de OR financial:ti,ab,de OR finance:ti,ab,de OR funding:ti,ab,de) OR 'cost minimization analysis'/exp OR cost NEXT/1 estimate$ OR cost NEXT/1 variable$ OR unit NEXT/1 cost$)	

Grey literature search

- Centre for Health Economics and Policy Analysis (CHEPA) ; Available from http://www.chepa.org/
- Cost Effectiveness Analysis Registry; Available from http://healtheconomics.tuftsmedicalcenter.org/cear4/SearchingtheCEARegistry/SearchtheCEARegistry.aspx
- HTAi vortal; Available from https://www.htai.org/index.php?id=579
- Google Scholar and Google; Available from https://scholar.google.com/, https://www.google.ie
- Health Service Executive (HSE); Available from https://www.hse.ie/eng/
- Health Research Board (HRB) Ireland; Available from http://www.hrb.ie/home/
- Institute of Health Economics (Alberta Canada); Available from https://www.ihe.ca/
- Lenus; Available from http://www.lenus.ie/hse/
- National Coordinating Centre for Health Technology Assessment (NCCHTA) ; Available from https://www.nihr.ac.uk/funding-and-support/funding-for-research-studies/funding-programmes/health-technology-assessment/
- National Centre for Pharmacoeconomics (NCPE); Available from http://www.ncpe.ie/
- National Institute for Health and Clinical Excellence (NICE); Available from https://www.nice.org.uk/
- NHS Evidence database (UK); Available from https://www.evidence.nhs.uk/
- Open Grey; Available from http://www.opengrey.eu/
- World Health Organization (WHO); Available from http://www.who.int/en/

Appendix A4.2 Study selection process

Table A4.3. List of excluded studies

Study	Reason
Alsumali A, Eguale T, Rittenhouse B, Bairdain S, Seoane-Vazquez E, Samnaliev M. Cost effectiveness of bariatric surgery for morbid obesity in USA. Value in Health. 2017;20(5):A222.	Insufficient information
An S, Park H-Y, Oh S-H, Heo Y, Park S, Jeon SM, et al. Cost-effectiveness of Bariatric Surgery for People with Morbid Obesity in South Korea. Obesity surgery. 2020;30(1):256-66.	Irrelevant population
Avenell A, Robertson C, Skea Z, Jacobsen E, Boyers D, Cooper D, et al. Bariatric surgery, lifestyle interventions and orlistat for severe obesity: the REBALANCE mixed-methods systematic review and economic evaluation. Health technology assessment (Winchester, England). 2018;22(68):1-246.	Irrelevant population
Bailey JG, Hayden JA, Davis PJB, Liu RY, Haardt D, Ellsmere J. Robotic versus laparoscopic Roux-en-Y gastric bypass (RYGB) in obese adults ages 18 to 65 years: a systematic review and economic analysis. Surgical endoscopy. 2014;28(2):414-26.	Irrelevant study design
Banka G, Wu C, Morton J, Garber A. Comparative effectiveness analysis of bariatric surgery versus medical treatment ALONE for patients with BMIS between 30 and 35. Journal of the American College of Cardiology. 2012;59(13):E1886.	Insufficient information
Belarbi S, Kusel J, Maruszczak M, Slater D, Thomas MG, Martini O. The cost-effectiveness of bariatric surgery in Germany. Value in Health. 2015;18(7):A393.	Insufficient information
Belarbi S, Kusel J, Thomas MG. The cost-effectiveness of bariatric surgery in Germany, France, Italy and the United Kingdom. Value in Health. 2016;19(7):A354.	Insufficient information
Bockelbrink A, Stober Y, Roll S, Vauth C, Willich SN, von der Schulenburg J-M. Evaluation of medical and health economic effectiveness of bariatric surgery (obesity surgery) versus conservative strategies in adult patients with morbid obesity. GMS health technology assessment. 2008;4:Doc06.	Irrelevant study design
Borisenko O, Burdukova E, Hargreaves J, Adam D. Cost-utility of bariatric surgery in France and Germany. Value in Health. 2015;18(7):A671.	Insufficient information
Borisenko O, Burdukova E, Hargreaves J, Adam D, Funch-Jensen P. Cost-utility of bariatric surgery in Belgium, Denmark, and Italy. Value in Health. 2015;18(7):A670-A1.	Insufficient information

Capehorn M, Carter D, Senior L. Service evaluation of the rotherham institute for obesity. Obesity Facts. 2012;5:187.	Insufficient information
Castilla I, Mar J, Valcarcel-Nazco C, Arrospide A, Ramos-Goni JM. Cost-utility analysis of gastric bypass for severely obese patients in Spain. Obesity surgery. 2014;24(12):2061-8.	Irrelevant population
Chang SH, Stoll CRT, Colditz GA. Cost-effectiveness of bariatric surgery: Should it be universally available? Maturitas. 2011;69(3):230-8.	Irrelevant population
Chen G, Kusel J, Buguth B, Higgins A, Belarbi S. Cost-effectiveness of bariatric surgery compared to conventional treatment from a societal perspective in Germany, France, Italy and the UK. Value in Health. 2017;20(9):A557.	Insufficient information
Chevallier JM, Daoud F, Szwarcensztein K, Volcot MF, Rupprecht MF. Medicoeconomic evaluation of the treatment of morbid obesity by swedish adjustable gastric banding (SAGB). Annales de Chirurgie. 2006;131(1):12-21	Non-English
Chiang AL, Tapper EB, Thompson CC. Cost-utility analysis of obesity therapy: A comparison of lifestyle intervention to surgical, and endoscopic strategies. Gastroenterology. 2016;150(4):S86.	Insufficient information
Clegg AJ, Colquitt J, Sidhu MK, Royle P, Loveman E, Walker A. The clinical effectiveness and cost-effectiveness of surgery for people with morbid obesity: A systematic review and economic evaluation. Health Technology Assessment. 2002;6(12).	Irrelevant population
Cuadrado C. The health and economic burden of obesity in Chile-an epidemiological and economic simulation model. Value in Health. 2016;19(7):A584.	Insufficient information
Dixon J. Obesity: Health economics of bariatric surgery-benefit versus cost. Nature Reviews Endocrinology. 2012;8(11):632-3.	Irrelevant study design
Faria G, Preto J, Da Costa EL, Almeida AB, Maia JC, Guimarães JT, et al. Gastric bypass is a cost saving procedure: Results from a comprehensive markov model. Obesity Surgery. 2012;22(9):1418.	Insufficient information
Gulliford MC, Booth HP, Charlton J, Fildes A, Khan O, Reddy M, et al. Costs and outcomes of increasing access to bariatric surgery for obesity: Cohort study and cost-effectiveness analysis using electronic health records. Obesity Facts. 2016;9:162.	Insufficient information
Hashemi L, Minshall ME. Cost-effectiveness of Roux-en-Y Gastric Bypass in type 2 diabetes pationts in Canada. Value in Health. 2010;13(3):A59.	Insufficient information
Heo Y, Park DJ, Kang JH, Kwon JW, Park Y. Prospective cohort study for comparing bariatiric surgery and medical treatment for severely obese patients: Efficacy, safety and costeffectiveness. Obesity Surgery. 2019;29(5):1009.	Insufficient information
Hoerger TJ, Zhang P, Segel JE, Kahn HS, Barker LE, Couper SP. Cost-effectiveness of bariatric surgery for obese persons with diabetes. Diabetes. 2010.	Insufficient information

Jacobsen E, Retat L, Boyers D, Avenell A, Corbould E, Webber L, et al. Cost-effectiveness of behaviour, lifestyle and surgical interventions for severe obesity (the REBALANCE project). Obesity Facts. 2019;12:62.	Insufficient information
Kaplan J, Kahn JG, Rogers S, Lin M, Schecter SC, Carter J. The benefit and cost effectiveness of laparoscopic gastric bypass stems largely from resolution of metabolic disease, not just weight loss. Surgery for Obesity and Related Diseases. 2015;11(6):S16-S7.	Insufficient information
Karim MA, Clifton E, Ahmed J, Mackay GW, Ali A. Economic evaluation of bariatric surgery to combat morbid obesity: a study from the West of Scotland. Asian journal of endoscopic surgery. 2013;6(3):197-202.	Irrelevant study design
Keating CL, Dixon JB, Moodie ML, Peeters A, Playfair J, O'Brien PE. Cost-efficacy of surgically induced weight loss for the management of type 2 diabetes: a randomized controlled trial. Diabetes care. 2009;32(4):580-4.	Duplicate
Kwon JW, Song HJ, Lee HJ, Lee JY, Choi JE, Oh SH. Cost-utility analysis of bariatric surgery for the treatment of obese patients in South Korea. Value in Health. 2012;15(4):A78.	Insufficient information
Lewis L, Taylor M. A cost-utility analysis of lighterlife total as a treatment for obesity in the United Kingdom. Value in Health. 2013;16(7):A385.	Insufficient information
Lewis L, Taylor M, Broom J, Johnston KL. The cost-effectiveness of the LighterLife weight management programme as an intervention for obesity in England. Clinical obesity. 2014;4(3):180-8.	Irrelevant outcomes
Luck ML, Cahill AG, Niu B, Ameel BM, Caughey AB. Cost-effectiveness of pre-pregnancy bariatric surgery on obstetric outcomes. American Journal of Obstetrics and Gynecology. 2017;216(1):S388.	Insufficient information
Ludwig K, Schneider-Koriath S, Bernhardt J, Hüttl TP. Risk-benefit analysis of bariatric surgery. Viszeralmedizin: Gastrointestinal Medicine and Surgery. 2010;26(1):21-5.	Non-English
McCombie L, Lean MEJ, Tigbe W. Cost-effectiveness of obesity treatment. Medicine. 2011;39(1):14-7.	Irrelevant study design
McEwen LN, Coelho RB, Baumann LM, Bilik D, Herman WH. The cost-utility of bariatric surgery in managed care. Diabetes. 2009;58.	Insufficient information
Medical Advisory S. Bariatric surgery: an evidence-based analysis. Ontario health technology assessment series. 2005;5(1):1-148.	Irrelevant study design
Medical Advisory S. Bariatric surgery for people with diabetes and morbid obesity: an evidence-based analysis. Ontario health technology assessment series. 2009;9(22):1-23.	Irrelevant study design
Minshall M, Swan T, Slusarek B, Ikramuddin S. Cost-effectiveness of the Roux-en-Y gastric bypass surgery compared with medical management for treatment of Type 2 Diabetes Mellitus (T2DM) in The UK, France, and Germany. Obesity	Insufficient information

Surgery. 2009;19(8):1003.	
Minshall M, Swan T, Slusarek B, Ikramuddin S. Cost-effectiveness of the Roux-en-Y gastric bypass surgery compared with medical management for treatment of Type 2 Diabetes Mellitus (T2DM) in Spain, Italy, and Sweden. Obesity Surgery. 2009;19(8):1003-4.	Insufficient information
Nasciben V, Saggia MG. A cost-effectiveness analysis of conventional treatment versus bariatric surgery for obese patients with type-2 diabetes and hypertension as comorbidities. preliminary results under the Brazilian private payer perspective. Value in Health. 2010;13(3):A209.	Insufficient information
Neovius M, Sjöholm K, Söderling J, Peltonen M, Carlsson L. Long-Term Cost-Effectiveness of Bariatric Surgery vs Conventional Treatment in Swedish Obese Subjects By Baseline Glycemic Status. Surgery for Obesity and Related Diseases. 2019;15(10):S2.	Insufficient information
Nguyen NT, Goldman C, Rosenquist CJ, Arango A, Cole CJ, Lee SJ, et al. Laparoscopic versus open gastric bypass: A randomized study of outcomes, quality of life, and costs. Annals of Surgery. 2001;234(3):279-91.	Irrelevant study design
Owen-Smith A, Kipping R, Donovan J, Hine C, Maslen C, Coast J. A NICE example? Variation in provision of bariatric surgery in England. BMJ (Online). 2013;346(7909).	Irrelevant study design
Paladini LM, Clark LGO, Clark O, Pegoretti B, Engel T, Faleiros EJM. Intragastric baloon (IGB) for morbidly obese (MOP) and super obese patients (SOP) : Systematic review (SR) and health technology assessment (HTA). Value in Health. 2010;13(3):A215.	Insufficient information
Pasricha A, Blackhouse G, Goeree R, Tarride JE, O'Reilly D. Cost-effectiveness of bariatric surgical procedures versus no treatment for morbid obesity. Value in Health. 2010;13(3):A211.	Insufficient information
Ribeiro RA, Luque A, Junqueira Junior SM. Delayed access to bariatric surgery in Brazil: Cost-effectiveness analysis. Value in Health. 2016;19(7):A587-A8.	Insufficient information
Rodicio Miravalles JL, Alonso Fernandez J, Moreno Gijon M, Rizzo Ramos A, Turienzo Santos E, Sanz Alvarez L, et al. Economic evaluation of surgical treatment of obesity. Evaluacion economica del tratamiento quirurgico de la obesidad. 2020;98(7):381-8.	Irrelevant study design
Salem L, Devlin A, Sullivan SD, Flum DR. Cost-effectiveness analysis of laparoscopic gastric bypass, adjustable gastric banding, and nonoperative weight loss interventions. Surgery for Obesity and Related Diseases. 2008;4(1):26-32.	Irrelevant outcomes
Sanchez R, Mariño E, Daniel A, Borisenko O, Collados C, Estevez S, et al. Cost-effectiveness of bariatric surgery for the treatment of morbid obesity patients compared with conservative management in Spain. Value in Health. 2016;19(7):A587.	Insufficient information
Sánchez-Santos R, Sabench Pereferrer F, Estévez Fernandez S, del Castillo Dejardin D, Vilarrasa N, Frutos Bernal D, et al. Is the morbid obesity surgery profitable in times of crisis? A cost-benefit analysis of bariatric surgery. Cirugia Espanola. 2013;91(8):476-84.	Non-English

Saumoy M, Schneider Y, Novikov AA, Afaneh C, Shukla A, Tyberg A, et al. A cost-utility analysis comparing endoscopic, surgical and lifestyle management of obesity. Gastroenterology. 2017;152(5):S831-S2.	Insufficient information
Song HJ, Kwon JW, Kim YJ, Oh S-H, Heo Y, Han S-M. Bariatric surgery for the treatment of severely obese patients in South Korea--is it cost effective? Obesity surgery. 2013;23(12):2058-67.	Irrelevant population
Song HJ, Lee HJ, Lee JY, Choi JE, Oh SH, Kwon JW. Clinical and cost effectiveness of bariatric surgery for obese patients: Economic evaluation in South Korea. Value in Health. 2012;15(4):A78.	Insufficient information
Szoka B, Batóg P, Macioch T, Niewada M, Belarbi S, Kusel J, et al. Cost-effectiveness of bariatric surgery compared with non-surgica l treatment of morbid obesity in Poland. Value in Health. 2016;19(7):A588.	Insufficient information
Tang Q, Sun Z, Zhang N, Xu G, Song P, Xu L, et al. Cost-Effectiveness of Bariatric Surgery for Type 2 Diabetes Mellitus. Medicine (United States). 2016;95(20).	Duplicate
Tatar M, Şentürk A, Turgut CG, Tandoğan A, Bektaş T. Cost effectiveness of bariatric surgery in turkey: From a long-term perspective. Value in Health. 2017;20(9):A584.	Insufficient information
Terranova L, Busetto L, Vestri A, Zappa MA. Bariatric surgery: cost-effectiveness and budget impact. Obesity surgery. 2012;22(4):646-53.	Irrelevant study design
Walter E, Langer F, Beckerhinn P, Hoffer F, Prager G. Impact of metabolic surgery on cost and long-term health outcome: A cost-effectiveness approach. Value in Health. 2017;20(9):A557.	Insufficient information
Warren JA, Ewing JA, Hale AL, Blackhurst DW, Bour ES, Scott JD. Cost-effectiveness of Bariatric Surgery: Increasing the Economic Viability of the Most Effective Treatment for Type II Diabetes Mellitus. The American surgeon. 2015;81(8):807-11.	Irrelevant study design
Welbourn R, Le Roux CW, Owen-Smith A, Wordsworth S, Blazeby JM. Why the NHS should do more bariatric surgery; how much should we do? BMJ (Online). 2016;353.	Irrelevant study design
Wentworth JM, Dalziel KM, O'Brien PE, Burton P, Shaba F, Clarke PM, et al. Cost-effectiveness of gastric band surgery for overweight but not obese adults with type 2 diabetes in the U.S. Journal of diabetes and its complications. 2017;31(7):1139-44.	Irrelevant population
Zanela O, Cabra HA, Anaya P, Rodriguez S, Melendez G, Rupprecht F. Use of a discrete event simulation model to estimate long term economic outcomes of bariatric surgery in morbidly-obese, type-2 diabetic patients in Mexico. Value in Health. 2011;14(7):A568.	Insufficient information
Zanela OO, Cabra HA, Melendez G, Anaya P, Rupprecht F. Economic Evaluation of Bariatric Surgery in Mexico Using Discrete Event Simulation. Value in health regional issues. 2012;1(2):172-9.	Irrelevant study design

Appendix A4.3 Study characteristics

Table A4.4. Summary of estimated effectiveness of surgery on T2D remission.

Author (year)	Characteristics of the modelled population	T2D remission rate	Source of T2D remission rate	Relevant assumptions
T2D populations or sub-cohorts				
Ackroyd (2006)	NR	Year 1 Usual care: 20% AGB: 64% GBP: 82% Year 2 Usual care: 0% AGB: 56% GBP: 50% Year 5 Usual care: 0% AGB: 50% GBP: 50%	Literature review	▪ Conventional treatment yields a temporary moderate reduction in BMI, with a return to baseline or more after year 1. ▪ BMI increase/decrease of 1 kg/m2 has the same utility irrespective of baseline BMI. ▪ The relative prevalence of T2D is related to BMI.
Anselmino (2009)	NR	See Ackroyd 2006	See Ackroyd 2006	See Ackroyd (2006)
Assumpção (2019)	NR	2 years: 72.3% (surgery); 16.4% (CMM) 10 years: 38.1% (surgery); 10% (CMM) 15 years: 30.4% (surgery); 6.5% (CMM)	SOS[308]	NR
Gil-Rojas (2019)	**Mean age:** 40 years **Mean BMI:** 45.6 kg/m2; **Mean T2D duration:** NR **Mean HbA1c:** NR	Efficacy 92.83% (GB); 85.53% (SG)	Literature review	▪ Remission can occur for up to 2 years after surgery ▪ Risk of stroke and AMI were linked with BMI in the model
Hoerger (2010)	NR	Newly diagnosed (HbA1c 6%): Remission 80.30% (bypass), 56.7% (banding); improvement 0% (bypass); 24% (AGB) (Relapse rate 8.3%)	Retrospective observational study and meta-analysis Buchwald, 2009 #690}[527]	▪ Age-group analyses assumed that remission, perioperative mortality, other direct surgical outcome rates and costs did not vary by age (i.e. driven by higher mortality rates in older populations). ▪ In the established diabetic population,

		Established (HbA1c 7%): 40% (bypass and banding)		GBP and GB have the same rates of remission and improvement (due to lack of data)
Ikramuddin (2009)	**Mean age:** 50.1 years (11.8% >60 years) **Mean BMI:** 48.4 kg/m^2 (12.8% <40 kg/m^2) **Mean T2D duration:** 8.7 years **Mean HbA1C:** 7.7%	Unclear	Prospective observational study	▪ Weight gain after RYGB does not occur (due to lack of date)
Keating (2009a)	*Mean parameters at end of RCT:* **Mean BMI**: CMM 37 kg/m^2; Surgery 29 kg/m^2; **Mean age:** 49 years **Mean T2D duration:** 3 years	2 years: 73% (surgery); 13% (CMM)	RCT (Dixon et al)	NA
Keating (2009b)	See Keating 2009a	2 years: 73% (surgery); 13% (CMM)	RCT (Dixon et al.); SOS; Greenville report	▪ Patients in T2DM remission have a similar QoL to the general population. ▪ Mortality risk for patients in T2DM remission assumed to be the same as patients without T2DM (due to lack of data).
Kim (2018)	**Mean age:** 53 years **Mean BMI:** NR **Mean T2D duration:** NR **Mean HbA1C:** NR	Unclear	NHANES datasets	NR
McGlone (2020)	**Mean age:** 51.1 (9.4) **Mean BMI:** 47.2 (7.3) **Mean T2D duration:** 0-5 years: 24.6% 6-10 years: 30.8% >10 years: 44.7%	Year 1: AGB: 5.1% SG: 30.0% RYGB: 37.6% Year 2 AGB: 17.7 SG: 26.9 RYGB: 42.2 Year 4: Overall: 31%	NBSR	▪ BMI that remained unchanged for patients treated with BMT. ▪ Escalation of treatment in the BMT arm would occur over the modelled time horizon. ▪ BMI was modelled as remaining unchanged between year 2 and year 5 in the surgery arm (based on NBSR data).
Pollock (2013)	**Mean age:** 46.9 (8.7) **Mean BMI:** 37.1 **Mean T2D duration:** 1 year (SD 4 months) **Mean HbA1c:** 7.7% (1.4)	Change from baseline HbA1c LAGB: -1.81 (1.24%) Usual care: -0.38 (1.26%) Remission rate: LAGB: 73%	RCT (Dixon et al)	▪ A mean duration of diabetes of 1 year was assumed, with a standard deviation of 4 months.

		Usual care 13%		
Rognoni (2020)	**Mean age:** 43 years **Mean BMI:** 1) 45 kg/m^2 2) 45 kg/m^2 3) 31 kg/m^2 **Mean HbA1c:** NR **Mean T2D duration:** NR	**BMI >35** Usual care: Year 1: 17.64%; year 15: 6.5% GBP: 95.15% (year 1); SG: 85.53% (year 1); AGB: 73.88% (year 1) All surgeries: 30.40% (year 15) **BMI 30-35** Diet: year 1: 17.64% year 2+: 0% GBP: 95.15% (year 1) SG: 85.53% (year 1); AGB: 73.88% (year 1); All surgeries: 17% (year 3)	Literature review (RCTs; SOS; meta-analysis)	NR
Tang (2016)	**Mean age:** LSG: 36.6 (8.0); LRYGB: 40.4 (12.3) **Mean BMI:** LSG: 38.4 (8.6); LRYGB: 37.8 (5.6) **Diabetes duration:** LSG: 5.1 (4.1); LRYGB: 6.5 (4.1)	Partial remission: 76.5% (LSG); 57.9% (LRYGB) Complete remission: 50.0% (LSG); 36.8% (LRYGB).	Extrapolation of trial data	NA
Tu (2019)	**Mean age**: RYGB 49.0 (11.1); CMM 49.6 (12.4); **Mean BMI:** RYGB 30.7 (3.0); CMM 24.8 (3.8); **Mean HbA1c:** RYGB: 8.6 (2.1); CMM 8.5(2.3) **Mean T2D duration:** RYGB: 8 (4.8); CMM 4.3 (2.8)	RYGB: 75.8% (year 1); 64.9% (year 2); 58.8% (year 3); 46.7% (year 4) CMM: 0%	Prospective cohort study	▪ Utility values assumed to change linearly with HbA1c
Viratanapanu (2019)	**Mean age:** 41.8 (12.2); **Mean BMI:** 50.1 (10.3) **Mean HbA1C:** 7.6% (1.9) **Mean T2D duration:** NR	RYGB: Remission = 84% (0.8356) Improvement = 4% (0.0411) Persistent T2D =1% (0.0099) Uncontrolled T2D) = 1.2% (0.01233) CMM: Remission = 0.01% (0.0001)	Retrospective cohort study	NR

		Improvement = 23% (0.23) Persistent T2D = 17% (0.17) Uncontrolled T2D = 60% (0.5998)		
Wan (2019)	Not reported	53.6% (surgery); 2.6% (CMM)	Retrospective cohort study	▪ QoL of patients in T2DM remission was the same as the general population ▪ The mortality risk for patients in T2DM remission was the same as a healthy person
Population subgroups with T2D				
Borisenko (2018)a	**Mean age:** 45·4 years, **Mean BMI:** 50·5 kg/m^2 **T2D prevalence:** 30%	2 years: 72% (surgery); 21% (CMM) 10 years: 36% (surgery); 13% (CMM)	Years 1-3: NBSR; Years 3-10: SOS[366]	▪ No resource use in relation to obesity management in the usual care arm. ▪ After 15 years, BMI remained constant until death ▪ After 10 years, no new episodes of remission occurred. ▪ Complications occur in first 2 years. No long-term complications.
Borisenko (2018)b	**Mean age:** 39.2 years **Mean BMI:** 41.44 **T2D Prevalence:** 9%	5 years: 5% (CMM); 29% (GBP); 23% (SG)	RCT (Schauer et al)	▪ After 15 years, BMI level was assumed to be permanent until death.
Borisenko (2017)a	**Mean age:** 40 years **Mean BMI:** 42 kg/m^2 **T2D prevalence:** 26%	2 years: 72% (surgery); 21% (CMM) 10 years: 36% (surgery); 13% (CMM)	SOS	▪ After 15 years, BMI remained constant until death.
Borisenko (2017)b	**Mean age:** 40.4 years **Mean BMI:** 48.8 kg/m^2 **T2D prevalence:** 20.6%	2 years: 72% (surgery); 21% (CMM) 10 years: 36% (surgery); 13% (CMM)	SOS	▪ After 15 years, BMI level was assumed permanent until death.
Borisenko (2015)	**Mean age:** 41 years **Mean BMI:** 42.8 kg/m^2 **T2D prevalence:** 18.39%	2 years: 72% (surgery); 21% (CMM) 10 years: 36% (surgery); 13% (CMM)	SOS[366]	▪ After 15 years, BMI remained constant until death. ▪ After 10 years, no new episodes of remission occurred.
Cohen (2017)	**Mean age:** 41 years **Mean BMI:** 48.6 kg/m^2 **T2D prevalence:** 22.3%	2 years: 72% (surgery); 21% (CMM) 10 years: 36% (surgery); 13% (CMM)	SOS	▪ Complications occur in the first year after surgery. ▪ CV events were only counted in the model and do not change mortality probability.
Faria (2013)	**Mean age:** 40 years	NR	NR	NR

	Mean BMI: 49.6 **T2D prevalence:** Unclear			
Gulliford (2017)	**Mean age:** 46 years (range 20–74) **BMI:** ≥ 40kg/m^2 **T2D prevalence:** 19%	AGB + SG + GBP: 40%; CMM: unclear	CPRD	▪ 2% of surgical patients require repeat procedures each year. ▪ Gains in utility associated with BMI reduction declines overtime, to account for a reduction in the initial QoL improvement after surgery.
James (2017)	**Mean age:** 30 years **BMI:** >35 kg/m^2 **T2D prevalence:** Unclear	NR	NR	▪ Complications occur within the first 2 years. ▪ T2DM costs were modelled to ▪ gradually increase at a rate of 5%,
Klarenbach (2010)	**Mean age:** 48 years **Mean BMI:** 47 kg/m^2 **T2D prevalence:** 15%	Short-term resolution: RYGB + SG: 83.7%; LAGB 47.9%; BPD 98.9% 2 years: 72% (surgery); 21% (CMM) 10 years: 36% (surgery); 13% (CMM)	Systematic review (SOS; meta-analysis)	▪ No further changes in BMI after 10 years ▪ No further change in the prevalence of obesity-related disease after 10 years ▪ QoL reduced to nil for one month post-surgery. ▪ All complications occur within year 1.
Lucchese (2017)	**Mean age:** 41 years **Mean BMI:** 46.2 kg/m^2 **T2D prevalence:** 20%	2 years: 72% (surgery); 21% (CMM) 10 years: 36% (surgery); 13% (CMM)	SOS	▪ After 15 years, BMI was assumed to be stable.
McEwen (2010)	**Mean age:** 42 (SD 10) years **Average BMI:** 52 (SD 9) kg/m^2 **T2D prevalence:** 36%	NR	NR	▪ Average annual costs beyond 24 months for a person not undergoing bariatric surgery increased at a rate of 4.3% per year. ▪ Average annual costs beyond 24 months for a person undergoing bariatric surgery decreased at a rate of 9.5% per year for years 3 and 4. This accounted for the decrease in costs due to resolution of postsurgical complications. ▪ We then assumed that costs increased at a rate of 2.7% per ▪ year to account for the increase in costs due to aging
Picot (2012)‡	**Mean Age:** LAGB 46.6 (7.4), Non-surgical 47.1 (8.7);	2 years: 70% (surgery); 13% (CMM)	RCT (Dixon et al.)	▪ After 10 years weight, SBP and lipid parameters return to baseline.

	Mean BMI: LAGB 37.0 (SD 2.7), Non-surgical 37.2 (SD 2.5) **T2D prevalence:** 100% by definition (within sub-cohort)			▪ After 10 years, T2D relapses.
Sanchez-Santos (2017)	**Mean age:** 41.1 years **Mean BMI:** 47.56 kg/m^2 **T2D prevalence**: 18.6%	2 years: 72% (surgery); 21% (CMM) 10 years: 36% (surgery); 13% (CMM)	SOS	Not reported

Key: AGB – adjustable gastric band; CMM – conventional medical management; GBP - gastric bypass (generally RYGB); LAGB – laparoscopic adjustable gastric band; LRYGB – laparoscopic Roux-en-Y Gastric Bypass; LSG – laparoscopic sleeve gastrectomy; NA – Not Applicable; NHANES - National Health and Nutrition Examination Survey; NR – not reported; ORYGB – open Roux-en-Y Gastric Bypass; P(_) – probability; RCT – randomised controlled trial; RYGB - Roux-en-Y Gastric Bypass; SG – sleeve gastrectomy; SOS – Swedish Obesity Study.

Appendix A4.4 Results

Table A4.5. Results of CEA or CUA (Additional analyses by time horizon, perspective and/or surgical procedure)

Author	Country	Base year	Additional analysis	Incremental cost-effectiveness ratio (ICER) (€/QALY)				
T2D populations or sub-cohorts								
Hoerger (2010)	United States	2005	GBP v usual care; Subgroup (age)	**Newly-diagnosed T2D** **Age 35-44 years:** 6,550/QALY **Age 65-74 years:** 15,720/QALY	**Established T2D** **Age 45–54 years:** 11,790/QALY **Age 65-74 years:** 23,579/QALY			
			GB v usual care; Subgroup (age)	**Newly-diagnosed T2D** **Age 35-44 years:** 11,790/QALY **Age 65-74 years:** 22,269/QALY	**Established T2D** **Age 45–54 years:**14,410/QALY **Age 65-74 years:** 24,889/QALY			
Kim (2018)	United States	2014	LRYGB; 5-year time horizon	**BMI 50 kg/m²** Male: 15,474; Female: 14,827	**BMI 45 kg/m²** Male: 16,570; Female: 15,719	**BMI 40 kg/m²** Male: 17,833; Female: 17,765	**BMI 35 kg/m²** Male: 19,270; Female: 17,975	**BMI 30 kg/m²** Male: 20,896; Female: 19,364
			LRYGB; Lifetime horizon	**BMI 50 kg/m²** Male: 5,728 Female: 5,646	**BMI 45 kg/m²** Male: 6,263 Female: 6,160	**BMI 40 kg/m²** Male: 6,905 Female: 6,773	**BMI 35 kg/m²** Male: 7,667 Female: 7,493	**BMI 30 kg/m²** Male: 8,560 Female: 8,331
			AGB; 5-year time horizon	**BMI 50 kg/m²** Male: 13,402 Female: 12,420	**BMI 45 kg/m²** Male: 14,307 Female: 13,132	**BMI 40 kg/m²** Male: 15,353 Female: 13,891	**BMI 35 kg/m²** Male: 16,457 Female: 14,879	**BMI 30 kg/m²** Male: 17,899 Female: 16,116
			AGB; Lifetime time horizon	**BMI 50 kg/m²** Male: 6,134 Female: 6,002	**BMI 45 kg/m²** Male: 6,575 Female: 6,391	**BMI 40 kg/m²** Male: 7,099 Female: 6,814	**BMI 35 kg/m²** Male: 7,672 Female: 7,356	**BMI 30 kg/m²** Male: 8,416 Female: 8,028
			ORYGB; 5-year time horizon	**BMI 50 kg/m²** Male: 28,535 Female: 28,995	**BMI 45 kg/m²** Male: 29,951 Female: 30,063	**BMI 40 kg/m²** Male: 31,547 Female: 31,309	**BMI 35 kg/m²** Male: 33,335 Female: 32,745	**BMI 30 kg/m²** Male: 35,331 Female: 34,387

			ORYGB; lifetime time horizon	**BMI 50 kg/m²** Male: 10,610 Female: 11,375	**BMI 45 kg/m²** Male: 11,346 Female: 12,072	**BMI 40 kg/m²** Male: 12,217 Female: 12,888	**BMI 35 kg/m²** Male: 13,233 Female: 13,835	**BMI 30 kg/m²** Male: 14,408 Female: 14,924
Pollock (2013)	United Kingdom	2010	Multiple time horizons	25,153/QALY (10 years)	8,681/QALY (20 years)	5,418/QALY (30 years)	5,275/QALY (40 years)	
Rognoni (2020)	Italy	2018	Public payer perspective; BMI category	**BMI ≥30-34.9 kg/m²** Dominant	**BMI ≥35 kg/m²** Dominant			
			Societal perspective; BMI category	**BMI ≥30-34.9 kg/m²** Dominant	**BMI ≥35 kg/m²** Dominant			
Population subgroups with T2D								
Borisenko (2018)a*	England	2015	10-year time horizon	**BMI 33kg/m²** Male: Dominant; Female: Dominant	**BMI 37 kg/m²** Male: 641/QALY; Female: Dominant	**BMI 42 kg/m²** Male: 641/QALY; Female: Dominant	**BMI 52 kg/m²** Male: Dominant; Female: Dominant	
Borisenko (2018)b*	Belgium	2012	10-year time horizon	**BMI 33kg/m²** Male: Dominant; Female: Dominant	**BMI 37 kg/m²** Male: Dominant; Female: Dominant	**BMI 42 kg/m²** Male: Dominant; Female: Dominant	**BMI 52 kg/m²** Male: Dominant; Female: Dominant	
Borisenko (2017)a*	Denmark	2012	10-year time horizon	**BMI 33kg/m²** Male: Dominant; Female: Dominant	**BMI 37 kg/m²** Male: Dominant; Female: Dominant	**BMI 42 kg/m²** Male: Dominant; Female: Dominant	**BMI 52 kg/m²** Male: Dominant; Female: Dominant	
Borisenko (2017)b*	Germany	2012	10-year time horizon	**BMI 33kg/m²** Male: Dominant; Female: Dominant	**BMI 37 kg/m²** Male: Dominant; Female: Dominant	**BMI 42 kg/m²** Male: Dominant; Female: Dominant	**BMI 52 kg/m²** Male: Dominant; Female: Dominant	
James (2017)	Australia	2015	Age at baseline; AGB	**Starts at age 30** Dominant	**Starts at age 40** Dominant	**Starts at age 50** Dominant	**Starts at age 60** Dominant	
			Age at baseline; RYGB	Dominant	Dominant	Dominant	Dominant	
			Age at baseline; SG	Dominant	Dominant	Dominant	Dominant	
Lucchese (2017)	Italy	2013	10-year time horizon	**BMI 33kg/m²** Male: Dominant; Female: Dominant	**BMI 37 kg/m²** Male: Dominant; Female: Dominant	**BMI 42 kg/m²** Male: Dominant; Female: Dominant	**BMI 52 kg/m²** Male: Dominant; Female: Dominant	

Klarenbach (2010)	Canada	2009	Multiple time horizons	9,967/QALY (10 years)	3,257/QALY (20 years)	Dominant (Lifetime)		
McEwen	United States	2007§	Multiple time horizons	59,617 (2 years)	10,651/QALY (Lifetime)			
Picot (2012)	UK	2009/ 2010	Multiple time horizons	30,388/QALY (2 years)	7,490/QALY (5 years)	2,462/QALY (20 years)		
Sanchez-Santos (2017)	Spain	2017	10-year time horizon	**BMI 33kg/m²** Male: 5,725; Female: 6,058	**BMI 37 kg/m²** Male: 5,430; Female: 5,552	**BMI 42 kg/m²** Male: 3,816; Female: 3,858	**BMI 52 kg/m²** Male: 2,786; Female: 2,859	

Key: AGB – adjustable gastric band; BMI – body mass index; GBP - gastric bypass (generally RYGB); LAGB – laparoscopic adjustable gastric band; LRYGB – laparoscopic Roux-en-Y Gastric Bypass; LSG – laparoscopic sleeve gastrectomy; ORYGB – open Roux-en-Y Gastric Bypass; QALY – quality-adjusted life year; RYGB - Roux-en-Y Gastric Bypass; SG – sleeve gastrectomy; T2D – type 2 diabetes.

Table A4.6. Summary of results of scenario analysis in T2D populations or sub-cohorts

Impact on conclusion																		
			Structure		Costs			QoL	Effects								Population	
Scenario	Worst case scenario	Best case scenario	Varying the time horizon	Varying the discount rate	Varying T2D treatment costs	Lower surgery cost	Varying T2D complication costs	Reducing BMI disutility	Excluding lipid parameters	Weight regain after surgery	Reducing effect of surgery on HbA1c	Varying surgery complication rate	Varying mortality rate	Incidence of hypo-glycemia in usual care	Varying T2D-related complication rate in T2D remission	Surgery benefits only one parameter (SBP or BMI or HbA1c)	Patient-level data	Different ethnic subgroups
NC No change **CE Change from dominant to cost effective** **NCE Change from cost-effective or dominant to not cost-effective** **D Change from cost-effective to dominant**																		
Ackroyd (2006)	NC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Anselmino (2009)	NC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Assumpção (2019)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Impact on conclusion																		
			Structure		Costs			QoL	Effects								Population	
Scenario	Worst case scenario	Best case scenario	Varying the time horizon	Varying the discount rate	Varying T2D treatment costs	Lower surgery cost	Varying T2D complication costs	Reducing BMI disutility	Excluding lipid parameters	Weight regain after surgery	Reducing effect of surgery on HbA1c	Varying surgery complication rate	Varying mortality rate	Incidence of hypo-glycemia in usual care	Varying T2D-related complication rate in T2D remission	Surgery benefits only one parameter (SBP or BMI or HbA1c)	Patient-level data	Different ethnic subgroups
NC No change **CE Change from dominant to cost effective** **NCE Change from cost-effective or dominant to not cost-effective** **D Change from cost-effective to dominant**																		
Gil-Rojas (2019)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hoerger (2010)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ikramuddin (2009)	-	-	NCE	-	-	NC	-	NCE	NC	NC	NC	NC	-	-	-	-	-	-
Keating (2009a)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Keating (2009b)	CE	-	-	-	CE	-	-	-	-	-	-	NC	NC	-	-	-	-	-
Kim (2018)	-	-	NC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
McGlone (2020)	-	-	-	-	-	-	-	-	-	-	-	-	-	NC	-	-	-	NC
Pollock (2013)	NCE	D	NC	NC	-	-	NC	NC	-	-	-	-	-	-	NC	NC	-	-
Rognoni (2020)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	NC	-
Tang (2016)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Tu (2019)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Viratanapanu (2019)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Wan (2019)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Key: "-" denotes not investigated.
BMI – body mass index; HbA1c – Haemoglobin A1c; QoL – quality of life; SBP – systolic blood pressure.

Table A4.7. Summary of results of scenario analysis for evaluations with T2D subpopulations

	Impact on conclusion																				
			Structure				Costs	QoL			Effect							Organisational		Population	
	Worst case scenario	Best case scenario	Changing the discount rate	Changing distribution of surgeries	Changing time horizon	Including the societal perspective	Changing surgery costs	No utility decrements	No QoL gain	Reduced QoL due to surgical complications	Weight gain or rebound	Reduce the effect of surgery on weight loss	Increased post-surgical complications	No effect on comorbidities	Higher perioperative mortality	Exclude PAD or HF or Angina	Alternative inputs	Increase high volume centres	Delays in accessing surgery	Changing baseline BMI	Increasing prevalence of comorbid conditions
NC No change **CE Change from dominant to cost effective** **NCE Change from cost-effective or dominant to not cost-effective** **U Unclear** **V Variable** **X Dominated**																					
Borisenko (2018)a	-	-	NC	NC	NC	-	NC	NC	-	NC	NC	CE	-	-	-	NC	CE	-	-	-	-
Borisenko (2018)b	-	-	-	-	NC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Borisenko (2017)a	-	-	-	-	NC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Borisenko (2017)b*	-	-	-	-	NC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Borisenko (2015)	-	-	NC	NC	-	NC	-	NC	-	NC	NC	NC	-	-	-	-	NC	NC	NC	-	-
Cohen (2017)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	NC	-	-
Faria (2013)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Gulliford (2017)	-	-	-	-	-	-	NC	-	-	-	-	NC	-	-	-	-	-	-	-	-	-

Impact on conclusion																				
			Structure				Costs	QoL			Effect							Organisational		Population	
	Worst case scenario	Best case scenario	Changing the discount rate	Changing distribution of surgeries	Changing time horizon	Including the societal perspective	Changing surgery costs	No utility decrements	No QoL gain	Reduced QoL due to surgical complications	Weight gain or rebound	Reduce the effect of surgery on weight loss	Increased post-surgical complications	No effect on comorbidities	Higher perioperative mortality	Exclude PAD or HF or Angina	Alternative inputs	Increase high volume centres	Delays in accessing surgery	Changing baseline BMI	Increasing prevalence of comorbid conditions
NC No change **CE Change from dominant to cost effective** **NCE Change from cost-effective or dominant to not cost-effective** **U Unclear** **V Variable** **X Dominated**																					
James (2017)	-	-	-	-	-	-	-	-	-	-	-	V*	NC	-	-	-	-	-	-	NC	-
Klarenbach (2010)	NCE	-	-	-	-	-	-	-	X	-	-	-	-	NC	NC	-	-	-	-	-	NC
McEwen (2010)	-	-	-	-	U†	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lucchese (2017)	-	-	-	-	NC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Picot (2012)	-	-	-	-	NC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sanchez-Santos (2017)	-	-	-	-	NC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Key: "-" denotes not investigated.
*Variable. The impact of weight regain on the ICER is dependent on timing of weight regain. With full weight regain at 5 or 10 years, the ICER exceeds the WTP threshold. At 20 years, cost-effectiveness is maintained.
† Unclear. WTP threshold not reported.

Appendix 5

Appendix A5.1 Key assumptions

The model structure was based on a simplification of the treatment algorithm used in the STAMPEDE trial, whereby patients were assumed to initiate oral anti-hyperglycaemic agents prior to introducing GLP-1 RAs, and then insulin. Treatment intensification involved increasing the number of dose of anti-hyperglycaemic agents (Table A5.1).

The following classes of antihyperglycemic drugs were available at the time the STAMPEDE trial started (2012):

- biguanides (that is, metformin)
- thiazolidinediones (that is, pioglitazone)
- exenatide (that is, Byetta®)
- secretagogues (that is, sulfonylureas such as glimepiride and meglitinides such as repaglinide)
- insulins (that is, NPH, glargine, aspart, regular, apidra).

As new medications were approved for therapy, they were added to the treatment algorithm.

Treatment algorithms were adhered to as strictly as possible with the understanding that clinical situations may arise that may require deviation from the algorithms (adverse reaction to medication, hypoglycemia, and earlier initiation of insulin for patients with extremely high glucose levels).

Table A5.1. Treatment algorithm for glycaemic therapy in the STAMPEDE trial

Treatment Algorithm for Glycemic Therapy *						
Agent at entry	**Step 1 (post randomization)**	**Step 2**	**Step 3**	**Step 4**	**Step 5**	**Step 6**
	HbA1c / SMBG **	Based on SMGB**	HbA1c / SMBG**	HbA1c / SMBG**	HbA1c / SMBG**	HbA1c / SMBG**
	Results of HbA1c and/or SMGB - Action Required? → No - continue current Rx; Yes – titrate / add medications according to sequence					
No oral agent	Initiate Metformin 500 mg bid	Titrate Metformin to 1500-2000 mg/day	- if max Metformin dose - Initiate TZD and titrate to max dose	Initiate Exenatide 5 mcg subq bid	Increase Exenatide to 10 mcg subq bid	Initiate sulfonylurea o repaglinide
Sulfonylurea	- - titrate Sulfonylurea - Initiate Metformin 500 mg bid	Titrate Metformin to 1500-2000 mg/day	- if max Metformin dose - Initiate TZD and titrate to max dose	Initiate Exenatide 5 mcg subq bid	Increase Exenatide to 10 mcg subq bid	Initiate insulin
Metformin	Titrate Metformin based on initial labs	Titrate Metformin to 1500-2000 mg/day	- if max Metformin dose - Initiate TZD and titrate to max dose	Initiate Exenatide 5 mcg subq bid	Increase Exenatide to 10 mcg subq bid	Initiate and titrate sulfonylurea
Sulfonylurea Metformin	- - titrate Sulfonylurea - Titrate Metformin based on initial labs	Titrate Metformin to 1500-2000 mg/day -initiate TZD and titrate	- if max Metformin dose - Initiate Exenatide 5 mcg subq	Increase Exenatide to 10 mcg subq bid	Initiate insulin	Increase insulin
TZD	Titrate TZD based on initial labs	-initiate metformin and Titrate over 3 months	Initiate exenatide 5 mcg Sub q bid	Increase Exenatide to 10 mcg subq bid	Initiate sulfonylurea or repaglinide if indicated	Initiate insulin
Metformin TZD	Titrate Metformin based on initial labs	Titrate Metformin to 1500-2000 mg/day	Initiate Exenatide 5 mcg subq bid	Increase Exenatide to 10 mcg subq bid	Initiate sulfonylurea or repaglinide	Increase insulin
Sulfonylurea TZD	- titrate Sulfonylurea - Titrate TZD based on initial labs	Titrate TZD to max dose	- if max TZD dose - Initiate Exenatide 5 mcg subq	Increase Exenatide to 10 mcg subq bid	Initiate insulin	Increase insulin

Treatment Algorithm for Glycemic Therapy`*						
Agent(s) at entry	**Step 1 (post randomization)**	**Step 2**	**Step 3**	**Step 4**	**Step 5**	**Step 6**
	HbA1c / SMBG **	Based on SMGB**	HbA1c / SMBG**	HbA1c / SMBG**	HbA1c / SMBG**	HbA1c / SMBG**
	Results of HbA1c and/or SMGB - Action Required? → No - continue current Rx; Yes – titrate / add medications according to sequence					
Sulfonylurea Insulin	- D/C Sulfonylurea - Initiate Metformin 500 mg bid	- Titrate Metformin to 1500-2000 mg/day -Initiate exenatide	- if max Metformin dose - Initiate TZD - titrate exenatide to max dose	-Titrate TZD - Initiate insulin for HbA1c > 8.5% - Initiate Exenatide 5 mcg subq bid	-Follow insulin titration protocol; initiate prandi coverage - Increase Exenatide to 10 mcg subq bid	Titrate insulin per insulin protocol
Metformin Insulin	- Titrate Metformin based on initial labs -initiate exenatide and titrate	- Titrate Metformin to 1500-2000 mg/day -initiate TZD	- if max Metformin dose - Titrate TZD to max dose - initiate sulfonylurea	- if max Metformin and TZD dose -initiate sulfonylurea -if HbA1c >8.5;start insulin + sulfonylurea - Initiate Exenatide 5 mcg subq bid	-Follow insulin titration protocol; initiate prandi coverage - Increase Exenatide to 10 mcg subq bid	Titrate insulin per insulin protocol
TZD Insulin	- Titrate TZD based on initial labs	Titrate TZD to max dose	- initiate/titrate Metformin to max dose	- if max Metformin and TZD dose - Initiate Exenatide 5 mcg subq bid	Increase Exenatide to 10 mcg subq bid	Titrate insulin per insulin protocol
Sulfonylurea Metformin Insulin	- D/C Sulfonylurea - Titrate Metformin based on initial labs	Titrate Metformin to 1500-2000 mg/day	- if max Metformin dose - Initiate TZD and titrate to max dose	- if max Metformin and TZD dose - Initiate Exenatide 5 mcg subq bid	Increase Exenatide to 10 mcg subq bid	Titrate insulin per insulin protocol
Sulfonylurea TZD Insulin	- D/C Sulfonylurea - Titrate TZD based on initial labs	Titrate TZD to max dose	- initiate/titrate Metformin to max dose	- if max Metformin and TZD dose - Initiate Exenatide 5 mcg subq bid	Increase Exenatide to 10 mcg subq bid	Titrate insulin per insulin protocol
Sulfonylurea TZD Metformin Insulin	- D/C Sulfonylurea - Titrate TZD and Metformin based on initial labs	Titrate TZD and Metformin to max dose	- if max Metformin and TZD dose - Initiate Exenatide 5 mcg subq bid	Increase Exenatide to 10 mcg subq bid	Titrate insulin per insulin protocol	Increase Insulin

* Glycemic target = HbA1c < 6.0%
** Threshold for “action required” if: 1) HbA1c > 6.0%, or 2) > 50% of SMBG results / 4 days = fasting/ac > 100 mg/dl or 2 hr pc > 140 mg/dl.
Notes:
Antihyperglycemic therapy will be advanced if “action required” criteria met at any patient visit.
If glycemic target achieved, continue current Rx and follow-up schedule.
If action required later, titrate/add medications according to sequence.
Bedtime glargine may be initiated earlier if HbA1c is greater than or equal to 8.5% since subjects may not respond to oral agents including sulfonylurea agents.
Source: Schauer et al. 2012.[284]

Table A5.2. Key assumptions and rationale

Assumption	Justification
Input parameters (clinical effectiveness and safety, cost and utility data)	
There is no clinically significant difference in the effectiveness of LSG and LRYGB.	Evidence from RCTs does not suggest a clinically significant difference in effectiveness for LRYGB and LSG in terms of glycaemic control or BMI reduction (see chapter 4). For the purposes of this assessment LRYGB and LSG are assumed to have equivalent clinical effectiveness. The effect of metabolic surgery on HbA1c and BMI is based on RCT evidence for the comparison LRYGB versus best medical care.
The risk of stroke and MI are linked to HbA1c.	The sample sizes and duration of follow-up of available RCT evidence is insufficient to determine the impact of metabolic surgery on hard cardiovascular endpoints. The Framingham equation has been shown to overestimate the risk of cardiovascular events in contemporary European populations, whilst under-estimating the cardiovascular risk in people with diabetes and in people from the socially deprived populations.(528) Insufficient data were available for all relevant risk factors to populate other available risk equations, or the underlying risk equations were not publicly available.(529, 530) In the absence of high quality data, the risk of stroke and MI was estimated based on the association between HbA1c and the risk of cardiovascular events in large observational datasets.[382, 383] Metabolic surgery may have additional beneficial effects on cardiovascular outcomes mediated through weight loss, improvements in cardiovascular risk factors or changes in inflammatory markers. No cardiovascular benefit is assumed when the mean difference in HbA1c between surgery and best medical care groups is <5.5 mmol/mol (<0.5%). The beneficial effects of surgery on the risk of stroke and MI may be underestimated.
After 13 and 16 years, metabolic surgery is assumed to have no benefit in terms of BMI and HbA1c reduction.	Due to a lack of available long-term data, it was considered appropriate to assume that the effects of treatment declined at a constant rate after the last time point reported from RCT evidence until baseline levels were reached. Once BMI and HbA1c return to baseline, they are assumed to remain constant for the remainder of the model (that is, no difference between metabolic surgery and best medical care cohorts).
Patients in the “no treatment” and “T2D managed with oral agents” health states have the same quality of life, while “T2D managed with GLP-1 RA” and “T2D managed with insulin” are associated with utility decrements.	As a conservative approach, due to the ongoing risk of T2D relapse and the associated requirements for ongoing monitoring of glycaemic control and micronutrients post-surgery, it was assumed that patients in the “no treatment” health state and patients with T2D managed with oral anti-hyperglycaemic agents have similar HR-QoL.

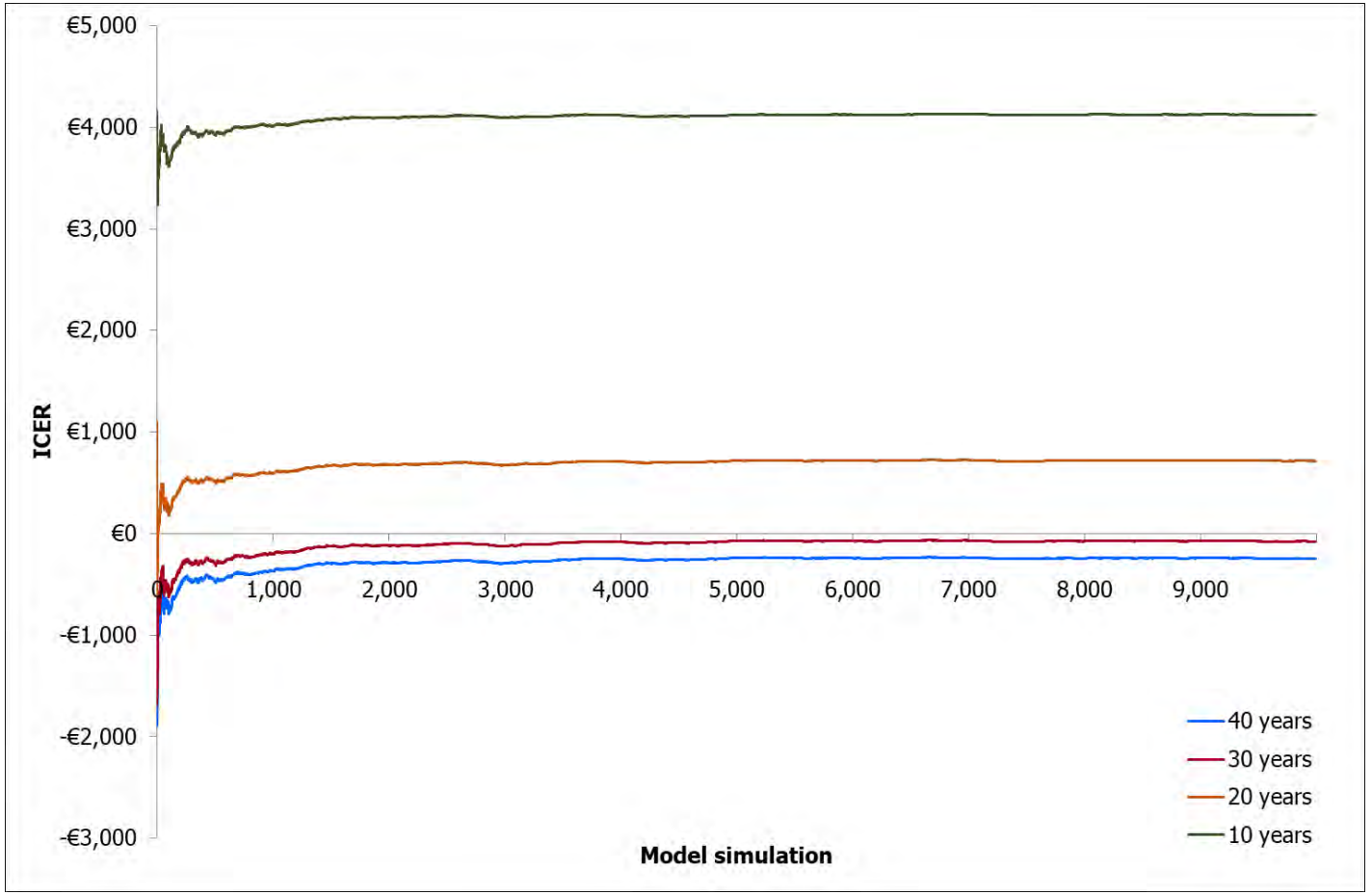
Assumption	Justification
	Decrements were applied for GLP-1 RAs and insulin to account for the inconvenience and lifestyle modifications associated with injectable agents.[211, 399]
Post-surgical complications occur up to five years post-surgery.	Data for post-surgical complications associated with SG were available for up to five years post-surgery from SOReg. (380) Thereafter, it was assumed that no surgery-related complications requiring hospital admission occurred. There is insufficient evidence on the potential longer-term complications of surgery (for example, nutritional deficiencies or gastro-oesophageal reflux disease) to estimate costs and outcomes.
The risk of severe hypoglycaemia for patients with medically treated T2D varies according to treatment strategy.	There is considerably variation in the frequency of hypoglycaemic events among those with medically-treated T2D in the literature which is influenced by the definition of hypoglycaemia used. Only severe cases of hypoglycaemia requiring medical attention were included in this CUA as cases that do not result in healthcare utilisation do not incur a cost from a payer perspective. There is uncertainty regarding the risk of hypoglycaemia after metabolic surgery in the population with T2D at baseline. Estimates of post-bariatric hypoglycaemia risk in the population with obesity may not be applicable to the population with T2D. Observational evidence suggests that the risk of post-bariatric hypoglycaemia is greater among those without T2D at baseline.[531-533] There is no evidence of an increased risk of severe hypoglycaemic in RCTs of metabolic surgery compared with best medical care (see Chapter 4), therefore for the purposes of this analysis an increased risk of hypoglycaemia was not applied post-metabolic surgery.
The cost of early complications is captured by the cost of the original hospital admission.	Complications such as bleeding or leakage typically occur during the early post-operative period. It was assumed that the cost of early post-operative complications was captured by the cost of the index hospital admission.
Reoperation/revision surgery was assumed to occur in the first year post-surgery.	The cost of and disutility associated with reoperation/revision surgery was applied in year one. Although in practice revision surgery may occur at later time points, this was considered a conservative approach as all costs incurred in the first year are not discounted and are therefore higher than discounted costs in subsequent years.
Recovery and lifestyle adjustment following metabolic surgery lead to a reduced HR-QoL for three months post-surgery.	No surgery-related disutility values specific to bariatric/metabolic surgery were identified in the literature. Estimated utility decrements associated with LRYGB and LSG were derived from utilities reported for laparoscopic surgery for hernia repair in the United Kingdom, as in previous CUAs,(341, 343, 404, 534) and was applied for three months. The utility decrement was assumed to be the same for surgery and revision surgery in the absence of evidence to support assigning different utility decrements. The disutility associated with post-surgical complications was assumed to be captured by the disutility of the initial surgery.

Assumption	Justification
Primary care visits vary according to the treatment strategy.	With consideration to guidance from the American Diabetes Association (ADA), it was assumed that patients with stable glycaemia would visit the GP twice per year, while patients with T2D above treatment targets (estimated to be 32%) or intensively managed T2D (patients managed with insulin) would visit the GP four times per year.[165, 176]
Structural assumptions	
After year one, treatment escalates over the modelled time horizon. Patients cannot revert to a previous health state.	It was assumed that improvements in glycaemic control requiring changes to anti-hyperglycaemic medication use occur during the first year post-surgery. It was assumed that medication would either stay the same or be intensified after the initial treatment period.
GLP-1 RAs are third-line therapy, after oral anti-hyperglycaemic agents have not produced adequate glycaemic control.	Although current guidance from the ADA suggests SGLT2 inhibitors and GLP1 RAs can both be considered second-line therapy in patients with T2D and obesity,[54] it was assumed that oral anti-hyperglycaemic agents would preferentially be prescribed during treatment intensification based on the treatment algorithm outlined in the STAMPEDE trial protocol, and patient preference for non-injectable agents.[284, 399]
Patients cannot enter the model into stroke or MI states.	Only new cases of stroke and MI occurred. This approach may underestimate the number of stroke and MI events, however given that the assumption is consistent in both cohorts, the overall effect is likely negligible.

Key: ADA – American Diabetes Association; BMI – body mass index; CUA – cost utility analysis; GLP-1 RA - Glucagon-like peptide-1 receptor agonists; GP – general practitioner; HbA1c – glycated haemoglobin; HR-QoL – health-related quality-of-life; (L)RYGB – (laparoscopic) Roux-en-Y gastric bypass; (L)SG – (laparoscopic) sleeve gastrectomy; MI- myocardial infarction; RCT – randomised controlled trial; SGLT2 - Sodium-glucose co-transporter-2; T2D – type 2 diabetes;.

Appendix A5.2 Results

Figure A5.1. Model convergence



Key: ICER – incremental cost-effectiveness ratio.