



**Health
Information
and Quality
Authority**

An tÚdarás Um Fhaisnéis
agus Cáilfocht Sláinte

**Protocol: Interventions in the
community setting, prior to diagnosis of
COVID-19, to prevent or minimise
progression to severe disease**

Published: 09 March 2021

Revision Record	
Revision Date	Description of change

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/POS 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

This evidence summary will address the following policy question:

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

The following research questions were developed to address this policy question, separated according to intervention type (i.e. pharmacological and non-pharmacological):

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?

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

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 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.

	<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 and cross-sectional studies.
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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 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 are system-level interventions that 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)	<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

	<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▪ 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. <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 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, 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. The AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews) will be used to appraise systematic reviews. 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.

10. 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 18 March 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, with a view to providing advice to NPHET on 23 March 2021.

Appendix 1 Search strategies

Pharmacological search strategies

	PubMed	Citations
1	(((((Coronavirinae[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]))))	121,489
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])))	6,466,498
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 (monoclonal antibodies[MeSH Terms])) OR (agents, antimalarial[MeSH Terms])) OR (agents, antiviral[MeSH Terms]))	2,631,852
4	(((((((((randomized controlled trial[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 blind* 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, systematic[MeSH Terms])) OR (meta analysis[MeSH Terms]))	1,718,462
5	1 AND 2 AND 3 AND 4	867
6	Filters: from 2020 - 2021	786
	Embase	Citations
1	exp Coronavirinae/ OR COVID-19.ab,ti. OR coronavirus.ab,ti. OR "corona virus".ab,ti. OR (Wuhan adj3 virus).ab,ti. OR ("2019-nCoV" or "2019 ncov").ab,ti. OR ("2019" and (new or novel) and coronavirus).ab,ti. OR ("severe acute respiratory syndrome coronavirus 2" or "SARS-CoV-2").ab,ti.	117,475

2	exp prevention/ OR exp prophylaxis/ OR (prevent* or reduc* or avoid* or ameliorat* or mitigat* or suppress* or protect* or prophyl*).ab,ti. OR ((symptom* or disease or presentation or manifestation) adj3 (mild* or moderate)).ab,ti. OR (Asymptomatic or non-hospitali?ed or nonhospitali?ed or outpatient* or out-patient* or non-severe).ab,ti.	8,833,231
3	(antiviral* or anti-viral* or anti-malarial* or antimalarial* or antibod*).ab,ti. OR exp antiviral agent/ OR exp antimalarial agent/ OR exp monoclonal antibody/ OR (prophyl* or chemoprophyl*).ab,ti. OR exp drug therapy/pc [Prevention]	2,711,881
4	exp Randomized Controlled Trial/ or randomized controlled trial.pt. 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*)).ti,ab. OR exp Systematic Review/ or exp Meta Analysis/ or ((systematic* adj2 (review* or overview*)) or (meta anal* or meta-anal*) or (literature adj3 (review* or overview*))).ti,ab.	1,682,775
5	1 AND 2 AND 3 AND 4	881
6	limit 5 to yr="2020 - 2022"	877
	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 search strategies

	PubMed	Citations
1	(((((Coronavirinae[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]))))	121,633
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])))	6,532,167
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 ((lifestyle[MeSH Terms]) OR (behavior, risk reduction[MeSH Terms]))) OR (lifestyle[Title/Abstract] OR "life style"[Title/Abstract])) OR ((modifiable[Title/Abstract]) AND (risk*[Title/Abstract] OR factor*[Title/Abstract]))) OR ((lifestyle, sedentary[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) AND (rehab*[Title/Abstract] OR therap*[Title/Abstract] OR exercis*[Title/Abstract]))) OR (((diet[MeSH Terms]) OR (diet therapy[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, weight loss[MeSH Terms])) OR (weight gain[MeSH Terms])) OR ((weight[Title/Abstract]) AND (decreas*[Title/Abstract] OR reduc*[Title/Abstract] OR loss[Title/Abstract] OR	5,375,541

	maintain*[Title/Abstract] OR chang*[Title/Abstract])) OR ((thinness[MeSH Terms]) OR (obesity[MeSH Terms])))	
4	((((((((((randomized controlled trial[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 blind* 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, systematic[MeSH Terms])) OR (meta analysis[MeSH Terms])) OR (((((((((((((((((((((((analysis, cohort[MeSH Terms]) OR (longitudinal study[MeSH Terms]) OR (prospective study[MeSH Terms])) OR (follow up study[MeSH Terms])) OR (retrospective study[MeSH Terms])) OR (cohort study[Title/Abstract])) OR (cohort analys*[Title/Abstract])) OR (cohort design[Title/Abstract])) OR (cohort method*[Title/Abstract])) OR (longitudinal study[Title/Abstract])) OR (longitudinal analys*[Title/Abstract])) OR (longitudinal design[Title/Abstract])) OR (longitudinal method*[Title/Abstract])) OR (prospective study[Title/Abstract])) OR (prospective analys*[Title/Abstract])) OR (prospective design[Title/Abstract])) OR (prospective 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]))	3,779,158
5	1 AND 2 AND 3 AND 4	1,763
6	Filters: from 2020 - 2021	1,696
	Embase	Citations
1	'coronavirinae'/exp OR coronavirinae OR 'covid 19':ab,ti OR 'coronavirus':ab,ti OR 'corona virus':ab,ti OR '2019-ncov' OR '2019 ncov':ab,ti OR '2019':ab,ti AND (new:ab,ti OR novel:ab,ti) AND coronavirus:ab,ti OR 'severe acute respiratory syndrome coronavirus 2':ab,ti OR 'sars-cov-2':ab,ti	120,476
2	'prevention'/exp OR 'prophylaxis'/exp OR prevent*:ab,ti OR reduc*:ab,ti OR avoid*:ab,ti OR ameliorat*:ab,ti OR mitigat*:ab,ti OR suppress*:ab,ti OR protect*:ab,ti OR prophyl*:ab,ti OR symptom*:ab,ti OR disease:ab,ti OR presentation:ab,ti OR manifestation:ab,ti OR asymptomatic:ab,ti OR 'non hospitali?ed':ab,ti	13,001,043

	OR nonhospitali?ed:ab,ti OR outpatient*:ab,ti OR 'out patient*':ab,ti OR 'non severe':ab,ti	
3	'non pharmacological':ab,ti OR nonpharmacological:ab,ti OR 'non pharmaceutical':ab,ti OR nonpharmaceutical:ab,ti OR 'non drug':ab,ti OR lifestyle:ab,ti OR 'life style':ab,ti OR 'modifiable risk factor':ab,ti OR 'risk reduction':ab,ti OR 'sedentary lifestyle':ab,ti OR 'health behavior':ab,ti OR 'unhealthy lifestyle':ab,ti OR 'smoking':ab,ti OR 'tobacco use':ab,ti OR 'drinking behavior':ab,ti OR 'alcohol':ab,ti OR 'exercise':ab,ti OR 'activity':ab,ti OR 'inactivity':ab,ti OR 'sedentar*':ab,ti OR 'exercis*':ab,ti OR 'pulmonary therap*':ab,ti OR 'lung therap*':ab,ti OR 'cardiopulmonary therap*':ab,ti OR 'respiratory therap*':ab,ti OR 'pulmonary rehab*':ab,ti OR 'lung rehab*':ab,ti 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	6,612,564
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	6,453,851
5	1 AND 2 AND 3 AND 4	3,099
6	limit 5 to yr="2020 - 2022"	2,987
	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)	117

	design[Title/Abstract])) OR (prospective 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	122
6	Filters: from 2020 - 2021	116
	Embase	Citations
1	(((((Coronavirinae[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]))))	117,475
2	exp prevention/ OR exp prophylaxis/ OR (prevent* or reduc* or avoid* or ameliorat* or mitigat* or suppress* or protect* or prophyl*).ab,ti. OR ((symptom* or disease or presentation or manifestation) adj3 (mild* or moderate)).ab,ti. OR (Asymptomatic or non-hospitali?ed or nonhospitali?ed or outpatient* or out-patient* or non-severe).ab,ti.	8,833,231
3	exp vitamin supplementation/ OR exp vitamin D/ OR ((vitamin or nutrient* or nutrition* or dietary) adj4 supplement*).ab,ti. OR exp zinc/ OR exp ascorbic acid/	416,056
4	exp Randomized Controlled Trial/ or randomized controlled trial.pt. 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*)).ti,ab. OR exp Systematic Review/ or exp Meta Analysis/ or ((systematic* adj2 (review* or overview*)) or (meta anal* or meta-anal*) or (literature adj3 (review* or overview*))).ti,ab. OR exp Cohort Analysis/ OR exp Longitudinal Study/ OR exp Prospective Study/ OR exp Follow Up/ OR exp Retrospective Study/ OR ((cohort OR longitudinal OR prospective OR follow up OR follow-up OR retrospective) adj2 (study OR analys* OR design OR method*)).ti,ab.	4,987,270
5	1 AND 2 AND 3 AND 4	156
6	limit 5 to yr="2020 -Current"	155
	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>	<i>Patient demographics:</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	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>	<i>Patient demographics:</i> Participants = X Mean age = X Male = X%	<i>Outcome results:</i> <i>Author conclusions:</i>

Data extraction template for systematic reviews

Study characteristics	PICO	Outcomes
<i>Author:</i> <i>DOI:</i> <i>Search date:</i> <i>Included studies:</i>	<i>Population(s):</i> <i>Intervention(s):</i> <i>Comparator(s):</i> <i>Outcome(s):</i>	<i>Outcome results:</i> <i>Author conclusions:</i>

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