



**Health
Information
and Quality
Authority**

An tÚdarás Um Fhaisnéis
agus Cáilfocht Sláinte

Protocol:

COVID-19 - Interventions and health-related factors that prevent infection or minimise progression to severe disease

Published: 20 April 2021

Revision Record	
Revision Date	Description of change
16 March 2021	Widened scope to include modifiable lifestyle factors associated with a higher risk of infection and risk of progression to severe COVID-19 disease.
10 May 2021	Changed "lifestyle factors" to "health-related factors"

1. Purpose and aim

The purpose of this protocol is to outline the process by which the Health Information and Quality Authority's (HIQA's) Health Technology Assessment (HTA) Team identifies and reviews relevant SARS-CoV-2 evidence. This review will inform advice that is provided to the National Public Health Emergency Team (NPHE), in their response to the COVID-19 pandemic. HIQA's HTA team develops evidence summaries based on specific research questions (RQs). This protocol details the process to be undertaken to inform the policy question relating to community-based interventions to prevent infection with and progression of COVID-19 in community dwelling populations.

2. Process outline

It is important that a standardised approach to the process is developed and documented, to allow for transparency and to mitigate risks which may arise due to changes in staff delivering the information.

Five distinct steps in the process have been identified. These are listed below and described in more detail in the sections below.

- 1.** Develop research question and formulate PICO/PEOS framework.
- 2.** Search relevant databases.
- 3.** Screen identified studies.
- 4.** Data extraction and quality appraisal of included studies.
- 5.** Summarise findings.

3. Research question and PICOS/PEOS

This evidence summary will address the following policy questions:

"What is the emerging evidence in relation to (i) pharmaceutical interventions, and (ii) lifestyle interventions prior to diagnosis of COVID-19 in the community aimed at preventing or minimising progression to severe disease?"

"With respect to COVID-19, what potentially modifiable lifestyle factors are associated with a reduction in risk of infection and or progression to severe disease?"

The following three research questions were developed to address these policy questions:

RQ1. What is the evidence on the effectiveness of pharmacological interventions in the community, prior to a diagnosis of COVID-19, aimed at preventing or minimising progression to severe disease?

RQ2. What is the evidence on the effectiveness of non-pharmacological interventions in the community, prior to a diagnosis of COVID-19, aimed at preventing or minimising progression to severe disease?

RQ3. What is the evidence of association between modifiable health-related factors and risk of COVID-19 or progression to severe COVID-19?

Table 1 and Table 2 outline the Population, Intervention, Comparator, Outcomes, Study Design (PICOS) criteria for RQ1 and RQ2 study selection, respectively. Table 3 outlines the Population, Exposure, Outcomes and Study Design (PEOS) for RQ3.

Table 1. PICOS criteria for RQ1

Population(s)	<p>Individuals of any age who are not hospitalised (community-dwelling individuals or residents of long term care facilities, nursing homes or other residential centres) who have not been diagnosed with COVID-19.</p> <p>Sub-groups of interest include:</p> <ul style="list-style-type: none"> ▪ children (≤ 18 years) ▪ medically vulnerable groups (for example, ≥ 70 years of age, individuals with underlying conditions such as chronic respiratory or cardiac disease) ▪ residents of long term care facilities.
Intervention(s)	<p>Include</p> <p>Any interventions delivered at an individual-level that aim to prevent infection with COVID-19 or optimise the physiological response to COVID-19, should an individual become infected. Individual-level interventions include:</p> <ul style="list-style-type: none"> ▪ Pharmacological interventions (for example, to bolster immune response or prophylactic treatment with antiviral agents). <p>Exclude</p> <ul style="list-style-type: none"> ▪ Interventions that regulatory agencies (such as the European Medicines Agency, Food and Drug Agency, Medicines and Healthcare products Regulatory Agency) have issued warnings against (for example, hydroxychloroquine) will be excluded. ▪ Vaccination interventions.
Comparator(s)	<p>Placebo, no intervention or head-to-head comparison with alternative included intervention(s).</p>
Outcome(s)	<p>Primary outcome is laboratory-confirmed COVID-19 diagnosis or symptomatic infection.</p> <p>Secondary outcomes include:</p> <ul style="list-style-type: none"> ▪ safety outcomes such as serious adverse events ▪ deterioration of clinical condition, that is, increased severity of COVID-19 disease which may include:

	<ul style="list-style-type: none"> ▪ hospitalisation ▪ ICU admission ▪ ventilation ▪ mortality ▪ duration of illness/self-reported recovery.
Study design(s)	<p>The following studies will be included:</p> <ul style="list-style-type: none"> ▪ randomised controlled trials (RCTs) and non-randomised controlled trials (NRCTs) ▪ systematic reviews and meta-analyses will be screened for eligible studies. <p>The following studies will be excluded:</p> <ul style="list-style-type: none"> ▪ ongoing trials without published results ▪ trials that did not reach any study endpoint ▪ observational studies such as cohort, case-control, case series and cross-sectional studies.

Table 2. PICOS criteria for RQ2

Population(s)	<p>Individuals of any age who are not hospitalised (community-dwelling individuals or residents of long term care facilities, nursing homes or other residential centres) who have not been diagnosed with COVID-19.</p> <p>Sub-groups of interest include:</p> <ul style="list-style-type: none"> ▪ children (≤ 18 years) ▪ medically vulnerable groups (for example, ≥ 70 years of age, individuals with underlying conditions such as chronic respiratory or cardiac disease) ▪ residents of long term care facilities.
Intervention(s)	<p>Include</p> <p>Any interventions delivered at an individual-level that aim to prevent infection with COVID-19 or optimise the physiological response to COVID-19, should an individual become infected. Individual-level interventions include:</p> <ul style="list-style-type: none"> ▪ Non-pharmacological interventions (for example, respiratory therapy intervention to optimise lung capacity, smoking cessation to reduce potential lung damage ahead of potential insult and dietary changes, alcohol reduction and increased exercise to bolster the immune response). <p>Exclude</p> <ul style="list-style-type: none"> ▪ Interventions that aim to avoid or reduce exposure of the individual to the virus (for example face mask wearing, physical distancing, hand hygiene, wiping surface areas) will be excluded as these interventions aim to reduce the spread of infection. ▪ Interventions such as delivery of care through community hubs and patient self-monitoring (for example, through peak flow or pulse oximetry) will be excluded as the aim of these interventions is to optimise the healthcare system response rather than individual response. ▪ Interventions such as information campaign strategies (for example, campaign promoting increased exercise or smoking cessation) will not be

	considered for inclusion as individuals must be actually engaging in the intervention rather than simply provided with information about an intervention.
Comparator(s)	Placebo, no intervention or head-to-head comparison with alternative included intervention(s).
Outcome(s)	<p>Primary outcome is laboratory-confirmed COVID-19 diagnosis or symptomatic infection.</p> <p>Secondary outcomes include:</p> <ul style="list-style-type: none"> ▪ safety outcomes such as serious adverse events ▪ deterioration of clinical condition, that is, increased severity of COVID-19 disease which may include: <ul style="list-style-type: none"> ▪ hospitalisation ▪ ICU admission ▪ ventilation ▪ mortality ▪ duration of illness/self-reported recovery.
Study design(s)	<p>The following studies will be included:</p> <ul style="list-style-type: none"> ▪ randomised controlled trials (RCTs), non-randomised controlled trials (nRCTs) and cohort studies using population-based registries or data ▪ systematic reviews and meta-analyses will be screened for eligible studies. <p>The following studies will be excluded:</p> <ul style="list-style-type: none"> ▪ ongoing trials without published results ▪ trials that did not reach any study endpoint ▪ other observational studies such as case-control, case series and cross-sectional studies.

Table 3. PEOS criteria for RQ3

Population(s)	<p>Individuals of any age.</p> <p>Sub-groups of interest include:</p> <ul style="list-style-type: none"> ▪ children (≤ 18 years) ▪ medically vulnerable groups (for example, ≥ 70 years of age, individuals with underlying conditions such as chronic respiratory or cardiac disease) ▪ residents of long-term care facilities.
Exposure(s)	<p>Include</p> <ul style="list-style-type: none"> ▪ Any modifiable health-related factor (that is those risk factors that are within an individual's capacity to modify) for example, smoking, obesity, excessive alcohol consumption, nutritional status, sedentary lifestyle. <p>Exclude</p> <ul style="list-style-type: none"> ▪ Any non-modifiable factors such as age, sex, ethnicity, housing, socioeconomic factors.

	<ul style="list-style-type: none"> ▪ Any modifiable factors related to diagnosed long-term conditions such as regulation of blood glucose levels in individuals with diabetes or adequate control of blood pressure in hypertensive individuals.
Outcome(s)	<p>Primary outcomes include:</p> <ul style="list-style-type: none"> ▪ deterioration of clinical condition, that is, increased severity of COVID-19 disease which may include: <ul style="list-style-type: none"> ▪ hospitalisation ▪ ICU admission ▪ ventilation ▪ duration of illness/self-reported recovery ▪ mortality. <p>Secondary outcome is laboratory-confirmed COVID-19 diagnosis or symptomatic infection.</p>
Study design(s)	<p>The following studies will be included:</p> <ul style="list-style-type: none"> ▪ cohort studies using population-based registries or data ▪ systematic reviews and meta-analyses will be screened for eligible studies. <p>The following studies will be excluded:</p> <ul style="list-style-type: none"> ▪ other observational studies such as case-control, case series and cross-sectional studies.

4. Search of relevant databases

The following databases will be searched using the search strategy defined in Appendix 1:

- PubMed
- Embase
- Europe PMC (for the retrieval of preprints)

PubMed underwent substantial changes in early 2020, including updates to its search algorithm. This has led to searches conducted in 'new' PubMed yielding different results to that of 'old' PubMed. All reasonable efforts have been made to ensure that all relevant evidence from PubMed is retrieved during the searching process. The search for this research question has been conducted exclusively in 'new' PubMed.

5. Screening of identified studies

All potentially eligible papers identified in the search strategy will be exported to Covidence and single screened against the PICOS and PEOS, as outlined in the associated standard operating procedure. Depending on the amount of literature

retrieved, full texts will be double or single screened. No language restrictions will be applied. Non-English studies will be translated via Google translate, and this will be noted as a potential caveat.

6. Data extraction and appraisal of included studies

For each study included, data on the study design, participant demographics and clinically relevant data will be extracted as required. Data extracted will be checked by a second reviewer. A template for the data extraction table is provided in Appendix 2.

If the paper has not been peer reviewed, this will be noted. For randomised controlled trials (RCTs), the Cochrane risk of bias tool version 2 will be used. ROBINS-I tool (Risk of bias in non-randomised studies of interventions) will be used for quality appraisal of non-randomised studies. The Joanna Briggs Institute Critical Appraisal Checklist for Cohort Studies will be used for cohort studies. Quality appraisal of studies will be checked by a second reviewer.

Data from pre-print publications may contain errors and or older data, which may be corrected and or updated when the final published version becomes available in a peer-reviewed journal. Prior to the final version of an evidence summary being published on the HIQA website, pre-print publications will be checked to identify if final published versions have become available since the original search was conducted. Any discrepancies identified will be corrected.

7. Summarise findings

A descriptive overview of the identified evidence to date for will be compiled and or a meta-analysis where appropriate. A PRISMA flow chart will be presented.

8. Quality assurance process

Each review question will be led by an experienced systematic reviewer. A small team of reviewers will be assigned to assist. Each key study will be read by a minimum of two reviewers who will check that the summary accurately reflects the body of literature. All summaries will be reviewed by a senior member of the team, to ensure processes are followed and quality maintained.

9. Timelines

This evidence summary will be conducted in line with the processes and timelines outlined for Phase 2 of HIQA's COVID-19 response. Work will commence on 22

February 2021 and a final draft will be completed by 29 April 2021, dependent on the amount and complexity of literature retrieved. Draft outputs from the evidence summary will be circulated to the COVID-19 Expert Advisory Group for review on 4 May 2021, with a view to providing advice to NPHE on 6 May 2021.

Appendix 1 Search strategies

Pharmacological search strategies

	PubMed	Citations
1	("coronaviridae"[MeSH Terms] OR ("covid-19"[Title/Abstract] OR "coronavirus"[Title/Abstract] OR "corona virus"[Title/Abstract] OR "wuhan virus"[Title/Abstract] OR "2019-nCoV"[Title/Abstract] OR "2019-nCoV"[Title/Abstract] OR "severe acute respiratory syndrome coronavirus 2"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract]) OR "coronavirus"[MeSH Terms])	127,062
2	("primary prevention"[MeSH Terms] OR ("prevent*"[Title/Abstract] OR "reduc*"[Title/Abstract] OR "avoid*"[Title/Abstract] OR "ameliorat*"[Title/Abstract] OR "mitigat*"[Title/Abstract] OR "prophyl*"[Title/Abstract] OR "suppress*"[Title/Abstract] OR "protect*"[Title/Abstract]) OR ("symptom*"[Title/Abstract] OR "disease"[Title/Abstract] OR "presentation"[Title/Abstract] OR "manifestation"[Title/Abstract] OR ("asymptomatic"[Title/Abstract] OR "non-hospitalised"[Title/Abstract] OR "nonhospitalised"[Title/Abstract] OR "non-hospitalized"[Title/Abstract] OR "nonhospitalized"[Title/Abstract] OR "non-severe"[Title/Abstract] OR "outpatient"[Title/Abstract] OR "out-patient"[Title/Abstract]))))	9,494,473
3	("antiviral*"[Title/Abstract] OR "anti viral*"[Title/Abstract] OR "anti malarial*"[Title/Abstract] OR "antimalarial*"[Title/Abstract] OR "antibod*"[Title/Abstract] OR "antivirus agent"[Title/Abstract] OR "antimalarial agent"[Title/Abstract] OR "monoclonal antibody"[Title/Abstract] OR ("prophyl*"[Title/Abstract] OR "chemoprophyl*"[Title/Abstract]) OR "drug therapy"[Title/Abstract] OR "drug therapy"[MeSH Terms] OR "antibodies, monoclonal"[MeSH Terms] OR "antimalarials"[MeSH Terms] OR "antiviral agents"[MeSH Terms])	2,637,787
4	("randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trial"[Title/Abstract] OR ("random*"[Title/Abstract] OR "nonrandom*"[Title/Abstract] OR "non random*"[Title/Abstract]) OR ("placebo*"[Title/Abstract] OR "single blind*"[Title/Abstract] OR "single blind*"[Title/Abstract] OR (((("double"[All Fields] OR "doubled"[All Fields] OR "doubles"[All Fields] OR "doubling"[All Fields] OR "doublings"[All Fields]) AND "blind*"[All Fields]) AND "double blind*"[Title/Abstract]) OR "triple blind*"[Title/Abstract] OR "triple-blind"[Title/Abstract]) OR "systematic review"[Title/Abstract] OR "meta-analysis"[Title/Abstract] OR "meta-analysis"[Title/Abstract] OR "overview"[Title/Abstract] OR ("review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "review"[All Fields]) AND "classification"[MeSH Terms]) OR "meta analysis as topic"[MeSH Terms])	1,725,502
5	1 AND 2 AND 3 AND 4	1,302
6	Filters: from 2020 - 2021	1,183
	Embase	Citations
1	Coronavirinae/exp OR COVID-19:ab,ti OR coronavirus:ab,ti OR "corona virus":ab,ti OR 2019-nCoV:ab,ti OR "2019 ncov":ab,ti OR "severe acute respiratory syndrome coronavirus 2":ab,ti OR SARS-CoV-2:ab,ti	128,891

2	prevention/exp OR prophylaxis/exp OR (prevent* or reduc* or avoid* or ameliorat* or mitigat* or suppress* or protect* or prophyl*):ab,ti OR (Asymptomatic or non-hospitali?ed or nonhospitali?ed or outpatient* or out-patient* or non-severe):ab,ti	8,892,700
3	(antiviral* or anti-viral* or anti-malarial* or antimalarial* or antibod*):ab,ti OR antiviral agent/exp OR antimalarial agent/exp OR monoclonal antibody/exp OR prophyl*):ab,ti OR chemoprophyl*):ab,ti OR drug therapy/exp	2,760,734
4	Randomized Controlled Trial/exp OR randomized controlled trial:ab,ti or (((random* or nonrandom* or non-random*) adj3 trial) or (placebo* or single blind* or single-blind* or double blind* double-blind* or triple blind* or triple-blind*)):ab,ti OR Systematic Review/exp or Meta Analysis/exp or ((systematic* adj2 (review* or overview*)) or (meta anal* or meta-anal*) or (literature adj3 (review* or overview*))) :ab,ti	1,616,174
5	1 AND 2 AND 3 AND 4	1,150
6	limit 5 to yr="2020 - 2022"	1,070
	EuropePMC	Citations
1	(KW:coronavirus OR covid-19 OR SARS-CoV-2 AND KW:prevention OR prophylaxis AND KW:drug AND "controlled trial" OR "review" OR "systematic review") AND (SRC:PPR)	0

Non-Pharmacological/modifiable health-related factors search strategies

	PubMed	Citations
1	("coronaviridae"[MeSH Terms] OR ("covid-19"[Title/Abstract] OR "coronavirus"[Title/Abstract] OR "corona virus"[Title/Abstract] OR "wuhan virus"[Title/Abstract] OR "2019-nCoV"[Title/Abstract] OR "2019-nCoV"[Title/Abstract] OR "severe acute respiratory syndrome coronavirus 2"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract]) OR "coronavirus"[MeSH Terms])	127,062
2	("primary prevention"[MeSH Terms] OR ("prevent*"[Title/Abstract] OR "reduc*"[Title/Abstract] OR "avoid*"[Title/Abstract] OR "ameliorat*"[Title/Abstract] OR "mitigat*"[Title/Abstract] OR "prophyl*"[Title/Abstract] OR "suppress*"[Title/Abstract] OR "protect*"[Title/Abstract]) OR ("symptom*"[Title/Abstract] OR "disease"[Title/Abstract] OR "presentation"[Title/Abstract] OR "manifestation"[Title/Abstract] OR ("asymptomatic"[Title/Abstract] OR "non-hospitalised"[Title/Abstract] OR "nonhospitalised"[Title/Abstract] OR "non-hospitalized"[Title/Abstract] OR "nonhospitalized"[Title/Abstract] OR "non-severe"[Title/Abstract] OR "outpatient"[Title/Abstract] OR "out-patient"[Title/Abstract])))	9,494,473
3	("non-pharmacological"[Title/Abstract] OR "nonpharmacological"[Title/Abstract] OR "non-pharmaceutical"[Title/Abstract] OR "nonpharmaceutical"[Title/Abstract] OR "non-drug"[Title/Abstract] OR "non-drug"[Title/Abstract] OR ("life style"[MeSH Terms] OR "risk reduction behavior"[MeSH Terms]) OR ("lifestyle"[Title/Abstract] OR "life style"[Title/Abstract]) OR ("modifiable"[Title/Abstract] AND ("risk*"[Title/Abstract] OR "factor*"[Title/Abstract])) OR ("sedentary behavior"[MeSH Terms] OR (("health*"[Title/Abstract] OR "unhealth*"[Title/Abstract]) AND ("behaviour*"[Title/Abstract] OR "behavior*"[Title/Abstract]))) OR ("smok*"[Title/Abstract] OR "tobacco"[Title/Abstract]) OR ("alcohol drinking"[MeSH Terms] OR "alcohol*"[Title/Abstract]) OR ("exercise therapy"[MeSH Terms] OR "exercise"[MeSH Terms] OR ("exercise"[MeSH Terms] OR "exercise therapy"[MeSH Terms]) OR ("activity"[Title/Abstract] OR "inactivity"[Title/Abstract] OR "sedentar*"[Title/Abstract] OR "exercis*"[Title/Abstract]) OR (("pulmonary"[Title/Abstract] OR "lung"[Title/Abstract] OR "cardiopulmonary"[Title/Abstract] OR "respiratory"[All Fields]) AND ("rehab*"[Title/Abstract] OR "therap*"[Title/Abstract] OR "exercis*"[Title/Abstract]))) OR ("diet"[MeSH Terms] OR "diet therapy"[MeSH Terms] OR ("nutritional support"[MeSH Terms] OR "nutrition therapy"[MeSH Terms]) OR ("nutrition"[Title/Abstract] OR "nutrient"[Title/Abstract] OR "diet*"[Title/Abstract])) OR ("body weight"[MeSH Terms] OR "ideal body weight"[MeSH Terms] OR "body weight changes"[MeSH Terms] OR "overweight"[MeSH Terms] OR "diet, reducing"[MeSH Terms] OR "weight gain"[MeSH Terms] OR ("weight"[Title/Abstract] AND ("decreas*"[Title/Abstract] OR "reduc*"[Title/Abstract] OR "loss"[Title/Abstract] OR "maintain*"[Title/Abstract] OR "chang*"[Title/Abstract])) OR ("thinness"[MeSH Terms] OR "obesity"[MeSH Terms]))	5,390,063

	OR 'cardiopulmonary rehab*':ab,ti OR 'respiratory rehab*':ab,ti OR 'pulmonary exercis*':ab,ti OR 'lung exercis*':ab,ti OR 'cardiopulmonary exercis*':ab,ti OR 'respiratory exercis*':ab,ti OR 'diet' OR 'diet therapy' OR 'nutrition therapy':ab,ti OR nutrition OR nutrient OR diet*:ab,ti OR 'body weight' OR 'ideal body weight' OR 'body weight change' OR 'body weight maintenance' OR 'obesity' OR 'body weight loss' OR 'body weight gain':ab,ti OR 'body mass' OR 'underweight':ab,ti	
4	'randomized controlled trial'/exp OR 'controlled clinical trial (topic)' OR 'random*':ab,ti OR 'nonrandom*':ab,ti OR 'non-random*':ab,ti OR 'placebo*':ab,ti OR 'single blind*':ab,ti OR 'single-blind*':ab,ti OR 'double blind*':ab,ti OR 'double-blind*':ab,ti OR 'triple blind*':ab,ti OR 'triple-blind*':ab,ti OR 'systematic review'/exp OR 'meta analysis'/exp OR 'systematic review':ab,ti OR 'meta analysis':ab,ti OR 'meta analyses':ab,ti OR 'literature review':ab,ti OR 'overview':ab,ti OR 'cohort analysis'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'follow up'/exp OR 'retrospective study'/exp OR 'cohort' OR 'longitudinal' OR 'prospective' OR 'follow-up' OR 'follow up' OR 'retrospective':ab,ti	6,483,903
5	1 AND 2 AND 3 AND 4	1,978
6	limit 5 to yr="2020 - 2022"	1,912
	EuropePMC	Citations
1	(KW:coronavirus OR covid-19 OR SARS-CoV-2 AND KW:prevention OR prophylaxis AND KW:"non-drug" OR "nondrug" OR "non drug" OR smoking OR alcohol OR exercise OR diet OR weight AND cohort OR observational OR longitudinal OR retrospective OR prospective OR review OR systematic review) AND (SRC:PPR)	127

	method*[Title/Abstract])) OR (follow-up study[Title/Abstract])) OR (follow-up analys*[Title/Abstract])) OR (follow-up design[Title/Abstract])) OR (follow-up method*[Title/Abstract])) OR (follow up study[Title/Abstract])) OR (follow up analys*[Title/Abstract])) OR (follow up design[Title/Abstract])) OR (follow up method*[Title/Abstract])) OR (retrospective study[Title/Abstract])) OR (retrospective analys*[Title/Abstract])) OR (retrospective design[Title/Abstract])) OR (retrospective method*[Title/Abstract]))	
5	1 AND 2 AND 3 AND 4	175
6	Filters: from 2020 - 2021	165
	Embase	Citations
1	Coronavirinae/exp OR COVID-19:ab,ti OR coronavirus:ab,ti OR "corona virus":ab,ti OR 2019-nCoV:ab,ti or "2019 ncov":ab,ti OR "severe acute respiratory syndrome coronavirus 2":ab,ti OR SARS-CoV-2:ab,ti	128,891
2	prevention/exp OR prophylaxis/exp OR (prevent* or reduc* or avoid* or ameliorat* or mitigat* or suppress* or protect* or prophyl*):ab,ti OR (Asymptomatic or non-hospitali?ed or nonhospitali?ed or outpatient* or out-patient* or non-severe):ab,ti	8,892,700
3	vitamin supplementation/exp OR vitamin D/exp OR vitamin supplement OR nutrient* supplement OR nutrition* supplement OR dietary supplement:ab,ti. OR zinc/exp OR ascorbic acid/exp	396,422
4	'randomized controlled trial'/exp OR 'controlled clinical trial (topic)' OR 'random*':ab,ti OR 'nonrandom*':ab,ti OR 'non-random*':ab,ti OR 'placebo*':ab,ti OR 'single blind*':ab,ti OR 'single-blind*':ab,ti OR 'double blind*':ab,ti OR 'double-blind*':ab,ti OR 'triple blind*':ab,ti OR 'triple-blind*':ab,ti OR 'systematic review'/exp OR 'meta analysis'/exp OR 'systematic review':ab,ti OR 'meta analysis':ab,ti OR 'meta analyses':ab,ti OR 'literature review':ab,ti OR 'overview':ab,ti OR 'cohort analysis'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'follow up'/exp OR 'retrospective study'/exp OR 'cohort' OR 'longitudinal' OR 'prospective' OR 'follow-up' OR 'follow up' OR 'retrospective':ab,ti	6,483,903
5	1 AND 2 AND 3 AND 4	226
6	limit 5 to yr="2020 -Current"	219
	EuropePMC	Citations
1	(KW:coronavirus OR covid-19 OR SARS-CoV-2 AND KW:prevention OR prophylaxis AND KW:vitamin D AND cohort OR observational OR longitudinal OR retrospective OR prospective OR review OR systematic review) AND (SRC:PPR)	0

Appendix 2. Data extraction templates

Data extraction template for RCTs and NRCTs

Study characteristics	PICO	Patient demographics	Outcomes
<i>Author:</i> <i>Country:</i> <i>DOI:</i> <i>Study design:</i> <i>Setting:</i>	<i>Population(s):</i> <i>Intervention(s):</i> <i>Comparator(s):</i> <i>Outcome(s):</i>	Intervention: Participants = X, Mean age = X, Male = X% Control: Participants = X, Mean age = X, Male = X%	<i>Outcome results:</i> <i>Author conclusions:</i>

Data extraction template for cohort studies

Study characteristics	Patient demographics	Outcomes
<i>Author:</i> <i>Country:</i> <i>DOI:</i> <i>Study design:</i> <i>Setting:</i>	Participants = X Mean age = X Male = X%	<i>Outcome results:</i> <i>Author conclusions:</i>

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