Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Evidence summary:

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

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Version History

Version number	Date	Details
V1.0	23 June 2021	
V1.1	13 August 2021	Addition of footnotes relating to one of the randomised controlled trials (RCTs), by Elgazzar et al., detailed in this report. This RCT has been removed from preprint publication following additional scrutiny of the reported data. However, exclusion of Elgazzar from this review's evidence base does not impact on the conclusions of this report.

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.

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List of abbreviations used in this report

25(OH)D	vitamin D
BMI	body mass index
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
EAG	expert advisory group
EMA	European Medicines Agency
HR	hazard ratio
HIQA	Health Information and Quality Authority
ICU	intensive care unit
IRR	incidence rate ratio
LTC	long term condition
nRCT	non-randomised controlled trial
NPHET	National Public Health Emergency Team

OR	odds ratio
RCT	randomised controlled trial
ROBINS-I	risk of bias in non-randomised studies of interventions
RQ	research question
RR	relative risk
RT-PCR	reverse transcription polymerase chain reaction
PCR	polymerase chain reaction
PPE	personal protective equipment
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
UK	United Kingdom
US	United States
VA	Veteran Affairs
WHO	World Health Organization

Key points

- This rapid review was designed to answer three research 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 disease?
- Fifty-one studies (four randomised controlled trials [RCTs][1], one non-RCT [nRCT] and 46 cohort studies) were identified and included in this evidence summary. The five controlled trials were relevant to RQ1 (pharmacological interventions), and 46 cohort studies were relevant to RQ3 (modifiable health-related risk factors); none of the studies identified were relevant to RQ2 (non-pharmacological interventions).
- Four of the five controlled trials considered ivermectin:
    - The studies examined the use of oral ivermectin alone or in combination with carrageenan or iota carrageen nasal spray; some also controlled for the use of PPE. Dosing regimens differed between the trials and length of follow-up was short or not reported.
    - One RCT was conducted in healthcare workers and administration staff, one in household and healthcare close contacts of COVID-19 cases and the other in household contacts of COVID-19 cases. The nRCT was conducted in asymptomatic healthcare workers involved in the care of COVID-19 patients.
    - Safety outcomes were either poorly reported or not reported at all; where reported, it was suggested that adverse events were mild, and did not warrant treatment discontinuation.

[1] It has come to the attention of the evaluation team that one of the RCTs (Elgazzar et al.) detailed in this report has been removed from preprint publication following additional scrutiny of the reported data.

  - All four studies[2] reported that ivermectin, alone or in combination with carrageenan or iota carrageen nasal spray, had a protective effect; however, all were deemed to be of 'very low' certainty. This designation indicates that the estimate of effect is very uncertain and should not be relied upon to inform decision-making.
  - Ivermectin medicines are not authorised for use in COVID-19 in the EU. The European Medicines Agency (EMA) has not received any application for such use, and currently advises against the use of ivermectin for the prevention or treatment of COVID-19 outside RCTs.

- The fifth controlled trial was a double-blind, RCT of bamlanivimab versus placebo for the prevention of COVID-19 infection in residents and staff of 74 skilled nursing and assisted living facilities in the US with at least one confirmed SARS-CoV-2 index case. While bamlanivimab significantly reduced the incidence of COVID-19 in the overall population compared with placebo; disaggregated results showed that this was only significant in the residents' subgroup, not the staff. This evidence from this trial was deemed to be of 'low' certainty and should not be relied upon to inform decision-making.
- Forty-six cohort studies reported the association between various modifiable health-related risk factors and COVID-19 outcomes. Across the 46 cohort studies, the risk factors identified were:
  - Being overweight and or obese (34 studies)
  - smoking (25 studies)
  - vitamin D status (10 studies)
  - level of physical activity (seven studies)
  - alcohol consumption (five studies)
  - processed meat consumption (one study).
- Associations between being overweight and or obese and COVID-19 outcomes, including diagnosis, hospitalisation, severity of COVID-19 and mortality were estimated in 34 included studies. All eight studies that analysed BMI as a continuous variable (for example, 1kg/m^2, 5kg/m^2 or 1-standard deviation

[2] It has come to the attention of the evaluation team that one of the RCTs (Elgazzar et al.) detailed in this report has been removed from preprint publication following additional scrutiny of the reported data.

increments) reported a positive association between higher BMI and poorer outcomes. Strengthening the findings from studies that measured BMI as a continuous variable, studies that reported across multiple BMI categories reported worsening outcomes with higher categories of obesity.

- Twenty-five studies estimated the association between smoking status (current, never, ever and non-smoker) and COVID-19 outcomes. Six studies reported that smoking was significantly associated with negative COVID-19 outcomes, eight studies reported mixed findings, seven studies reported no association between smoking and COVID-19 outcomes.
- While four studies reported that smoking was protective, this finding should be viewed with extreme caution due to the limitations reported by the study authors. Moreover, there are likely confounders mediating this effect. For example, adjusting for comorbidities such as chronic obstructive pulmonary disease (COPD) and use of inhaled corticosteroids in COPD.
- Ten included studies estimated the association between vitamin D status (25(OH)D concentration) or vitamin D use and COVID-19 outcomes. Four studies reported no association between 25(OH)D concentration and COVID-19 outcomes, three studies reported that 25(OH)D deficiency was significantly associated with negative COVID-19 outcomes, two studies reported a protective effect of habitual vitamin D supplement use and increased vitamin D concentration and one study reported mixed findings between 25(OH)D concentration and increased risk of COVID-19 outcomes.
- Seven included studies estimated the association between physical activity and COVID-19 outcomes. Four studies reported mixed findings between physical activity and risk of COVID-19 outcomes, two studies reported that decreased physical activity was significantly associated with negative COVID-19 outcomes, one study reported a protective effective of physical activity.
- Five included studies estimated the associations between alcohol use and COVID-19 outcomes. Two studies reported mixed findings between alcohol use and COVID-19 outcomes, while one study reported a significant association between alcohol use and negative COVID-19 outcomes. One study used the US Veteran Affairs (VA) database and reported a protective effective of alcohol use disorder and a COVID-19 diagnosis. However, it should be noted that the US VA population, in general, has a high relative alcohol consumption and is therefore a very skewed population. Furthermore, this study was conducted in

May 2020, before there was widespread testing for COVID-19. One study reported no association between alcohol use and COVID-19 outcomes.

- One included study estimated the association between processed meat intake and COVID-19 diagnosis; this study reported no association.
- Twenty-nine of the 46 cohort studies were rated as good quality. However, eighteen of these 46 cohort studies used data from the UK Biobank, as such, it is likely that there is considerable overlap in the populations included in these studies. They are also subject to the following limitations of UK Biobank data:
    - the UK Biobank is a prospective cohort study of over 500,000 men and women aged 40–69 years at the time of recruitment, from urban and rural settings across the UK.
    - exposure data were collected at baseline (between 2006-2010) therefore, participants' self-reported exposures may have changed.
    - the cohort is not representative of the general UK population. The response rate to the baseline survey was 5.5%; it may be the case that this self-selected cohort is healthier and has a higher education level relative to the general population.
- The COVID-19 pandemic has disproportionately affected those from lower socioeconomic status. However, this review does not consider socioeconomic factors as these are largely non-modifiable and these were typically not appropriately adjusted for within the analysis of included studies.
- In addition to the 51 studies included in this evidence summary, 60 planned or ongoing trials of interventions for the prevention of COVID-19 were identified; none had formally published results at the time of writing.
- At the time of writing there is a lack of high-quality evidence of benefit to support pharmacological or non-pharmacological interventions (including use of Vitamin D supplements) to prevent COVID-19 or to minimise risk of progression to severe disease.
- While there are mixed results reported from the included cohort studies, in general those who are overweight or obese, who smoke, who have inadequate levels of Vitamin D, are physically inactive and consume excessive amounts of alcohol are more likely to contract COVID-19 or have poorer outcomes.

- This information can be used to inform clinical decision making around risk reduction. In general, maintaining a healthy weight, not smoking, engaging in physical activity, moderating alcohol consumption, good nutrition and being Vitamin D sufficient have beneficial effects on general health and should continue to be encouraged.

1.0 Background

The Health Information and Quality Authority (HIQA) has developed a series of evidence syntheses to inform advice from HIQA to the National Public Health Emergency Team (NPHET). The advice takes into account expert interpretation of the evidence by HIQA's COVID-19 Expert Advisory Group.

This evidence summary addresses 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 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?

2.0 Methods

A detailed summary of the methods used for this evidence summary is provided in the protocol: *Interventions and health-related factors for COVID-19 that prevent infection or minimise progression to severe disease.* Available here.

A systematic search of published peer-reviewed articles and non-peer-reviewed pre-prints was undertaken from 1 January 2020 up to 14 June 2021 and no language restrictions were applied. All potentially eligible papers were exported to Covidence (www.covidence.org) for single screening of titles, abstracts, and full texts for relevance based on the inclusion and exclusion criteria outlined in the protocol.

One systematic literature search was constructed to identify studies relevant to any of the three RQs, however inclusion and exclusion criteria differed for each RQ; these are detailed in the protocol.

Of note, for RQ1 (pharmacological interventions):

- The study population were those who had not been diagnosed with COVID-19 at study enrolment.
- Any pharmacological intervention that aimed to prevent infection with COVID-19 or optimise the physiological response to COVID-19, should an individual become infected was considered eligible for inclusion.
- Interventions that regulatory agencies (such as the European Medicines Agency (EMA), US Food and Drug Agency (FDA), UK Medicines and Healthcare Products Regulatory Agency (MHRA)) have issued warnings against (for example, hydroxychloroquine) were excluded, as were vaccine interventions.
- Only randomised controlled trials (RCTs) and non-RCTs (nRCTs) were considered eligible for inclusion, systematic reviews were screened for eligible studies, but all other study designs were excluded.

For RQ2 (non-pharmacological interventions):

- The study population were those who had not been diagnosed with COVID-19 at study enrolment.
- Any non-pharmacological intervention (for example, respiratory therapy intervention to optimise lung capacity, smoking cessation to reduce potential lung damage ahead of potential insult, and dietary changes or increased exercise to bolster the immune response) that aimed to prevent infection with COVID-19 or optimise the physiological response to COVID-19, should an individual become infected was considered eligible for inclusion.
- The following interventions were excluded, interventions:
    - that aimed to avoid or reduce exposure of the individual to the virus (for example use of face masks, physical distancing, hand hygiene, wiping surface areas) as these aim to reduce the spread of infection.
    - such as delivery of care through community hubs and patient self-monitoring (for example, through peak flow or pulse oximetry) as these aim to optimise the healthcare system response rather than the individual response.
    - such as information campaign strategies (for example, campaign promoting increased exercise or smoking cessation) as individuals had to be engaging in the intervention rather than simply being provided with information about an intervention.

- Only RCTs, nRCTs and cohort studies using population-based registries or data were eligible for inclusion.

For RQ3 (modifiable health-related risk factors):

- Eligible exposures were 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 and sedentary lifestyle.
- Non-modifiable factors such as age, sex, ethnicity, housing and socioeconomic factors were not eligible for inclusion, nor were 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.
- Only cohort studies that used population-based registries or population-based data were eligible for inclusion.

Data extraction and quality appraisal of included studies was completed by a single reviewer and checked by a second reviewer. Quality appraisal of RCTs was completed using the Cochrane risk of bias tool version 2,[(1)] ROBINS-I tool (Risk of bias in non-randomised studies of interventions)[(2)] was used for quality appraisal of nRCTs and the Joanna Briggs Institute Critical Appraisal Checklist for Cohort Studies[(3)] was used for cohort studies.

Grading of Recommendations Assessment, Development and Evaluation (GRADE)[(4)] was used to evaluate the quality of evidence by outcomes. GRADE assesses the following five domains: (i) risk of bias, (ii) inconsistency, (iii) indirectness, (iv) imprecision and (v) publication bias.

In June 2020, the GRADE team published additional guidance on using GRADE in situations of emergencies and urgencies during the COVID-19 pandemic.[(5)] This publication was used to refine our GRADE assessment of the certainty of the body of evidence. The following seven questions were asked:

1. Are the study designs used appropriate?

2. Are there important limitations in the research design or execution of the research?

3. Are the results consistent across studies when the settings, populations, interventions, comparators, and outcomes are reasonably similar?

4. How directly do the results apply to the population (including setting), intervention, comparator, and outcomes (PICO) of interest?

5. Are the results precise enough or likely due to chance?

6. Is this all the research that has been conducted on the PICO question of interest?

7. Is there anything, in particular very large effects of an intervention, dose response gradients, or unfavourable scenarios still leading to convincing effect that makes us more confident?

There are four possible certainty ratings for each outcome: high, moderate, low and very low. The rating for a RCT starts at 'high' and can be marked down one or two levels for each domain; the rating for a nRCT starts at 'low'. Outcomes can also be marked up for the following attributes: (i) large magnitude of effect, (ii) dose-response gradient and (iii) all residual confounding would decrease magnitude of effect.

Each of the evidence quality ratings are explained below:

- High – Further research is very unlikely to change our confidence in the estimate of effect
- Moderate – Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low – Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
- Very low – Any estimate of effect is very uncertain.

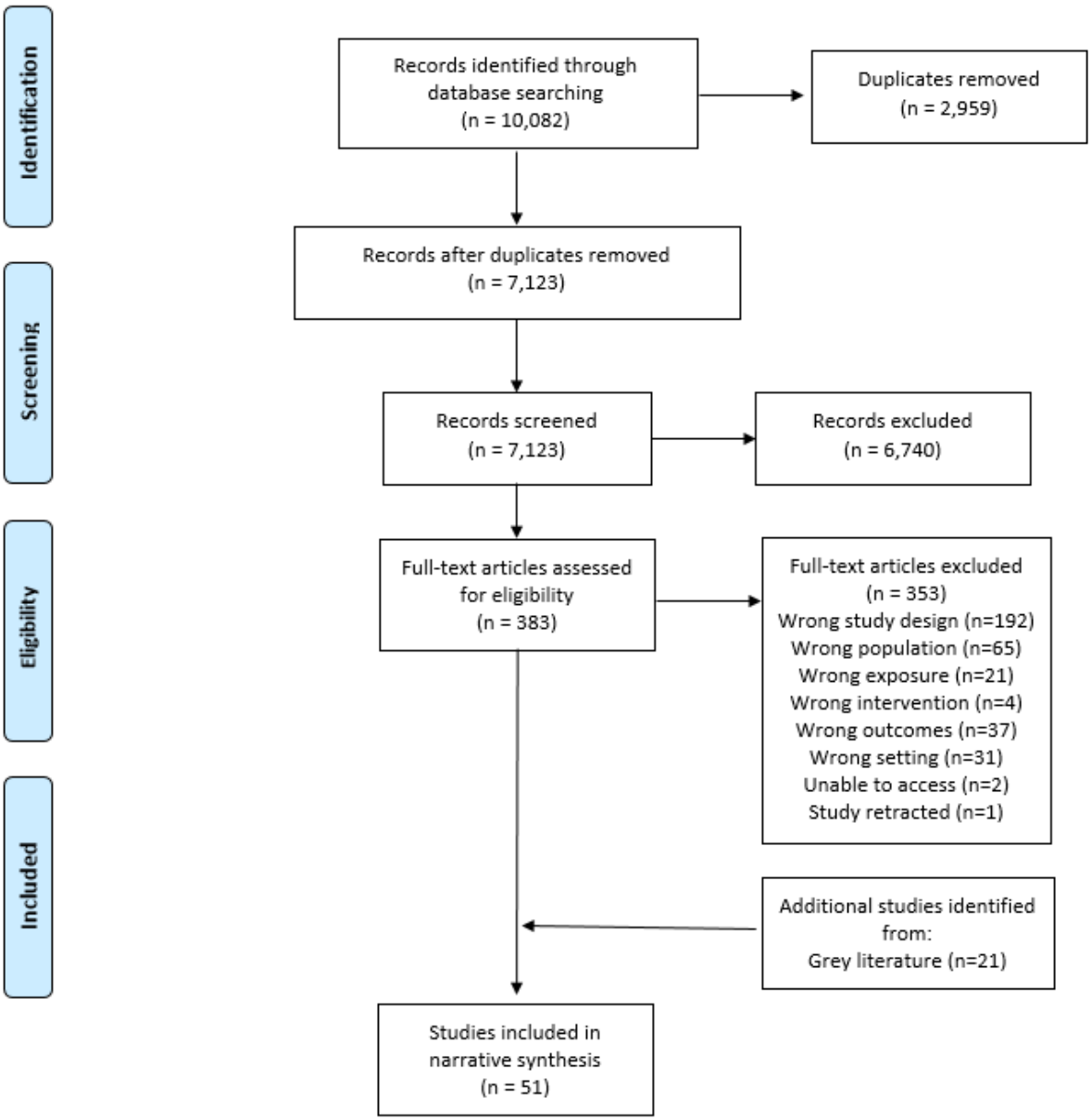
3.0 Results

3.1 Search results

Across all the databases searched, the collective search up until 14 June 2021 resulted in 10,082 citations. Following removal of duplicates 7,123 citations were screened for relevance, with 383 full-texts assessed for eligibility and 353 subsequently excluded; an additional 21 studies were also identified from grey literature searching. In total, 51 studies (four RCTs,[6-9] one nRCT[10] and 46 cohort

studies),[(11-56)] were included in this evidence summary. The five controlled trials[3] were relevant to RQ1 (pharmacological interventions). None of the studies identified were relevant to RQ2 (non-pharmacological interventions), while the 46 cohort studies were relevant to RQ3 (modifiable health-related risk factors). See Figure 1 for a PRISMA flow diagram of the studies included in this evidence summary.

Figure 1. PRISMA flow diagram of included studies



[3] It has come to the attention of the evaluation team that one of the RCTs (Elgazzar et al.) detailed in this report has been removed from preprint publication following additional scrutiny of the reported data.

3.2 Pharmacological interventions to prevent COVID-19 (RQ1)

Four of the five controlled trials[4] included in this evidence summary tested slightly different versions of the same pharmacological intervention, oral ivermectin, alone or in combination with a barrier nasal spray, and using different dosing schedules. The first RCT,[8] tested ivermectin and iota-carrageenan plus standard biosecurity care and personal protective equipment (PPE) versus standard biosecurity care and PPE only. The second RCT[6] tested ivermectin and PPE versus PPE alone; the third RCT[7] tested ivermectin versus no treatment. The nRCT[10] tested ivermectin with carrageenan nasal spray plus PPE versus PPE only. The fifth controlled trial was a double-blind, RCT of bamlanivimab versus placebo for the prevention of COVID-19 infection.[9] These trials are discussed in more detail below.

3.2.1 Randomised controlled trials

Ivermectin was considered within three RCTs. The first RCT, by Chahla et al.,[8] was conducted in Argentina and individuals participated in the study from October to December 2020. The intervention group comprised n=117 healthcare workers and administration staff, mean age 39.6 years (±9.4). The control group comprised n=117 healthcare workers and administration staff, mean age 38.4 years (±7.4). The intervention group received ivermectin orally (12mg every 7 days) and iota-carrageenan nasal spray 6 sprays per day for 4 weeks, plus standard biosecurity care and PPE. The control group received standard biosecurity care and PPE only.[8] The number of subjects diagnosed with COVID-19 was lower in the intervention group; 4/117 (3.4%) compared with 25/117 (21.4%) in control group ($p=1.10^{-5}$). The odds of being diagnosed with COVID-19 was lower in the treatment group, (adjusted odds ratio [aOR] 0.11, 95% confidence interval [CI] 0.03-0.33); adjusted for comorbidity, age, sex and designation (healthcare versus non healthcare);[8] see Appendix 1 for an overview of the characteristics of each study.

The second RCT,[4] by Elgazzar et al., was conducted in Egypt and data were collected between 8 June and 15 September 2020.[6] The main study was conducted in two COVID-19 isolation hospitals, but the two groups of relevance to this evidence summary were healthcare or household contacts of mild, moderate or severe COVID-19 patients. In the intervention group (that is Group V), 100 healthcare or household contacts were given PPE plus ivermectin 400mcg/kg as a single oral dose; this dose was repeated after one week. In the comparator group (that is, Group VI), 100 healthcare or household contacts were given PPE only.[6] At two weeks follow-up, those who developed COVID-19 infection (detected by reverse transcription

[4] It has come to the attention of the evaluation team that one of the RCTs (Elgazzar et al.) detailed in this report has been removed from preprint publication following additional scrutiny of the reported data.

polymerase chain reaction [RT-PCR]) was significantly lower in the intervention group compared to the control group (2% versus 10%, p<0.05);[6] see Appendix 1.

The third RCT, by Shoumann et al.,[7] was also conducted in Egypt during June and July 2020. The aim of the study was to evaluate prophylactic use of ivermectin in asymptomatic family close contacts of patients with COVID-19. In the intervention arm, contacts received two doses of ivermectin according to their body weight on the day of diagnosis of the index case (day 1) and again at day 3. The weight adjusted dose was 15mg per day for those with a body weight 40-60kg, 18mg per day for those with a body weight 60-80kg and 24mg per day for those with a body weight >80kg.[7] The control group received no treatment. At two weeks follow-up, 15 contacts (7.4%) had developed COVID-19 symptoms in the intervention group compared to 59 (58.4%) in the control group (these are further broken down in to mild, moderate and severe symptoms for each group). Multivariate analysis (adjusted for index case severity, age, sex, any comorbidity) showed that ivermectin had a protective effect (aOR 11.45, 95% CI 4.44-29.48; p<0.001).[7] See Appendix 1.

One RCT, by Cohen et al.,[9] that compared bamlanivimab to placebo, was conducted in the US from 2 August 2020 until 20 November 2020, with data collected up to 13 January 2021. The study population included residents and staff of 74 skilled nursing and assisted living facilities in the US, with at least one confirmed SARS-CoV-2 index case. In total, n=966 participants were included in the prevention cohort (n=300 residents and n=666 staff). In the residents group, n=161 received a single intravenous infusion of bamlanivimab, 4200mg (intervention group) and n=139 received placebo. In the staff group, n=323 received the same intervention and n=343 received placebo. The evaluation period was eight weeks, with follow-up to 24 weeks.[9] In the overall prevention population, bamlanivimab significantly reduced the incidence of COVID-19 in the intervention group (n=484) compared with the placebo group (n=482). The incidence of COVID-19 was 8.5% in the intervention group versus 15.2% in the control group, (OR 0.43, 95%CI 0.28-0.68); p<0.001. Disaggregated results (for residents and staff separately) showed that the reduction in incidence was statistically significant in residents only. The incidence of COVID-19 was 8.8% in the intervention group versus 22.5% in the control group, (OR 0.20, 95%CI 0.08-0.49; p<0.001), compared with 8.4% vs 12.2% in the intervention and control groups, respectively for staff (OR 0.58, 95%CI 0.33-1.02); p=0.6).[9]

3.2.2 Non-randomised controlled trial

The nRCT, by Hector et al.,[10] was conducted in Argentina from 1 June until 1 August 2020. The study population included 788 healthcare workers in the

intervention arm and 407 healthcare workers in the control arm. To be eligible for inclusion, healthcare workers had to be involved in the care of COVID-19 patients and have a negative RT-PCR at the time of enrolment.[10] Those in the intervention arm received four sprays of carrageenan (0.17g/spray carrageenan) followed by one drop of ivermectin (0.6mg/ml). This was repeated five times daily for 2 weeks. The intervention group also received PPE; those in the control arm used PPE only. At three months follow-up, the infection rate in the control group was 58.2%; compared to no infections (0%) in the intervention group;[10] see Appendix 2 for an overview of the characteristics of this study.

3.2.3 Quality appraisal of controlled trails

The quality of the RCTs was appraised using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials,[57] a summary of which is presented in Table 1. Of the three RCTs of ivermectin, two were deemed to be at high overall risk of bias, while some concerns were identified for the third RCT. Specific domains of concern were potential bias in the measure of outcomes and bias arising from the randomisation process. Furthermore, the trials by Chahla et al.[8] and Elgazzar et al.[6] are published as pre-prints which means they have not yet been formally peer-reviewed and reported results may change following peer-review.[5] The RCT of bamlanivimab was deemed to be at low overall risk of bias; see Table 1.

Table 1. Summary of quality appraisal for randomised controlled trials

Domain	Chahla[8]	Elgazzar[6]	Shoumann[7]	Cohen[9]
Bias arising from the randomisation process	Some concerns	Some concerns	Some concerns	Low
Bias due to deviations from the intended interventions	Low	High	Low	Low
Bias due to missing outcome data	Low	High	Low	Low
Bias in measurement of outcome	Some concerns	High	High	Low
Bias in selection of the reported result	Low	Some concerns	Some concerns	Low
Overall bias	Some concerns	High	High	Low

Using Robins-I,[2] the nRCT, by Hector et al.,[10] was deemed to have a serious risk of bias, particularly in relation to the following domains: bias due to confounding, measurement of outcomes, and selection of the reported result; see Table 2.

[5] It has come to the attention of the evaluation team that one of the RCTs (Elgazzar et al.) detailed in this report has been removed from preprint publication following additional scrutiny of the reported data.

Table 2. Summary of quality appraisal for non-randomised controlled trials

Domain	Hector[10]
Bias due to confounding	Serious
Bias in selection of participants into the study	Low
Bias in classification of interventions	Low
Bias due to deviations from intended interventions	Moderate
Bias due to missing data	Low
Bias in measurement of outcomes	Serious
Bias in selection of the reported result	Serious
Overall bias	Serious

3.2.4 Certainty of evidence

The certainty of evidence for the use of ivermectin to prevent COVID-19 infection was considered 'very low'. All studies were downgraded for limitations due to research design, that is, non-blinded designs, inappropriate adjustment for confounding variables and premature stopping of the non-intervention arm in one RCT. Studies were also downgraded for imprecision due to small sample sizes and short durations of follow-up. This designation indicates that the estimate of effect is very uncertain and should not be relied upon to inform decision-making. The certainty of evidence for the use of bamlanivimab to prevent COVID-19 infection was considered 'low'. This RCT was downgraded for limitations due to research design (that is, nasal swabs alone, which may have lower sensitivity than nasopharyngeal swabs, were obtained for subsequent SARS-CoV-2 detection during the evaluation and follow-up period) and imprecision due to small sample sizes and short durations of follow-up. This designation indicates that the estimate of effect is uncertain and should not be relied upon to inform decision-making; see Appendix 3

3.2.5 Planned or ongoing trials of interventions to prevent COVID-19

In addition to the four RCTs and one nRCT included in this evidence summary, 60 planned or ongoing trials of a range of interventions were also identified; of which 59 are registered on a clinical trials database. Appendix 4 provides an overview of planned or ongoing trials for the prevention of COVID-19 and includes the trial and or protocol number, intervention being tested and trial status.

3.3 Non-pharmacological interventions to prevent COVID-19 (RQ2)

No studies for RQ2 (non-pharmacological interventions) were eligible for inclusion in this evidence summary. Nor were any planned or ongoing trials relating to non-pharmacological interventions identified.

3.4 Modifiable health-related risk factors' association with COVID-19 (RQ3)

In total, six modifiable health-related risk factors, overweight and or obesity (34 studies),[11-15, 18, 21, 23-27, 29-31, 33, 34, 36-39, 42-49, 51, 52, 54-56] smoking (25 studies),[14, 15, 19-22, 24-27, 29, 30, 33, 34, 36, 38-40, 42, 44, 47-50, 55] vitamin D status (10 studies),[15, 22, 23, 28, 31, 32, 35, 39, 45, 53] physical activity (seven studies),[21, 24, 30, 34, 41, 50, 55] alcohol consumption (five studies)[16, 21, 24, 30, 40] and processed meat intake (one study),[39] were identified in the included studies.

Of the 46 cohort studies[11-56] that assessed the association between modifiable health-related risk factors and COVID-19 outcomes, 18 studies[11, 14-16, 21-24, 30-32, 34, 37-39, 41, 42, 50] were conducted using data from the UK Biobank. The UK Biobank is a prospective cohort study of over 500,000 men and women aged 40–69 years at the time of recruitment, from urban and rural settings across the UK.[58] Between 2006 and 2010, recruitment occurred through postal invite to individuals, identified through National Health Service registers, who lived within 10 miles of one of 22 UK Biobank assessment centres. Baseline data collection consisted of socio-demographics, lifestyle, health and physical measures as well as blood biochemistry.[58] Using the international classification of disease and data linkage with Hospital Episode Statistics and Public Health England, health outcomes, including COVID-19 test results of UK Biobank participants has been possible;[59] see Appendix 5 for an overview of the characteristics of each study that used UK Biobank data.

In addition to the 18 studies that used UK Biobank data, 28 studies were identified that used data from other populations. These studies originated from the US,[17, 26, 28, 40, 43, 53, 55] the UK,[25, 33, 45, 48] Israel,[27, 35, 49] Mexico,[13, 36, 51] Spain,[12, 18, 47] Ireland[56] and Brazil.[44] Data sources included primary care and or health service records,[12, 18, 25, 27, 35, 43-49, 53, 55] national surveillance data,[13, 33, 36, 51, 56] Veterans Affairs (VA) data[17, 26, 40] and de-identified clinical laboratory data.[28] Additionally, five studies[19, 20, 29, 52, 54] used registry data from multiple countries. Two studies[52, 54] used data from the Health Outcome Predictive Evaluation for COVID-19 (HOPE COVID-19) registry which is an international, retrospective cohort registry.[60] All in-patients receiving treatment for COVID-19 at one of the participating centres, who had been discharged or had died at the time of the evaluation, were eligible for inclusion. Data were entered by each centre into an online database.[60] One study[19] used data from the Thoracic Cancers International COVID-19 Collaboration registry, TERAVOLT.[61] This is a global registry aimed at understanding the effect of SARS-CoV-2 infection on patients with thoracic malignancies which comprises data collected from 42 institutions across eight countries (Italy, Spain, France,

Switzerland, Netherlands, USA, UK, and China).[61] One study[29] used data from the COVID-19 and Cancer Consortium (CCC19) database which was designed to study the clinical characteristics and course of COVID-19 among patients with a current or past diagnosis of cancer. Data collection started on 17 March 2020.[62] One study[20] used data from the COVID-19 Global Rheumatology Alliance registry.[63] This registry consists of online portals and case report forms that allow healthcare professionals internationally to record information on individuals with rheumatic disease who have been diagnosed with COVID-19;[63] see Appendix 6 for an overview of the characteristics of each study that used non-UK Biobank data.

3.4.1 Overweight and or obesity

In total, 34 studies reported COVID-19 outcomes in overweight (body mass index [BMI]: 25-29.9kg/m^2) or obese (BMI: ≥30kg/m^2) patients. Primary outcomes included the association between overweight and obesity with COVID-19 diagnosis, COVID-19 hospitalisation, mortality and severe disease (such as ICU admission or intubation/ventilation). Across studies, a range of measures of association were reported, including odds ratios, risk ratios and hazard ratios; most (but not all) studies reported adjusted estimates. All studies that provided adjusted estimates included age and sex as covariates; other covariates that differed across studies included a range of comorbidities (such as chronic obstructive pulmonary disease (COPD), hypertension, diabetes) and other risk factors (such as smoking and alcohol intake).

As 13 studies accessed data collected through the UK Biobank database system, a substantial amount of overlap may be present within these studies. Due to overlapping datasets (that is, studies that used UK Biobank data) and the heterogeneity in patient populations and statistical methods employed by primary study authors (that is, studies that used UK Biobank data and those that did not), a meta-analysis was not considered appropriate.

The following sections narratively report study results by outcome across categories of BMI (overweight: BMI ≥25-29.9kg/m^2; obese: BMI≥30kg/m^2; morbidly obese: BMI≥40kg/m^2). When BMI ranges were not reported, obesity was assumed to correspond to any BMI≥30kg/m^2. Most studies reported outcomes across a range of BMI categories. Due to the substantial confounding and correlation between risk factors, when both adjusted and unadjusted estimates are reported, adjusted estimates are taken as the more reliable measure of association.

COVID-19 diagnosis

Out of 34 studies that reported on the risk factor 'obesity', 13 reported the association between overweight/obesity and COVID-19 diagnosis.[11, 12, 14, 15, 24, 27, 31,

[34, 38, 39, 42, 45, 47] Table 3 provides a summary of studies that reported the outcome COVID-19 diagnosis.

Table 3. Summary of studies that reported the association between overweight and or obesity and diagnosis of COVID-19

Author	SARS-CoV-2 positive cohort (n)	Exposure index	Primary outcome	Point estimate (95% CI)
UK Biobank studies				
Aung[11]	1,211	1 SD increment in BMI	aOR for COVID-19 diagnosis	**1.13 (1.07–1.20)**
		1 SD increment in WC	aOR for COVID-19 diagnosis	**1.15 (1.08–1.23)**
Cho[14]	908	BMI of 27-29kg/m^2	aOR for COVID-19 diagnosis (males)	**1.64 (1.12-2.39)**
		BMI of ≥30kg/m^2	aOR for COVID-19 diagnosis (males)	**1.60 (1.10-2.35)**
Darling[15]	580	BMI of 25-29kg/m^2 (assumption)	OR for COVID-19 diagnosis (unadjusted)	**1.51 (1.13-2.02)**
		BMI of ≥30kg/m^2 (assumption)	OR for COVID-19 diagnosis (unadjusted)	**1.67 (1.24-2.26)**
Ho[24]	518	1 SD increment in BMI	aOR for inpatient COVID-19 diagnosis (model 1[a])	**1.36 (1.25-1.48)**
		BMI 25-29.9kg/m^2 (assumption)	aOR for inpatient COVID-19 diagnosis (model 1[a])	**1.43 (1.10-1.87)**
		BMI of ≥30kg/m^2 (assumption)	aOR for inpatient COVID-19 diagnosis (model 1[a])	**2.08 (1.58-2.74)**
Li[31]	1,082	Metabolically healthy obesity[b]	aOR for testing positive with COVID-19	**1.42 (1.14–1.76)**
		Metabolically unhealthy obesity[b]	aOR for testing positive with COVID-19	**1.83 (1.49–2.25)**
McQueenie[34]	1,324	BMI≥40kg/m^2 and no LTC compared with BMI<40kg/m^2 and no LTC	aOR for testing positive with COVID-19	1.30 (0.49–3.50)
		BMI≥40kg/m^2 and 1 LTC compared with BMI<40kg/m^2 and no LTC	aOR for testing positive with COVID-19	1.34 (0.63–2.85)
		BMI≥40kg/m^2 and 2 LTC compared with BMI<40kg/m^2 and no LTC	aOR for testing positive with COVID-19	**2.66 (1.88–3.76)**
Raisi-Estabragh[38]	1439	5kg/m^2 increase in BMI	aOR for testing positive with COVID-19	**1.19 (1.13-1.25)**
Raisi-Estabragh[39]	1326	1kg/m^2 increase in BMI	aOR for testing positive with COVID-19	**1.02 (1.01-1.03)**
Shi[42]	256	BMI of ≥30kg/m^2 (assumption) in cancer patients	OR for testing positive with COVID-19 (unadjusted)	1.01 (CI 0.62-1.63)

Author	SARS-CoV-2 positive cohort (n)	Exposure index	Primary outcome	Point estimate (95% CI)
		BMI of ≥30kg/m^2 (assumption) in non-cancer patients	OR for testing positive with COVID-19 (unadjusted)	1.01 (0.81-1.27)
Non-UK biobank studies				
Burn[12] (Spain)	109,367	BMI between 30 and 60kg/m^2, or a recorded weight between 120 and 200kg within 5 years of the index date	aHR for testing positive with COVID-19	**1.17 (1.15-1.18)**
Israel[27] (Israel)	4,235	BMI of ≥30kg/m^2	aOR for testing positive with COVID-19	**1.17 (1.08-1.27)**
Subramanian[45] (UK)	618	1kg/m^2 increase in BMI	aHR for COVID-19 diagnosis (suspected or confirmed)	**1.02 (1.01–1.03)**
Vila-Córcoles[47] (Spain)	380	BMI of ≥30kg/m^2 (assumption)	aOR for COVID-19 diagnosis	0.87 (0.68-1.11)

Key: [a] For BMI categories, only 'model 1' is reported (adjusted for age, sex, ethnicity and deprivation index). Model 2 is the fully adjusted model; [b]'Metabolically healthy' determined by metabolic disorders, hypertension, hypercholesterolemia and diabetes. Exposure was compared with metabolically healthy normal weight; aHR, adjusted hazard ratio; aOR, adjusted odds ratio; aRR, adjusted risk ratio; BMI, body mass index; CI, confidence interval; LTC, long term condition; NR, not reported; OR, odds ratio; RR, risk ratio; SD, standard deviation; WC, waist circumference. Significant associations are in bold.

Two of the 13 studies reported crude (unadjusted) estimates only,[15, 42] while 11 studies reported adjusted estimates. Only adjusted estimates are discussed below. Note that studies typically reported outcomes across more than one BMI range. Of note, the comparator differed by study; for example, some studies reported risk relative to those with a BMI <25 kg/m^2 while others compared with a BMI <30 kg/m^2. Of the 11 studies that reported associations between COVID-19 diagnosis and obesity (and reported adjusted outcomes):

- Five reported the association between COVID-19 diagnosis and BMI as a continuous variable. [11, 24, 38, 39, 45] Of these five studies, two studies reported the change in risk by 1 SD (standard deviation)-increments; 1 SD-increments in BMI were positively associated with COVID-19 diagnosis (aOR 1.13, 95%CI 1.07–1.20) and (aOR 1.36, 95%CI 1.25-1.48).[11, 24] Two studies reported change in risk by 1kg/m^2-increments,[39, 45] which were positively associated (aHR 1.02, 95%CI 1.01–1.03) and (aOR 1.02, 95%CI 1.01-1.03), and one study reported change in risk by 5kg/m^2 increments,[38] also positively associated (aOR 1.19, 95%CI 1.13-1.25).

- Two studies[14, 24] reported the risk in overweight patients (BMI 25-29.9kg/m^2), both of which reporting positive associations (aOR 1.43, 95%CI 1.10-1.87)[24] and (aOR 1.64, 95%CI 1.12-2.39), although the latter observation was limited to men only.[14]

- Eight studies[12, 14, 15, 24, 27, 31, 34, 47] reported the risk in obese patients (BMI≥30kg/m^2), including one study[31] that separately reported risk in metabolically healthy and metabolically unhealthy obese patients and one study[34] that reported specifically in the morbidly obese group (BMI≥40kg/m^2). Of these, only one study[47] did not report a positive association and the remaining studies did. Excluding the study that only enrolled patients with a BMI≥40kg/m^2, the reported risk in those with BMI≥30kg/m^2 ranged from an (aOR 1.17, 95%CI 1.08-1.27)[27] to 2.08 (95%CI 1.58-2.74).[24] In the study that categorised obesity by metabolic health, the adjusted risk was higher in those categorised as metabolically unhealthy compared with those who were metabolically unhealthy (aOR 1.83, 95%CI 1.49–2.25) and (aOR 1.42, 95%CI 1.14–1.76), respectively.[31]

- Only one study[34] reported outcomes specific to a BMI≥40kg/m^2. Patients were categorised by the number of long term conditions (LTCs) and all analyses were compared with those with BMI<40kg/m^2 and no LTCs. There was no association in those with BMI≥40kg/m^2 and zero or one

LTCs, whereas an increased risk was observed in those with BMI≥40kg/m^2 and two LTCs (aOR 2.66, 95%CI 1.88–3.76).[34]

COVID-19 hospitalisation

Eleven studies[12, 13, 18, 21, 26, 27, 30, 31, 43, 44, 56] reported the association between obesity and COVID-19 hospitalisation (Table 4).

Table 4. Summary of studies that reported the association between overweight and or obesity and hospitalisation for COVID-19

Author	SARS-CoV-2 positive cohort (n)	Exposure index	Primary outcome	Point estimate (95% CI)
UK Biobank studies				
Hamer[21]	760	BMI of ≥30kg/m^2	aRR for COVID-19 hospitalisation	**2.05 (1.68-2.49)**
Lassale[30]	640	1kg/m^2 increase in BMI	aOR for hospitalisation with COVID-19	**1.03 (1.02–1.05)**
		0.1 unit increase in WC	aOR for hospitalisation with COVID-19	**1.25 (1.09–1.42)**
Li[31]	1,082	Metabolically healthy obesity[b]	aOR for hospitalisation with COVID-19	**1.28 (1.13–1.46)**
		Metabolically unhealthy obesity[b]	aOR for hospitalisation with COVID-19	**1.96 (1.75–2.19)**
Non-UK biobank studies				
Bennett[56] **(Ireland)**	Cohort 1, 19,789 (community and hospital)	BMI ≥40kg/m^2 compared to BMI<40kg/m^2	aOR for hospitalisation[c]	**5.82 (4.50-7.51)**
			aOR for hospitalisation[d]	**4.29 (3.27-5.65)**
Burn[12] **(Spain)**	109,367	BMI between 30 and 60kg/m^2, or a recorded weight between 120 and 200kg within 5 years of the index date	aHR for hospitalisation with COVID-19	**1.74 (1.66-1.82)**
Carillo-Vega[13] **(Spain)**	10,544	BMI of ≥30kg/m^2 (assumption)	aHR for hospitalisation with COVID-19	**1.64 (1.37-1.95)**
Fresan[18] **(Spain)**	1,105 COVID-19 hospitalisations out of 433,995 (total population)	BMI ≥40kg/m^2	aRR for hospitalisation with COVID-19	**2.20 (1.66-2.93)**
Ioannou[26] **(US)**	10,131	BMI 30.0-34.9kg/m^2 vs BMI 18.5-24.9kg/m^2	aHR for hospitalisation with COVID-19	0.80 (0.72-0.98)
		BMI ≥35kg/m^2 vs 18.5-24.9kg/m^2	aHR for hospitalisation with COVID-19	0.87 (0.77-0.98)
Israel[27] **(Israel)**	4,235	BMI of ≥30kg/m^2	aOR for hospitalisation with COVID-19	**1.13 (0.79-1.62)**

Author	SARS-CoV-2 positive cohort (n)	Exposure index	Primary outcome	Point estimate (95% CI)
Singh[43] (US)	41,513	BMI of ≥30kg/m^2	Risk ratio (after PM) for intubation	**1.83 (1.62–2.07)**
Soares[44] (Brazil)	10,713	BMI of ≥30kg/m^2 (assumption)	aOR for hospitalisation	**1.74 (1.35–2.23)**

Key: [b]'Metabolically healthy' determined by metabolic disorders, hypertension, hypercholesterolemia and diabetes. Exposure was compared with metabolically healthy normal weight; [c]Adjusted for age (linear, quadratic, cubic); [d]Adjusted for age (linear, quadratic, cubic), chronic heart disease, chronic neurological disease, chronic respiratory disease, chronic kidney disease, chronic liver disease, asthma (requiring meds), immunodeficiency, diabetes, cancer, other comorbidity, unknown comorbidity, community health office, residential care facility and route of transmission; aHR, adjusted hazard ratio; aOR, adjusted odds ratio; aRR, adjusted risk ratio; BMI, body mass index; CI, confidence interval; LTC, long term condition; NR, not reported; OR, odds ratio; PM, propensity matching; RR, risk ratio; SD, standard deviation; WC, waist circumference. Significant associations are in bold.

All studies reported adjusted estimates. Note that studies typically reported outcomes across more than one BMI range. Of the 11 studies:

- Only one study[30] investigated BMI as a continuous variable. In this study, 1kg/m^2-increments in BMI were positively associated with hospitalisation (aOR 1.03, 95%CI 1.02–1.05). The remaining studies reported the association between COVID-19 diagnosis and BMI as a categorical variable; one[55] reporting on overweight patients (BMI 25-29kg/m^2), nine[12, 13, 21, 26, 27, 31, 43, 44, 55] reporting on obese patients (BMI≥30kg/m^2) and two reporting on morbidly obese patients (BMI≥40kg/m^2).[18, 55]

- In the only study that reported on overweight patients (BMI 25-29kg/m^2), no association was found.[55]

- Nine studies reported on obese patients (BMI≥30kg/m^2), eight of which reported a positive association. One study[31] reported separately in metabolically healthy and metabolically unhealthy obese patients; aORs were 1.28 (95%CI 1.13–1.46) and 1.96 (95%CI 1.75–2.19), respectively.[31] Two studies reported aORs ranging from (aOR 1.12, 95%CI 1.01-1.24)[55] to (aOR 2.05, 95%CI 1.68-2.49).[21] One study reported a reduced risk of hospitalisation in those with a BMI of 30.0-34.9kg/m^2 and a BMI of ≥35kg/m^2, compared with a BMI of 18.5-24.9kg/m^2; (aOR 0.80, 95%CI 0.72-0.98) and (aOR 0.87, 95%CI 0.77-0.98), respectively.[26]

- Three studies reported data relating to morbid obesity (BMI≥40kg/m^2); all three found positive associations; aORs ranged from 1.77 (95%CI 1.55-2.02)[55] to 4.29 (95%CI 3.27-5.65).[56]

Severe COVID-19

Eight studies reported one or more outcomes relating to severe COVID-19 disease (such as ICU admission, respiratory insufficiency, sepsis or intubation and or mechanical ventilation).[26, 31, 43, 49, 51, 52, 55, 56] Table 5 provides a summary of the studies that report the severe COVID-19 outcomes.

Table 5. Summary of studies that reported the association between overweight and or obesity and severe COVID-19 outcomes

Author	SARS-CoV-2 positive cohort (n)	Exposure index	Primary outcome	Point estimate (95% CI)
UK Biobank studies				
Li[31]	1,082	Metabolically healthy obesity[b]	aOR for developing severe COVID-19 disease	**1.50 (1.14–1.98)**
		Metabolically unhealthy obesity[b]	aOR for developing severe COVID-19 disease	**1.94 (1.50–2.50)**
Non-UK biobank studies				
Abumayyaleh[52] (Multicentre)	3,635	BMI<25kg/m^2 compared with BMI of 25-30kg/m^2	aOR for respiratory insufficiency	0.73 (0.54-1.00)
			aOR for sepsis	0.93 (0.61-1.45)
		BMI>30kg/m^2 compared with BMI of 25-30kg/m2	aOR for respiratory insufficiency	1.12 (0.85-1.50)
			aOR for sepsis	0.96 (0.64-1.46)
Bennett[56] (Ireland)	Cohort 2, 2,811 (hospital)	BMI ≥40kg/m^2 compared to BMI<40kg/m^2	aOR for ICU admission[c]	**7.91 (5.39-11.59)**
			aOR for ICU admission[d]	**7.53 (4.94-11.48)**
Denova-Gutiérrez[51] (Mexico)	3,844	BMI of ≥30kg/m^2 (assumption)	aOR of severe COVID-19 on admission	**1.43 (1.11-1.83)**
Ioannou[26] (US)	10,131	BMI 30.0-34.9kg/m^2 vs BMI 18.5-24.9kg/m^2	aHR for mechanical ventilation	1.03 (0.80-1.33)
		BMI ≥35kg/m^2 vs 18.5-24.9kg/m^2	aHR for mechanical ventilation	1.22 (0.93-1.61)
Sallis[55] (US)	103,337	BMI of 25-29kg/m^2	aOR for ICU admission	0.98 (0.81-1.19)
		BMI of 30-39kg/m^2	aOR for ICU admission	1.17 (0.97-1.41)
		BMI of ≥40 kg/m^2	aOR for ICU admission	**1.95 (1.54-2.45)**
Singh[43] (US)	41,513	BMI of ≥30kg/m^2	Risk ratio (after PM) for intubation	**1.83 (1.62–2.07)**

Author	SARS-CoV-2 positive cohort (n)	Exposure index	Primary outcome	Point estimate (95% CI)
Yanover[49] (Israel)	4,353	BMI of ≥30kg/m^2 in patients aged 18-50 years	OR for serious COVID-19 complication (unadjusted)	**11.09 (4.15-32.67[e])**

Key: [b]'Metabolically healthy' determined by metabolic disorders, hypertension, hypercholesterolemia and diabetes. Exposure was compared with metabolically healthy normal weight; [c]Adjusted for age (linear, quadratic, cubic); [d]Adjusted for age (linear, quadratic, cubic), chronic heart disease, chronic neurological disease, chronic respiratory disease, chronic kidney disease, chronic liver disease, asthma (requiring meds), immunodeficiency, diabetes, cancer, other comorbidity, unknown comorbidity, community health office, residential care facility and route of transmission; aHR, adjusted hazard ratio; aOR, adjusted odds ratio; aRR, adjusted risk ratio; BMI, body mass index; CI, confidence interval; LTC, long term condition; NR, not reported; OR, odds ratio; PM propensity matching; RR, risk ratio; SD, standard deviation; WC, waist circumference. Significant associations are in bold.

Of the eight studies that reported one or more outcomes relating to severe COVID-19 disease:

- Four [49, 51, 55, 56] included ICU admission as part of their measured outcome. The first study[51] reported an increased risk of severe COVID-19 (defined by the presence of pneumonia and other organ failure that required monitoring and treatment in the ICU) in patients with a BMI of ≥30kg/m^2 (1.43, 95%CI 1.11-1.83).[51] The second study[49] reported the outcome of 'serious complication', such as experiencing moderate or severe symptoms of COVID-19, admission to the ICU, or death. Patients with a BMI of ≥30kg/m^2 aged 18-50 years had a greatly increased risk (OR of 11.09, 95%CI 4.15-32.67), compared with patients aged 18-50 with a BMI ≤30kg/m^2. However, these analyses were not adjusted for confounders and are therefore not comparable to other studies.[49] The third study[55] measured the association between ICU admission by BMI category. Morbid obesity BMI of ≥40 kg/m^2 was associated with an increased aOR of ICU admission (1.95, 95%CI 1.54-2.45), while BMI in the 25-29kg/m^2 or 30-39kg/m^2 ranges were not associated.[55] The fourth study assessed ICU admission in Irish hospitals in morbidly obese patients.[56] Compared with a BMI<40kg/m^2, those with a BMI ≥40kg/m^2 had an aOR of 7.53 (95% CI: 4.94-11.48) for ICU admission, adjusted for a number of confounders.

- Two studies[26, 43] reported the outcome of intubation and or mechanical ventilation. One reported a risk ratio (after propensity matching) of 1.83, (95%CI 1.62–2.07) in BMI of ≥30kg/m^2 compared with a BMI of <30kg/m^2.[43] The other reported no association in patients with a BMI of 30.0-34.9kg/m^2 or ≥35kg/m^2 compared with a BMI of 18.5-24.9kg/m^2.[26]

- One study[31] reported an increased risk of developing 'severe COVID-19 disease' (specific definitions of 'severe' not reported) in metabolically healthy and metabolically unhealthy obese patients. Positive associations were noted, with aORs of 1.50 (95%CI 1.14–1.98) and 1.94 (95%CI 1.50–2.50) in metabolically healthy and unhealthy obese patients compared to metabolically healthy, respectively.[31]

- One study[52] measured the association between overweight/obesity and respiratory insufficiency and sepsis. Compared with BMI of 25-30kg/m^2, a BMI >30kg/m^2 or a BMI <25kg/m^2 were not associated with an elevated risk of respiratory insufficiency or sepsis.[52]

Mortality from COVID-19

Sixteen studies[12, 13, 18, 23, 25, 29, 33, 36, 37, 42, 46, 48, 52, 54-56] reported the association between overweight/obesity and mortality (Table 6).

Table 6. Summary of studies that reported the association between overweight and or obesity and COVID-19 mortality

Author	SARS-CoV-2 positive cohort (n)	Exposure index	Primary outcome	Point estimate (95% CI)
UK Biobank studies				
Hastie[23]	656 (of which 203 died). Number COVID-19 positive at baseline NR	BMI of ≥30kg/m^2 (assumption)	aHR for COVID-19 mortality	**1.68 (1.11–2.56)**
Peters[37]	410	1 SD increment in BMI	aHR for COVID-19 mortality in women	**1.51 (1.34-1.71)**
		1 SD increment in BMI	aHR for COVID-19 mortality in men	**1.26 (1.11-1.44)**
		1 SD increment in waist-to-hip ratio	aHR for COVID-19 mortality in women	**1.34 (1.23-1.4)**
		1 SD increment in waist-to-hip ratio	aHR for COVID-19 mortality in men	**1.57 (1.37-1.79)**
Shi[42]	256	BMI of ≥30kg/m^2 (assumption) in cancer patients	OR for mortality in COVID-19 patients (unadjusted)	1.38 (0.48-3.97)
		BMI of ≥30kg/m^2 (assumption) in non-cancer patients	OR for mortality in COVID-19 patients (unadjusted)	**2.12 (1.28-3.52)**
Non-UK biobank studies				
Abumayyaleh[52] (Multicentre)	3,635	BMI<25kg/m^2 compared with BMI of 25-30kg/m^2	aHR for mortality	1.15 (0.89-1.51)
		BMI>30kg/m^2 compared with BMI of 25-30kg/m2	aHR for mortality	1.15 (0.89-1.48)
Bennett[56] (Ireland)	Cohort 1, 19,789 (community and hospital)	BMI ≥40kg/m^2 compared to BMI<40kg/m^2	aOR for mortality[c]	**2.48 (1.59-3.87)**
			aOR for mortality[d]	**2.89 (1.80-4.64)**
	Cohort 2, 2,811 (hospital)	BMI ≥40kg/m^2 compared to BMI<40kg/m^2	aOR for mortality[c]	**1.81 (1.14-2.86)**
			aOR for mortality[d]	**2.19 (1.34-3.56)**

Author	SARS-CoV-2 positive cohort (n)	Exposure index	Primary outcome	Point estimate (95% CI)
Burn[12] (Spain)	109,367	BMI between 30 and 60kg/m^2, or a recorded weight between 120 and 200kg within 5 years of the index date	aHR for mortality in COVID-19 positive	0.98 (0.90-1.07)
			aHR for mortality in COVID-19 hospitalised patients	**1.10 (1.02-1.18)**
Carillo-Vega[13] (Spain)	10,544	BMI of ≥30kg/m^2 (assumption)	aHR for COVID-19 mortality	**1.74 (1.35-2.26)**
Fresan[18] (Spain)	1,105 COVID-19 hospitalisations out of 433,995 (total population)	BMI ≥40kg/m^2	aRR for severe COVID-19 (admission to ICU or death)	**2.30 (1.20-4.40)**
Holman[25] (England)	9,991 COVID-19 deaths in T2DM	T2D with BMI 30-34.9kg/m^2	aHR for COVID-19 mortality, compared with T2D and BMI 25.0-29.9 kg/m^2	1.04 (0.98-1.10)
		T2D with a BMI of 35-39.9kg/m^2	aHR for COVID-19 mortality, compared with T2D and BMI 25.0-29.9 kg/m^2	**1.17 (1.08-1.26)**
		T2D with BMI ≥40.0kg/m^2	aHR for COVID-19 mortality, compared with T2D and BMI 25.0-29.9 kg/m^2	**1.60 (1.47-1.75)**
Kuderer[29] (US, Canada, Spain)	928 with COVID-19 and previous or active cancer	BMI of ≥30kg/m^2 (assumption)	aOR for 30-day mortality	0.99 (0.58–1.71)
McGurnaghan[33] (Scotland)	1082 with fatal or critical care unit-treated COVID-19	BMI >30-35kg/m^2	aOR fatal or critical care unit treatment, compared with BMI 20-25kg/m^2	0.93 (0.77-1.12)
		BMI >35-40kg/m^2 and diabetes	aOR fatal or critical care unit treatment, compared with BMI 20-25kg/m^2	0.97 (0.76-1.23)
		BMI >40kg/m^2 and diabetes	aOR fatal or critical care unit treatment, compared with BMI 20-25kg/m^2	1.19 (0.89-1.60)

Author	SARS-CoV-2 positive cohort (n)	Exposure index	Primary outcome	Point estimate (95% CI)
Núñez-Gil[54] (Spain, Ecuador, Germany and Italy)	1,021	BMI of ≥30kg/m^2 (assumption)	aOR mortality (whole cohort)	1.52 (0.83-2.76)
			aOR mortality (<70 years)	**4.93 (1.77-13.74)**
			aOR mortality (>70 years)	0.85 (0.40-1.80)
Parra-Bracamonte[36] (Mexico)	331,298	BMI of ≥30kg/m^2	aOR for mortality	**1.22 (1.17–1.28)**
Sallis[55] (US)	103,337	BMI of 25-29kg/m^2	aOR for mortality	**0.79 (0.64-0.97)**
		BMI of 30-39kg/m^2	aOR for mortality	0.89 (0.72-1.10)
		BMI of ≥40 kg/m^2	aOR for mortality	**1.90 (1.43-2.54)**
Tartof[46] (US)	6,916	BMI 40-44kg/m^2, compared with patients with a BMI of 18.5-24kg/m^2	aRR mortality at 21 days	**2.68 (1.43-5.04)**
		BMI >45kg/m^2, compared with patients with a BMI of 18.5-24kg/m^2	aRR mortality at 21 days	**4.18 (2.12-8.26)**
Williamson[48] (UK)	10,926 COVID-19 deaths	BMI 30-34.9kg/m^2, compared with BMI<30kg/m^2	aOR for mortality	**1.05 (1.00–1.11)**
		BMI 35-39.9kg/m^2, compared with BMI<30kg/m^2	aOR for mortality	**1.40 (1.30–1.52)**
		BMI≥40kg/m^2, compared with BMI<30kg/m^2	aOR for mortality	**1.92 (1.72–2.13)**

Key: [c]Adjusted for age (linear, quadratic, cubic); [d]Adjusted for age (linear, quadratic, cubic), chronic heart disease, chronic neurological disease, chronic respiratory disease, chronic kidney disease, chronic liver disease, asthma (requiring meds), immunodeficiency, diabetes, cancer, other comorbidity, unknown comorbidity, community health office, residential care facility and route of transmission; aHR, adjusted hazard ratio; aOR, adjusted odds ratio; aRR, adjusted risk ratio; BMI, body mass index; CI, confidence interval; LTC, long term condition; NR, not reported; OR, odds ratio; RR, risk ratio; SD, standard deviation; WC, waist circumference. Significant associations are in bold.

All but one study[42] reported adjusted estimates. Only adjusted estimates from these 15 studies are discussed below. Note that studies typically reported outcomes across more than one BMI range. Of the 15 studies:

- One study[37] reported the association between mortality and BMI as a continuous variable. In this study, the association between 1 SD-increments in BMI and mortality were estimated separately in men and women. The aHR for COVID-19 mortality was 1.51 (95%CI 1.34-1.71) in women and 1.26 (95%CI 1.11-1.44) in men.[37]

- Two studies[52, 55] reported the risk in overweight patients (BMI 25-29.9kg/m^2). In the first study,[52] no association was present after controlling for confounders. In the second,[55] a lower mortality was reported (aOR 0.79, 95%CI 0.64-0.97).

All studies reported the mortality risk in obese patients (BMI≥30kg/m^2), including six studies[25, 33, 46, 48, 55, 56] that also reported the risk in morbidly obese patients (BMI≥40kg/m^2).

Of the 15 studies reporting the mortality risk in obese patients (BMI≥30kg/m^2), nine studies reported adjusted estimates in general obese populations:

- One study[12] reported separately for mortality in COVID-19 positive and in COVID-19 hospitalised patients; an association was only found in COVID-19 hospitalised patients (aHR: 1.10, 95%CI 1.02-1.18).

- One study[18] reported a combined outcome of mortality or admission to ICU, reporting a positive association (aRR of 2.30, 95%CI 1.20-4.40).

- One study[48] reported stronger associations at higher BMI categories (BMI 30-34.9kg/m^2: aOR 1.05, 95%CI 1.00–1.11; BMI 35-39.9kg/m^2: aOR 1.40, 95%CI 1.30–1.52; BMI≥40kg/m^2: aOR 1.92, 95%CI 1.72–2.13; note all comparisons are with BMI<30kg/m^2).

- One study[54] reported associations separately by age category; BMI≥30kg/m^2 was associated with mortality in those under 70 years of age (aOR 4.93, 95%CI 1.77-13.74), but not in those over 70 years or in the overall cohort.

- Six studies[13, 23, 29, 43, 52, 55] reported associations at any BMI≥30kg/m^2; only two reported positive associations aRR 1.17 (95%CI 1.01–1.36[43] and aHR 1.74 (95%CI 1.35-2.26).[13]

Two studies specifically enrolled obese participants with diabetes.[25, 33]

- In the first study,[25] compared with patients with type 2 diabetes with a BMI of 25-29.9 kg/m^2, no increased hazard of mortality was observed in those with a BMI 30-34.9kg/m^2, while the risk was increased in those with a BMI of 35-39.9kg/m^2 or ≥40kg/m^2, aHRs were 1.17 (95%CI 1.08-1.26) and 1.60 (95%CI 1.47-1.75), respectively.[25] Lower BMIs were also associated with an increased hazard of mortality the aHR in BMI<20kg/m^2 was 2.33 [95%CI 2.11-2.56] and the aHR in BMI of 20-24.9 kg/m^2 was 1.34, [95%CI 1.27-1.42].[25]

- In the second study,[33] which was again limited to patients with diabetes, the combined outcome of mortality or critical care unit treatment was measured. In this study, compared with non-diabetics with a BMI of 20-25kg/m^2, no increased risk of mortality was observed in those with a BMI 30-34.9kg/m^2, 35-39.9kg/m^2 or ≥40.0kg/m^2. However, an increased risk of mortality (aOR 2.40, 95%CI 1.77-3.26) was observed in those with a BMI<20kg/m^2.[33]

Four studies[46, 48, 55, 56] reported the association between morbid obesity (BMI of ≥40 kg/m^2) in general populations and mortality; all four reported strong associations.

- Two studies[48] compared a BMI≥40kg/m^2 with BMI<30kg/m^2, resulting in aORs of 1.92 (95%CI 1.72–2.13) and 1.90 (95%CI 1.43-2.54).[55]

- One study[46] compared a BMI≥40kg/m^2 with a BMI of 18.5-24kg/m^2. Risk of mortality was increased with aRR of 2.68 (95%CI 1.43-5.04) and 4.18 (95%CI 2.12-8.26) in those with a BMI of 40-44kg/m^2 and a BMI≥45kg/m^2, respectively.

- One study[56] compared a BMI ≥40kg/m2 with BMI<40kg/m2 in Irish individuals. The aOR for mortality was 2.89 (95% CI: 1.80-4.64).

3.4.2 Smoking

In total, 25 studies[14, 15, 19-22, 24-27, 29, 30, 33, 34, 36, 38-40, 42, 44, 47-50, 55] assessed the association between smoking and COVID-19 outcomes; of which 11 studies[14, 15, 21, 22, 24, 30, 34, 38, 39, 42, 50] used data from the UK Biobank. The other cohort studies that assessed the association between smoking and COVID-19 were conducted in Brazil,[44] England,[25] Israel,[27, 49] Mexico,[36] Scotland,[33] Spain,[47] the UK[48] and US;[26, 40, 55] a further three studies used registry data from across various countries.[19, 20, 29] See Table 7 for a summary of the findings reported by studies that assessed the association between smoking and COVID-19 outcomes.

Various outcomes were reported, including COVID-19 diagnosis,[14, 15, 22, 24, 27, 34, 38-40, 42, 47, 50] severe COVID-19 (which includes mechanical ventilation, requirement for critical care and complications),[26, 27, 33, 49, 55] hospitalisation,[20-22, 26, 30, 44, 50, 55] and mortality.[19, 25, 29, 36, 42, 48, 50, 55] While most of the studies based their analyses on the general population, Holman et al.,[25] reported on COVID-19 outcomes in people with Type I and Type II Diabetes. Smoking status was described in various ways in the studies, such as, 'current-smoker versus never-smoker', 'current-smoker versus past-smoker' and 'smoker versus non-smoker'. The number of participants in the included studies ranged from 200[19] to 331,298.[36] The differences in risk were reported variously as adjusted relative risks (RR), aORs, and hazard ratios (adjusted and non-adjusted); only those studies that reported adjusted estimates are included below.

Table 7. Summary of studies that reported outcomes for smoking

Author	SARS-CoV-2 positive cohort (n)	Exposure index	Primary outcome	Point estimate (95% CI)
UK Biobank studies				
Cho[14]	908	Current smoker versus never smoker	aOR for COVID-19 diagnosis (men)	1.12 (0.75-1.68)
			aOR for COVID-19 diagnosis (women)	1.38 (0.89-2.15)
Darling[15]	580	Regular smoker versus non-smoker	OR for COVID-19 diagnosis (unadjusted)	**0.58 (0.39-0.86)**
Hamer[21]	760	Past smoker versus never smoker	aRR for hospitalisation with COVID-19	**1.36 (1.15-1.59)**
		Current smoker versus never smoker	aRR for hospitalisation with COVID-19	**1.36 (1.08-1.71)**
Hastie[22]	449	Current smoker versus non-smoker	aOR for COVID-19 diagnosis	0.93 (0.69-1.25)
Ho[24]	518	Current/past smoker versus non-smoker	aOR for COVID-19 diagnosis (Model 1[a])	**1.45 (1.19-1.79)**
			aOR for COVID-19 diagnosis (Model 2[b])	**1.39 (1.13-1.71)**
Lassale[30]	640	Past smoker versus non-smoker	aOR for hospitalisation with COVID-19	**1.30 (1.10–1.55)**
		Current smokers versus non-smoker	aOR for hospitalisation with COVID-19	1.25 (0.96–1.62)
McQueenie[34]	1,324	Current/past smoker versus non-smoker	aOR for COVID-19 diagnosis	**1.26 (1.02–1.57)**
Raisi-Estabragh[38]	1,439	Current/past smoker versus non-smoker	aOR for COVID-19 diagnosis (Comparison 1[c])	**1.26 (1.13-1.40)**
			aOR for COVID-19 diagnosis (Comparison 2[d])	1.02 (0.90-1.15)
			aOR for COVID-19 diagnosis (Comparison 3[e])	**1.24 (1.17-1.31)**
Raisi-Estabragh[39]	1,326	Current/past smoker versus never smoker	aOR for COVID-19 diagnosis	1.02 (0.89-1.16)
Shi[42]	256	Smoker versus non-smoker	OR for COVID-19 diagnosis (unadjusted)	1.32 (1.00-1.74)
			OR for mortality from COVID-19 (unadjusted)	0.86 (0.44-1.65)
Zhang[50]	1,596	Past smoker versus never smoker	aOR for COVID-19 diagnosis	**1.38 (1.01 to 1.40)**
			aOR for hospitalisation with COVID-19	**1.57 (1.04-2.36)**
			aOR for mortality from COVID-19	1.93 (0.91-4.12)
		Current smoker versus never smoker	aOR for COVID-19 diagnosis	**1.76 (1.09 to 1.05)**
			aOR for hospitalisation with COVID-19	**1.95 (1.03-3.69)**
			aOR for mortality from COVID-19	**3.37 (1.06-10.73)**

Author	SARS-CoV-2 positive cohort (n)	Exposure index	Primary outcome	Point estimate (95% CI)
Non-UK Biobank studies				
Garassino[19] (various)	200	Current/past smoker versus never smoker	aOR for mortality from COVID-19	**3.18 (1.11-9.06)**
Gianfrancesco[20] (various)	600	Current/past smoker versus never smoker	aOR for hospitalisation with COVID-19	1.18 (0.90-1.53)
Holman[25] (England)	464 Type 1 diabetic	Current smoker versus never smoker	aHR for mortality from COVID-19	0.88 (0.62-1.25)
		Past smoker versus never smoker	aHR for mortality from COVID-19	1.09 (0.89-1.35)
	10,525 Type 2 diabetic	Current smoker versus never smoker	aHR for mortality from COVID-19	**0.67 (0.62-0.74)**
		Past smoker versus never smoker	aHR for mortality from COVID-19	**1.13 (1.08-1.18)**
Ioannou[26] (US)	10,131	Current smoker versus never smoker	aHR for hospitalisation with COVID-19	1.10 (0.98-1.25)
			aHR for mechanical ventilation for COVID-19	0.94 (0.69-1.28)
		Past smoker versus never smoker	aHR for hospitalisation with COVID-19	1.01 (0.94-1.10)
			aHR for mechanical ventilation for COVID-19	1.02 (0.85-1.22)
Israel[27] (Israel)	4,151	Current smoker versus never smoker	aOR for COVID-19 diagnosis	**0.45 (0.41-0.51)**
			aOR for severe COVID-19	**0.77 (0.69-0.86)**
		Past smoker versus never smoker	aOR for COVID-19 diagnosis	0.59 (0.27-1.30)
			aOR for severe COVID-19	1.11 (0.73-1.69)
Kuderer[29] (various)	928	Former smoker versus never smoker	aOR for mortality from COVID-19	**1.60 (1.03–2.47)**
		Current smoker versus never smoker	aOR for mortality from COVID-19	1.34 (0.49–3.67)
McGurnaghan[33] (Scotland)	2,724	Former smoker versus never smoker	aOR for requiring fatal or critical care unit treatment	**1.30 (1.13-1.49)**
		Current smoker versus never smoker	aOR for requiring fatal or critical care unit treatment	1.13 (0.91-1.42)
Parra-Bracamonte[36] (Mexico)	331,298	Smoking habit (not defined as current or former)	aOR for mortality from COVID-19	**0.93 (0.87-0.99)**
Rentsch[40]	585	Current smoker versus non-smoker	aOR for COVID-19 diagnosis	**0.45 (0.35-0.57)**

Author	SARS-CoV-2 positive cohort (n)	Exposure index	Primary outcome	Point estimate (95% CI)
(US)				
Sallis[55] (US)	48,440	Ever smoker versus never smoker	aOR for hospitalisation with COVID-19	**1.09 (1.01-1.18)**
			aOR for admission to ICU with COVID-19	1.08 (0.95-1.23)
			aOR for mortality from COVID-19	**1.24 (1.05-1.47)**
Soares[44] (Brazil)	10,713	Current smoker versus non-smoker	aOR for hospitalisation with COVID-19	**2.91 (2.04–4.12)**
Vila-Córcoles[47] (Spain)	380	Smoking (not defined as current or former)	aHR for COVID-19 diagnosis	**0.62 (0.41-0.93)**
Williamson[48] (UK)	10,926	Current smoker versus never smoker	aHR for mortality from COVID-19	**1.43 (1.37-1.49)**
		Former smoker versus never smoker	aHR for mortality from COVID-19	**1.14 (1.05-1.23)**
Yanover[49] (Israel)	4,353	Current smoker versus non-smoker	OR for risk of complications, age<50 years (unadjusted)	1.29 (0.31-3.97)
			OR for risk of complications, age≥50 years, age<65 years (unadjusted)	1.52 (0.62-3.37)
			OR for risk of complications, ≥65 years (unadjusted)	1.22 (0.64-2.21)

Key: [a]Model 1 adjusted for age, sex, ethnicity and deprivation index; [b]Model 2 adjusted for behavioural (smoking and alcohol drinking) and physical (adiposity, blood pressure, spirometry and physical capability) factors that were found to be significant in Model 1; [c]Comparison 1 - COVID-19 positive versus COVID-19 negative plus untested; [d]Comparison 2 - COVID-19 positive versus COVID-19 negative; eComparison 3 - COVID-19 positive versus untested; aHR, adjusted hazard ratio; aOR, adjusted odds ratio; CI, confidence interval; ICU, intensive care unit; OR, odds ratio. Statistically significant associations are in bold.

COVID-19 diagnosis

Twelve studies reported on the association between smoking status and the risk of being diagnosed with COVID-19[14, 15, 22, 24, 27, 34, 38-40, 42, 47, 50] with mixed findings reported. Several analyses reported a statistically significant increased risk in current smokers compared with past-smokers or never-smokers,[24, 34, 38, 50] with adjusted odds ratios ranging from (aOR 1.24, 95%CI 1.17-1.31[38] to (aOR 1.76, 95%CI 1.09-1.05).[50] Some analyses did not report a statistically-significant difference in the risk.[14, 22, 38, 39, 42] In contrast, four studies,[15, 27, 40, 47] reported statistically significant reductions in the risk of COVID-19 diagnosis in those who smoked, ranging from (aOR 0.45, 95%CI 0.41-0.51)[27] to (aOR 0.62, 95% CI 0.41-0.93).[47]

Hospitalisation with COVID-19

Seven studies considered the association between smoking status and hospitalisation with COVID-19.[20, 21, 26, 30, 44, 50, 55] Compared to those who never smoked or were 'non-smokers', those who smoked or had smoked in the past were reported to have a statistically significant higher risk of hospitalisation from COVID-19 in five studies.[21, 30, 44, 50, 55] The increased risks ranged from (aOR 1.09, 95%CI 1.01-1.18)[55] to (aOR 2.91, 95%CI 2.04–4.12).[44] While an increased risk of hospitalisation in smokers relative to non-smokers was observed in the other two studies, the difference was not statistically significant.[20, 26]

Severe COVID-19

Five studies[26, 27, 33, 49, 55] reported the association between smoking status and severe COVID-19; this included the need for mechanical ventilation,[26] fatal or critical care,[33] ICU admission[55] and risk of complications.[49] One study reported no statistically significant difference in the risk of requiring mechanical ventilation in current or past smokers compared with those who never smoked.[26] Similarly, using data from Kaiser Permanente Southern California, another study reported that, compared to those who never smoked, those who ever smoked did not have an increased risk of ICU admission with COVID-19, (aOR 1.08, 95%CI 0.95-1.23).[55]

Israel et al.[27] found a statistically significant reduction in risk of developing severe COVID-19 in current smokers compared to those who never smoked (aOR 0.77, 95%CI 0.69-0.86), but no statistically significant difference between past smokers and those who never smoked. Yanover et al.[49] did not find a difference in in risk of complications in smokers compared with those who never smoked. McGurnaghan et al.[33] reported an increased risk in the requirement for fatal or critical care in former smokers compared to those who never smoked (aOR1.30, 95%CI 1.13-1.49), but not in current smokers compared with those who never smoked.

Mortality from COVID-19

Eight studies examined the association between smoking and mortality.[19, 25, 29, 36, 42, 48, 50, 55] Analyses from six studies reported a statistically significant increased risk of mortality in smokers compared to non-smokers,[19, 25, 29, 48, 50, 55] with effect estimates ranging from (aHR 1.13, 95%CI 1.08-1.18)[25] to (aOR 3.37, 95%CI 1.06-10.73),[50] while no association between smoking and mortality was observed in four studies.[25, 29, 42, 50] Conversely, two studies reported a statistically significant decreased risk of mortality in those who smoked; (aHR 0.67, 95%CI 0.62-0.74)[25] and (aOR 0.93, 95%CI 0.87-0.99).[36]

3.4.3 Vitamin D

Ten studies[15, 22, 23, 28, 31, 32, 35, 39, 45, 53] considered the association between Vitamin D and COVID-19 outcomes; of which six studies[15, 22, 23, 31, 32, 39] used data from the UK Biobank. Vitamin D status, as measured at baseline in the UK Biobank during the period 2006 to 2010, was used in the analyses in all studies. In addition, the categorical variables 'deficient/not deficient' (25(OH)D <25 nmol/L) and 'insufficient/not insufficient' (25(OH)D <50 nmol/L) were used in two studies.[22, 23] Genetically predicted Vitamin D level and habitual use of supplementary Vitamin D were used in one study.[32] The studies that used UK Biobank data reported the numbers of participants who had tested positive for COVID-19 and these figures varied between the studies. These differences may reflect the numbers of positive cases at different time periods, when these linked data were gathered. See Table 8 for a summary of the findings reported by studies that assessed the association between Vitamin D status and COVID-19 outcomes.

Table 8. Summary of studies that reported outcomes for Vitamin D status

Author	SARS-CoV-2 positive cohort (n)	Exposure index	Primary outcome	Point estimate (95% CI)
UK Biobank studies				
Darling[15]	580	Q1 25(OH)D bottom 25%	OR for COVID-19 diagnosis (unadjusted)	1.00
		Q2 25(OH)D	OR for COVID-19 diagnosis (unadjusted)	0.93 (0.67-1.28)
		Q3 25(OH)D	OR for COVID-19 diagnosis (unadjusted)	1.03 (0.74-1.44)
		Q4 25(OH)D top 25%	OR for COVID-19 diagnosis (unadjusted)	1.11 (0.79-1.56)
Hastie[22]	449	25(OH) deficient (<25 nmol/L)	aOR for COVID-19 diagnosis	0.92 (0.71–1.21)
		25(OH) insufficient (<50 nmol/L)	aOR for COVID-19 diagnosis	0.88 (0.72–1.08)
Hastie[23]	656 (of whom 203 died)	25(OH) deficient (<25 nmol/L)	aHR for mortality from COVID-19	1.21 (0.83–1.76)
			aIRR for inpatient COVID-19 infection	1.10 (0.88–1.37)
		25(OH) insufficient (<50 nmol/L)	aHR for mortality from COVID-19	1.02 (0.75–1.38)
			aIRR for inpatient COVID-19 infection	1.06 (0.89–1.26)
Li[31]	1,082	25(OH) insufficient (<50 nmol/L)	aOR for hospitalisation with COVID-19	**1.21 (1.13-1.30)**
			aOR for COVID-19 diagnosis	**1.20 (1.06-1.37)**
			aOR for severe COVID-19	**1.21 (1.03-1.41)**
Ma[32]	1,378	Habitual use of vitamin D supplements	aOR for COVID-19 diagnosis	**0.66 (0.45–0.97)**
Raisi-Estabragh[39]	1,326	Season-adjusted 25(OH)D concentration	aOR for COVID-19 diagnosis	1.00 (1.00-1.00)
Non-UK Biobank studies				
Katz[53] **(US)**	887	Vitamin D deficiency (defined by International classification of diseases-10 diagnosis codes)	aOR for COVID-19 diagnosis	**2.27 (1.79-2.87)**[a] **to 5.16 (3.97-6.69)**[b]
Kaufman[28] **(US)**	9.3% of 191,779	Per ng/mL increase in 25(OH)D	aOR for COVID-19 diagnosis	**0.98 (0.98–0.99)**
Merzon[35]	782	25(OH) <30 ng/mL	aOR for COVID-19 diagnosis	**1.50 (1.13–1.98)**

Author	SARS-CoV-2 positive cohort (n)	Exposure index	Primary outcome	Point estimate (95% CI)
(Israel)			aOR for hospitalisation with COVID-19	1.95 (0.98–4.78)
Subramanian[45] (England)	618	Vitamin D deficiency recorded by read codes	aHR for suspected/confirmed COVID-19	**1.61 (1.05–2.47)**

Key: [a]adjusted for sex and obesity; [b]adjusted for age; aHR, adjusted hazard ratio; aIRR, adjusted incidence rate ratio; aOR, adjusted odds ratio; OR, odds ratio. Significant associations are in bold.

COVID-19 diagnosis

Four studies that used data from the UK Biobank[15, 22, 23, 39] reported no association between baseline Vitamin D levels and confirmed COVID-19 infection, when adjusted for confounders. However, Hastie et al.[22] reported that the median baseline concentration of Vitamin D was significantly lower in patients who subsequently had confirmed COVID-19 infection (28.7 (IQR 10.0–43.8) nmol/L) than other participants (32.7 (IQR 10.0–47.2) nmol/L). Although Ma et al.[32] reported no association between genetically predicted Vitamin D levels and confirmed COVID-19 infection, habitual Vitamin D supplementation was found to be significantly associated with a 34% lower risk of COVID-19 infection when adjusted for confounders (aOR 0.66, 95%CI 0.45–0.97). Moreover, Li et al.[31] reported that 'insufficiency' (25(OH)D <50 nmol/L) was significantly associated with infection (aOR 1.20, 95%CI 1.06-1.37).

In addition to the cohort studies that used data from the UK Biobank, four further cohort studies assessed the association between vitamin D deficiency and COVID-19 infection.[28, 35, 45, 53] Katz et al.[53] used data from the University of Florida i2b2 patient registry platform; the registry provides data aggregates from patient visits to various University of Florida health centres. The dataset consists of 987,849 patients, of which 887 were diagnosed with COVID-19 and 950 were diagnosed with vitamin D deficiency; overall 87 patients had both COVID-19 and vitamin D deficiency.[53] Those with vitamin D deficiency had an increased risk of COVID-19 infection; aORs ranged from aOR 2.27, (95%CI 1.79-2.87) when adjusted for sex and obesity, to aOR 5.16, (95%CI 3.97-6.69) when adjusted for age.[53]

Three studies reported an association between circulating 25(OH)D levels and SARS-CoV-2 positivity rates. Kaufman et al.[28] used de-identified test results from a clinical laboratory; the study population consisted of 191,779 participants from all 50 US states and the District of Columbia, 9.3% of whom were SAR-CoV-2 positive. Multivariate analysis showed that lower SARS-CoV-2 positivity rates were significantly associated with higher circulating 25(OH)D levels, (aOR 0.98, 95%CI 0.98–0.99) per ng/mL increase; however, the covariates used in the analysis were not reported.[28]

Merzon et al. used data from the Leumit Health Services database, a large health maintenance organisation in Israel that provides services to approximately 730,000 members nationwide.[35] Multivariate analyses that controlled for demographic variables and psychiatric and somatic disorders, showed that low plasma 25(OH)D was significantly associated with an increased likelihood of COVID-19 infection, (aOR 1.45, 95%CI 1.08–1.95).[35]

Using data from The Health Improvement Network (THIN) database, and anonymised longitudinal data from the primary care electronic medical records database including 365 active general practices in the UK, Subramanian et al. reported the association between vitamin D deficiency (identified from read codes) and COVID-19 infection in a cohort of women with polycystic ovary syndrome.[45] The authors reported that Vitamin D deficiency was associated with an increased risk of suspected and or confirmed COVID-19 infection, (aHR 1.61, 95%CI 1.05–2.47); however, the covariates used in the analysis were not reported.[45]

Hospitalisation with COVID-19

Using data from the UK Biobank, Li et al.[31] reported that vitamin D 'insufficiency' (25(OH)D <50 nmol/L) was significantly associated with risk of hospitalisation (aOR 1.21, 95%CI 1.13-1.30). However, in the study by Merzon et al.[35] (referred to above), there was no association between low plasma 25(OH)D and increased risk of hospitalisation due to COVID-19, (aOR 1.95, 95%CI 0.98–4.85) when adjusted for demographic variables and psychiatric and somatic disorders.

Severe COVID-19

Li et al.[31] reported that vitamin D 'insufficiency' (25(OH)D <50 nmol/L) was significantly associated with developing severe COVID-19 disease (aOR 1.21, 95%CI 1.03-1.41).

Mortality from COVID-19

In addition to finding no association between Vitamin D level and risk of COVID-19 infection, Hastie et al.[23] also reported no association between baseline Vitamin D level, Vitamin D deficiency (25(OH)D <25 nmol/L) or Vitamin D insufficiency (25(OH)D <50 nmol/L) and mortality in the UK Biobank cohort, when adjusted for confounders.

3.4.4 Physical activity

Seven studies assessed the association between different measures of physical activity and COVID-19 outcomes; six studies used UK Biobank data;[21, 24, 30, 34, 41, 50] one study used data from Kaiser Permanente Southern California (an integrated healthcare system that serves approximately 4.7 million residents in Southern California) .[55] See Table 9 for a summary of the findings reported by these studies.

Table 9. Summary of studies that reported outcomes for physical activity

Author	Lab-confirmed SARS-CoV-2 positive cohort (n)	Exposure index	Primary outcome	Point estimate (95% CI)
UK Biobank studies				
Hamer[21]	760	Physical inactivity	aRR for COVID-19 diagnosis	**1.32 (1.10-1.58)**
		Insufficient physical activity*	aRR hospitalisation with COVID-19	0.99 (0.84-1.18)
		No physical activity	aRR hospitalisation with COVID-19	**1.38 (1.15-1.64)**
Ho[24]	518	Slow walking pace (self-reported)	aOR for COVID-19 diagnosis (Model 1)	**1.99 (1.48-2.68)**
			aOR for COVID-19 diagnosis (Model 2)	**1.53 (1.12-2.08)**
		Brisk walking pace (self-reported)	aOR for COVID-19 diagnosis (Model 1)	0.80 (0.64-1.00)
			aOR for COVID-19 diagnosis (Model 2)	0.95 (0.75-1.20)
Lassale[30]	640	Active but below UK guidance*	aOR hospitalisation with COVID-19	0.93 (0.77–1.13)
		Inactive	aOR hospitalisation with COVID-19	**1.22 (1.00–1.48)**
McQueenie[34]	1,324	Did not meet physical activity guidelines*	aOR for COVID-19 diagnosis	**1.44 (1.09–1.91)**
Rowlands[41]	207	Overall physical activity level	aOR for severe COVID-19	0.85 (0.70-1.04)
			aOR for COVID-19 diagnosis	0.93 (0.79-1.09)
		Moderate-to-vigorous physical activity	aOR for severe COVID-19	0.81 (0.66-1.01)
			aOR for COVID-19 diagnosis	1.00 (0.84-1.18)
		Good balance between activity and sleep/rest	aOR per SD for severe COVID-19	**0.71 (0.62-0.81)**
			aOR per SD for COVID-19 diagnosis	**0.86 (0.75-0.98)**
		Greater variability in timing of sleep/rest	aOR for COVID-19 diagnosis	**1.21 (1.08-1.35)**
Zhang[50]	1,596	Acceleration vector magnitude physical activity	aOR per SD increase for COVID-19 diagnosis	**0.80 (0.69-0.93)**
			aOR per SD increase for attending as an outpatient for COVID-19	**0.74 (0.58-0.95)**
Non-UK Biobank studies				
Sallis[55] (US)	48,440	Consistently inactive versus consistently active	aOR for hospitalisation with COVID-19	**2.26 (1.81-2.83)**
			aOR for admission to ICU with COVID-19	**1.73 (1.18-2.55)**

			aOR for mortality from COVID-19	**2.49 (1.33-4.67)**
		Inconsistently active versus consistently active	aOR for hospitalisation with COVID-19	**1.89 (1.53-2.33)**
			aOR for admission to ICU with COVID-19	**1.58 (1.10-2.27)**
			aOR for mortality from COVID-19	**1.88 (1.02-3.47)**

Key: *UK guidance for physical activity is ≥150min/week moderate-to-vigorous physical activity or ≥75 min/week vigorous activity; aOR, adjusted odds ratio; aRR, adjusted relative rate; ICU, intensive care unit; SD, standard deviation. Significant associations are in bold.

COVID-19 diagnosis

Five studies reported the association between physical activity and COVID-19 diagnosis. Hamer et al.[21] reported that physical inactivity was associated with an increased risk of COVID-19 diagnosis (aRR 1.32, 95%CI 1.10-1.58) after adjusting for age, sex, obesity, smoking and alcohol consumption.[21] Similarly, McQueenie et al.[34] reported that those who did not meet UK guidance relating to physical activity had an increased risk of diagnosis with COVID-19, (aOR 1.44, 95%CI 1.09–1.91). Ho et al.[24] reported that self-reported slow walking pace was associated with an increased risk of COVID-19 diagnosis when adjusted for age, sex, ethnicity and deprivation index (Model 1), (aOR 1.99, 95%CI 1.48-2.68) and when additionally adjusted for behavioural (smoking and alcohol drinking) and physical (adiposity, blood pressure, spirometry and physical capability) factors that were found to be significant in Model 1 (Model 2), (aOR 1.53, 95%CI 1.12-2.08).[24] Conversely, brisk walking was not associated with a decreased risk of COVID-19 diagnosis.[24] It should be noted that walking pace was not considered a surrogate for physical activity, but rather an indication of physical health.

Rowlands et al.[41] reported that overall physical activity level and moderate-to-vigorous physical activity were not associated with a diagnosis of COVID-19. However, a good balance between activity and sleep and or rest, was associated with decreased risk of testing positive for COVID-19 (aOR per SD, 0.86, 95%CI 0.75-0.98),[41] while greater variability in the timing of sleep and or rest was associated with increased risk of testing positive for COVID-19 (aOR 1.17, 95%CI 1.04-1.35).[41] Similar to the findings from Rowlands et al.,[41] Zhang et al.[50] reported no association between moderate-to-vigorous physical activity and risk of COVID-19 diagnosis. However, they did report a decreased risk in COVID-19 diagnosis per standard deviation increase in acceleration vector magnitude (that is, objectively measured) physical activity, (aOR 0.80, 95%CI 0.69-0.93).[50]

Hospitalisation with COVID-19

Four studies reported the association between physical activity and hospitalisation for COVID-19. Hamer et al.[21] reported that, compared to those who met UK guidance for physical activity (that is ≥150min/week moderate-to-vigorous physical activity or ≥75 min/week vigorous activity), those who did no physical activity had an increased risk of hospitalisation with COVID-19, (aRR 1.38, 95%CI 1.15-1.64), adjusted for age, sex, education, ethnicity, diabetes, hypertension, cardiovascular disease (heart attack, angina, or stroke). There was no increased risk of hospitalisation with COVID-19 in those who were physically active, but did not meet the UK guidance for physical activity (aRR 0.99, 95%CI 0.84-1.18).[21] Similarly,

Lassale et al.[30] reported an increased risk of hospitalisation with COVID-19 in those who were inactive, (aOR 1.22, 95%CI 1.00–1.48). Zhang et al.[50] reported no association between moderate-to-vigorous physical activity and risk of hospital attendance (as an in-patient or out-patient) for COVID-19. However, they did report a decreased risk in outpatient attendance per SD increase in acceleration vector magnitude physical activity (aOR 0.74, 95%CI 0.58-0.95).[50]

Sallis et al.[55] reported that, compared to those who were consistently active, those who were consistently inactive and inconsistently active, had an increased risk of hospitalisation with COVID-19, (aOR 2.26, 95%CI 1.81-2.83) and (aOR 1.89, 95%CI 1.53-2.33), respectively.

Severe COVID-19

Two studies reported the association between physical activity and severe COVID-19. Rowlands et al.[41] reported that overall physical activity level and moderate-to-vigorous physical activity were not associated with developing severe COVID-19. However, a good balance between activity and sleep and or rest, was associated with decreased risk of severe COVID-19 (aOR per SD, 0.71, 95%CI 0.62-0.81).[41] Greater variability in the timing of sleep and or rest was also associated with increased risk of severe infection, (aOR 1.21, 95%CI 1.08-1.35).[41] Data from Kaiser Permanente Southern California showed that compared to those who were consistently active, those who were consistently inactive and inconsistently active, had an increased risk of ICU admission with COVID-19, (aOR 1.73, 95%CI 1.18-2.55) and (aOR 1.58, 95%CI 1.10-2.27), respectively.[55]

Mortality from COVID-19

In accordance with other outcomes reported by Sallis et al.,[55] compared to those who were consistently active, those who were consistently inactive and inconsistently active, had an increased risk of mortality from COVID-19, (aOR 2.49, 95%CI 1.33-4.67) and (aOR 1.88, 95%CI 1.02-3.47), respectively.

3.4.5 Alcohol consumption

Five studies[16, 21, 24, 30, 40] assessed the association between alcohol intake and COVID-19 outcomes, of which four used UK Biobank data[16, 21, 24, 30] and one[40] used the VA Birth Cohort which includes all Veterans born between 1945 and 1965 (in total, over 2 million living individuals aged 54-75 years). See Table 10 for a summary of the findings reported by these studies.

Table 10. Summary of studies that reported outcomes for alcohol consumption

Author	SARS-CoV-2 positive cohort (n)	Exposure index	Primary outcome	Point estimate (95% CI)
UK Biobank studies				
Fan[16]	1,570	Heavy drinkers (>7 drinks per week for women; >14 drinks per week for men) with obesity (BMI>30)	aHR death from COVID-19	**2.07 (1.24-3.47)**
		Frequent drinkers compared to infrequent/never, with obesity (BMI>30)	aHR death from COVID-19	**1.57 (1.01-2.42)**
		Weekly drinkers compared to infrequent/never, with obesity (BMI>30)	aHR death from COVID-19	**1.46 (1.05-2.03)**
		Heavy drinkers compared to never/infrequent, with obesity (BMI>30)	aOR admission to ICU	**2.43 (1.35-4.40)**
Hamer[21]	760	Heavy alcohol intake (≥14 units in women; ≥21 units in men)	aRR for COVID-19 diagnosis	1.12 (0.93-1.35)
		Rarely/never consumed alcohol	aRR hospitalisation due to COVID-19	**1.57 (1.31-1.88)**
		Consumed alcohol above the current guidance (≥14 units for women and ≥21 units for men)	aRR hospitalisation due to COVID-19	**1.24 (1.03-1.50)**
Ho[24]	518	Former alcohol consumer compared to never	aOR for COVID-19 diagnosis	0.90 (0.49-1.65)
		Current alcohol consumer compared to never	aOR for COVID-19 diagnosis	0.65 (0.43-1.00)
Lassale[30]	640	Rarely/never consumed alcohol	aOR hospitalisation due to COVID-19	**1.30 (1.07–1.59)**
		Consumed alcohol above the current guidance (≥14 units for women and ≥21 units for men)	aOR hospitalisation due to COVID-19	1.10 (0.90–1.34)
Non-UK Biobank studies				
Rentsch[40] (US)	585	Alcohol use disorder defined by read codes	aOR for COVID-19 diagnosis	**0.58 (0.41-0.83)**

Key: aHR, adjusted hazard ratio; aOR, adjusted odds ratio; aRR, adjusted relative risk; ICU, intensive care unit. Significant associations are in bold.

COVID-19 diagnosis

Three studies used UK Biobank data to report the association between alcohol use and the risk of COVID-19 infection. No association was reported between alcohol consumption[16] or heavy alcohol consumption[21] and an increased risk of COVID-19 infection. Ho et al.[24] reported no increased risk of COVID-19 infection in those who were former or current alcohol consumers.

On the contrary, using data from the VA Birth Cohort, Rentsch et al.[40] reported that alcohol use disorder was significantly associated with a decreased likelihood of COVID-19 infection, (aOR 0.58, 95%CI 0.41-0.83); covariates included in the analysis were age, ethnicity, angiotensin-converting-enzyme (ACE) inhibitor and or angiotensin receptor blocker (ARB) use and non-steroidal anti-inflammatory drugs (NSAID) use. This finding was surprising given that those with alcohol use disorder are at an increased risk of pneumonia.[40]

Hospitalisation with COVID-19

Compared with individuals who (regularly) consume alcohol, but within the current UK guidance (that is, <14 units/week for women and <21 units/week for men), an increased risk of hospitalisation due to COVID-19 was observed in those who rarely and or never consumed alcohol (aRR 1.57, 95%CI 1.31-1.88) and also in those who consumed alcohol above the current guidance (aRR 1.24, 95%CI 1.03-1.50).[21] In another study using UK Biobank data, and again compared with those who regularly consume alcohol, but within the current UK guidance, an increased risk of hospitalisation with COVID-19, (aOR 1.30, 95%CI 1.07–1.59) was observed in those who rarely and or never consumed alcohol; however no increase was observed in those whose alcohol intake was above the current guidance (aOR 1.10, 95%CI 0.90–1.34).[30]

Severe COVID-19

Fan et al. reported that within the UK Biobank cohort, among individuals who were obese, heavy drinkers had a higher likelihood of admission to ICU due to COVID-19 compared with infrequent and or non-heavy drinkers (aOR 2.43, 95%CI 1.35-4.40).[16]

Mortality from COVID-19

In addition to having an increased risk of admission to ICU due to COVID-19, Fan et al.[16] also reported that heavy drinkers who were obese had an increased risk of death from COVID-19 (aHR 2.07, 95%CI 1.24-3.47), as did obese patients who reported consuming alcohol weekly (compared with those drinking none or

infrequently), (aHR 1.57, 95%CI 1.01-2.42).[16] Again, compared with those drinking none or infrequently, those who were weekly alcohol consumers (and obese) also had a higher risk of death (aHR 1.46, 95%CI 1.05-2.03); these associations were absent in those who were not obese.[16]

3.4.6 Processed meat intake

COVID-19 diagnosis

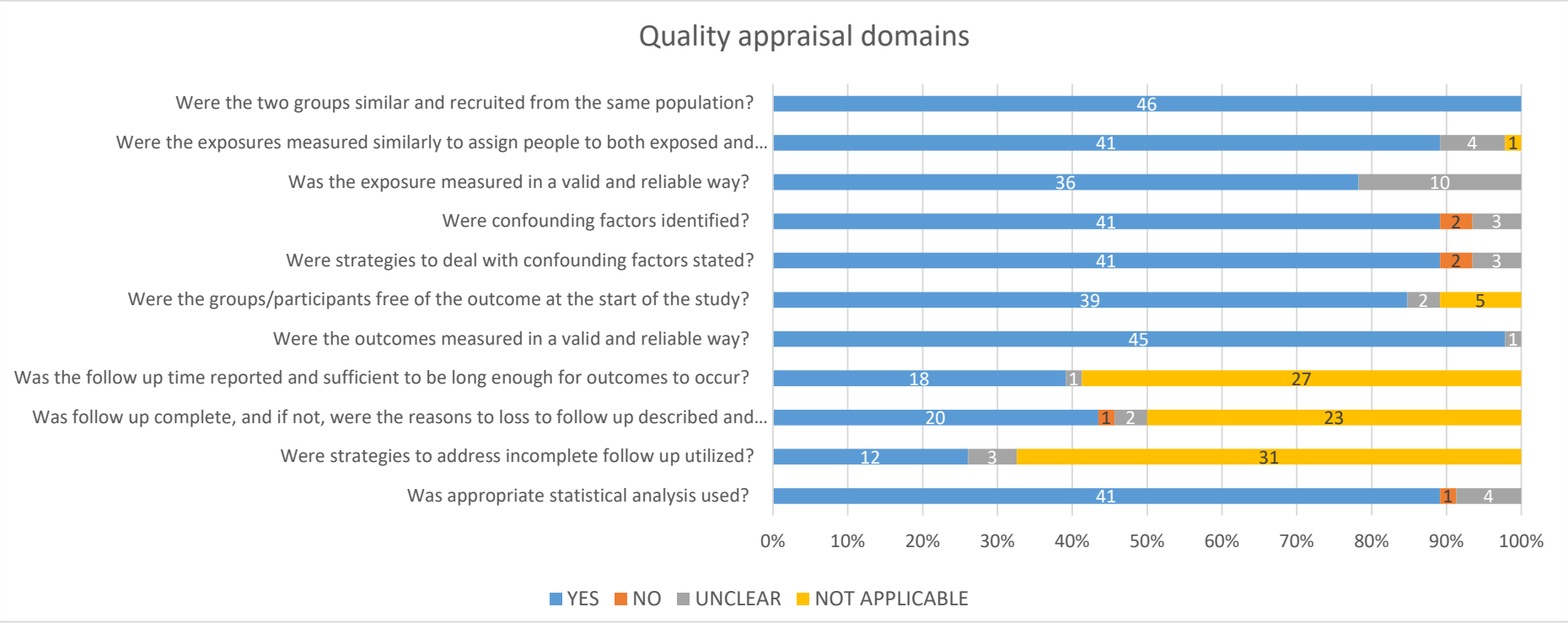
One study, by Raisi-Estabragh et al.,[39] used UK Biobank data to determine the association between processed meat consumption and COVID-19 infection. The study population consisted of 4,510 participants for whom COVID-19 test results were available (n=1,326 positive versus n=3,184 negative). Multivariate analysis, adjusted for sex, age and ethnicity demonstrated no statistically significant association between processed meat consumption and COVID-19 infection, (aOR 1.26, 95%CI 0.81-1.94).[39]

3.4.7 Quality appraisal of cohort studies

There were 46 cohort studies[11-56] that considered modifiable risk factors, including 18 studies[11, 14-16, 21-24, 30-32, 34, 37-39, 41, 42, 50] that were based on data from the UK Biobank. The quality of all of these studies was appraised using the Joanna Briggs Institute Checklist for Cohort Studies.[3] Thirteen of the studies that used UK Biobank data were rated as good quality, with five studies,[15, 30, 31, 42, 50] rated moderate in quality due to uncertainty as to how confounding factors were identified and dealt with in the analyses. Furthermore, four studies[14-16, 42] are pre-prints which means they have not yet been formally peer-reviewed and reported results may change following peer-review.

The quality of the non-Biobank studies were largely rated as good[12, 17-19, 25, 33, 35, 36, 43, 44, 46-49, 55, 56] to moderate.[13, 20, 26, 28, 29, 40, 51, 53, 54] Studies were down-graded from good to moderate quality usually because of uncertainty about how the 'exposure' in question, that is, the modifiable risk factor that the study examined, was measured. Three studies were rated low quality due to a lack of information on several aspects of the design and implementation of the studies.[27, 45, 52] Furthermore, three studies[12, 13, 27] are pre-prints, which means they have not yet been formally peer-reviewed and reported results may change following peer-review. See Figure 2 for an overview of the quality appraisal of cohort studies included in this review.

Figure 2. Overview of quality appraisal of included cohort studies



4.0 Discussion

The aim of this report was to summarise the evidence on the effectiveness of pharmacological and non-pharmacological interventions in the community, prior to a diagnosis of COVID-19, aimed at preventing or minimising progression to severe disease. An additional aim was to determine the association between modifiable health-related factors and the risk of COVID-19 or progression to severe COVID-19. In total, 51 studies were eligible for inclusion (three RCTs of ivermectin,[6-8] [two of which were pre-prints][6],[6, 8] one RCT of bamlanivimab,[9] one nRCT of ivermectin and carrageenan,[10] and 46 cohort studies,[11-56] that considered the association between various modifiable health-related risk factors and risk of COVID-19 or progression to severe COVID-19). No eligible studies of non-pharmacological interventions were identified for inclusion in this evidence summary. Additionally, 60 planned or ongoing trials of interventions for the prevention of COVID-19 were identified; none had formally published results at the time of writing this evidence summary.

As of 14 June 2021, there have been no non-vaccine interventions authorised by the EMA for the prevention of COVID-19. The effectiveness of interventions to prevent COVID-19 has also been reviewed by a number of international agencies. The Canadian Agency for Drugs and Technologies in Health (CADTH) has published a review Ongoing Trials for Drugs in the Prevention and Treatment of COVID-19, which was last updated on 16 April 2021.[64] The World Health Organization (WHO), in collaboration with the Magic Evidence Ecosystem Foundation, and through communication by the BMJ Rapid Recommendations, has published updates to its living guideline on drugs to prevent COVID-19, the most recent of which was published on 26 April 2021.[65] The findings, which were supported by two living systematic reviews with network analysis,[66, 67] resulted in a strong recommendation against the use of hydroxychloroquine as prophylaxis in individuals who do not have COVID-19. It was also stated that, because of the high certainty evidence from which this recommendation emerged, funders and researchers should reconsider the initiation and or continuation of trials using hydroxychloroquine.[65]

[6] It has come to the attention of the evaluation team that one of the RCTs (Elgazzar et al.) detailed in this report has been removed from preprint publication following additional scrutiny of the reported data.

4.1 Pharmacological and non-pharmacological interventions

This evidence summary identified five controlled trials of pharmacological interventions and several planned or ongoing trials for the prevention of COVID-19. Four of the five trials[7] included tested variations of the same intervention, ivermectin and the fifth trial tested bamlanivimab.

Oral ivermectin was used alone or in combination with (iota) carrageenan nasal spray. The latter has been investigated as a physical barrier to prevent binding and or entry of a range of different viruses including human rhinoviruses and the flu virus.(68) In the EU, ivermectin is approved in humans for treatment of some parasitic worm infestations and skin conditions like rosacea; it is also approved for veterinary use.(69) While ivermectin has been shown to inhibit SARS-CoV-2 in vitro,(70) the dose required to achieve adequate concentrations in the lungs to be effective against SARS-CoV-2, is much higher than currently authorised for use in other conditions.(71) This intervention has received substantial media coverage, and there are a plethora of observational studies suggesting a potential role for ivermectin in treatment and prophylaxis of COVID-19. However, there is not enough evidence from rigorous RCTs to inform policy.(72) Indeed, the trials(6-8, 10) included in this evidence summary were small, had a high risk of bias and therefore would not be sufficient to support a recommendation for prophylactic use of ivermectin for COVID-19.[7] Moreover, safety outcomes were either poorly reported or not reported; where reported, it was suggested that they were predominantly mild with no adverse events identified that required stopping or withdrawing the drug. The finding that there is insufficient evidence to support a recommendation of ivermectin for the prevention of COVID-19 is consistent with recommendations from a rapid evidence report published by the COVID-19 Scientific Advisory Group (Alberta, Canada) on 2 February 2021. It stated that, "At this time, ivermectin is not recommended for prophylaxis against COVID-19, outside of clinical trials." The rationale for this recommendation stated that studies were of low quality and further research is needed.(73)

On 22 March 2021, the EMA issued a statement, endorsed by the COVID-19 EMA pandemic Task Force, that advised against the use of ivermectin for the prevention or treatment of COVID-19 outside RCTs.(71) This statement arose following a review, by the EMA, of the latest published evidence from laboratory studies, observational studies, clinical trials and meta-analyses on the use of ivermectin. It concluded that ivermectin cannot currently be recommended outside controlled clinical trials, and

[7] It has come to the attention of the evaluation team that one of the RCTs (Elgazzar et al.) detailed in this report has been removed from preprint publication following additional scrutiny of the reported data.

that rigorous RCTs were needed to determine if ivermectin is safe and effective for the prevention and treatment of COVID-19.[71]

A living systematic review and network meta-analysis by Bartoszko et al.[66] aimed to determine the effects of drug prophylaxis on COVID-19. In total, nine trials were included, three of which investigated the effect of ivermectin for prophylaxis of COVID-19 and are included in this evidence summary; the other six trials included by Bartoszko et al. were of hydroxychloroquine. In the review by Bartoszko et al.,[66] the authors concluded that the evidence for ivermectin with or without iota-carrageenan is very uncertain in relation to its ability to reduce the risk of COVID-19 and mortality. This uncertainty is due to serious risk of bias and a lack of accuracy. Moreover, the effect estimates are likely to change substantially with additional evidence from ongoing trials.[66]

The other pharmacological intervention identified was bamlanivimab, a monoclonal antibody designed to attach to the spike protein of SARS-CoV-2 to prevent it from entering the body's cells.[9] While the study included in this evidence summary reported that bamlanivimab significantly reduced the incidence of COVID-19 in the overall prevention population (compared with placebo), disaggregated results showed that this was only significant in the residents' subgroup, not the staff. The authors concluded that further research is needed to assess the preventive efficacy of this therapy.[9] On 5 March 2021, the EMA issued a statement confirming that bamlanivimab (with or without etesevimab, which is also a monoclonal antibody) can be used to treat confirmed COVID-19 in patients who do not require supplemental oxygen and who are at high risk of severe COVID-19 disease.[74] On 9 November 2020, the US FDA issued an emergency use authorisation for the use of bamlanivimab monotherapy for mild to moderate COVID-19 in adults and paediatric patients (aged 12 years of age and older weighing at least 40 kg), who are at high risk for progressing to severe COVID-19 and or hospitalisation. However, in light of emerging variants of concern, this emergency use authorisation for bamlanivimab monotherapy was revoked (on 16 April 2021), due to concerns that said variants may be resistant to bamlanivimab monotherapy.[75] Neither the EMA nor FDA have issued any statement with respect to the use of bamlanivimab for prevention of COVID-19.

In addition to the controlled trials included in this evidence summary, phase I RCT data were identified with respect to the safety of another monoclonal antibody, meplazumab. However, no COVID-19 outcomes were included and it is unclear if it is intended that this agent would be used for the prevention of COVID-19.[76] Meplazumab is not thought to be readily available for use in Ireland.[77]

The updated search (conducted on 14 June 2021) identified one study[78] that tested a non-pharmacological intervention, neem (Azadirachta indica A. Juss). Neem is a tree which has been widely used as a traditional Ayurveda medicine for centuries. The study was a double-blinded RCT conducted in India. The study population (n=190) were healthcare workers caring for COVID-19 patients or close contacts of patients with COVID-19. There were 95 participants in both the intervention and control groups. Intervention participants received 50mg of neem-leaf extract (which was a proprietary, patent-pending product) twice daily for 28 days; those in the control group received placebo capsules orally, twice daily for 28 days. At 56 days follow-up, of the 154 participants who completed the follow-up, 11 tested positive for COVID-19 (three in the intervention group and eight in the control group); treatment-emergent adverse events (TEAEs) reported in both groups were minimal. However, this study was not powered to test the statistical significance of the intervention.[78] The authors concluded that neem-leaf is a low cost, safe prophylaxis option for COVID-19. No neem-based product is currently registered as a herbal medicinal product by the Health Products Regulatory Authority in Ireland. Neem-based products derived from the neem leaf, bark and seed are available as food supplements as well as a range of topical products in Ireland. The similarity between these products and the proprietary product used in this trial is uncertain.[79]

4.2 Modifiable health-related risk factors

Modifiable risk factors (for example, sedentary lifestyle, smoking, excessive alcohol consumption and obesity) play an important role in many non-communicable diseases such as cardiovascular disease, diabetes and chronic obstructive pulmonary disease. Such factors can also influence immunity.[80] As such, researchers internationally have sought to understand the link between these factors and poorer COVID-19 outcomes, that is, severity and mortality.

4.2.1 Overweight and or obesity

Thirty-four studies were identified that estimated the associations between obesity and a range of COVID-19 outcomes, such as diagnosis, hospitalisation and mortality. All studies either reported a positive association or no association between obesity (BMI of ≥30kg/m^2) and one of these outcomes, only one study[26] reporting a negative association between higher BMI and risk of hospitalisation. Differences in risk factor definition (BMI category), how confounders were measured and dealt with, as well as differences in the methods of statistical analysis used made comparisons across studies particularly difficult.

While many studies failed to demonstrate an association between obesity and poorer outcomes, all eight studies[11, 23, 24, 30, 37-39, 45] that analysed BMI as a continuous

variable (for example, 1kg/m^2, 5kg/m^2 or 1-standard deviation increments) reported an association. For example, one study[39] estimated that each 1kg/m^2 increase in BMI resulted in an increased adjusted odds ratio of 1.02 (95%CI 1.01-1.03) for testing positive with COVID-19 (indicating that each 1kg/m^2 is associated with a 2% increased risk of COVID-19 diagnosis), and another study[30] reported that each 1kg/m^2 increase in BMI resulted in an increased adjusted odds ratio of 1.03 (95%CI 1.02–1.05) for hospitalisation with COVID-19 (indicating that each 1kg/m^2 is associated with a 3% increased risk of COVID-19 hospitalisation).

Strengthening the findings from studies that measured BMI as a continuous variable, studies that reported across multiple BMI categories also found stronger associations with higher BMI values. For example, three studies[46, 48, 55] reported the risk of mortality across multiple categories, including those with a BMI of ≥40 kg/m^2. In the first study,[55] the lowest BMI category (25-29kg/m^2) was associated with a reduced risk of death (aOR of 0.79, 95% CI 0.64-0.97); there was no association with mortality in the obese range (30-39kg/m^2, aOR of 0.89, 95%CI 0.72-1.10), while the morbid obese group (≥40 kg/m^2) was associated with an increased risk (aOR of 1.90, 95% CI 1.43-2.54). In the second study,[48] increasing levels of obesity above 30kg/m^2 were associated with increasing risks of mortality, with aORs of 1.05 (95%CI 1.00–1.11), 1.40 (95%CI 1.30–1.52) and 1.92 (95%CI 1.72–2.13) with BMIs of 30-34.9kg/m^2, 35-39.9kg/m^2 and ≥40kg/m^2, respectively. The third study[46] looked specifically at the morbidly obese group; BMIs of 40-44kg/m^2 and ≥45kg/m^2 were associated with aRRs of 2.68 (95%CI 1.43-5.04) and 4.18 (95%CI 2.12-8.26), respectively.

The updated search identified a further four studies that reported on the association between obesity and COVID-19 outcomes. The studies were conducted in England,[81, 82] Mexico[83] and the US.[84] The first study conducted in England used data from OpenSAFELY, a data analytics platform created to address urgent COVID-19 related questions. The included cohort comprised over 17million individuals; obesity class I (BMI 30.0 to 34.9), class II (BMI 35.0 to 39.9) and class III (BMI≥40) were found to be significantly associated with increased risk of COVID-19 mortality.[81] The second study conducted in England used de-identified patient-level data from the QResearch database of general practices; the cohort consisted of 6.9 million eligible individuals.[82] In those with a BMI >23 kg/m^2, a linear increase in risk of severe COVID-19 leading to admission to hospital and death was observed. Furthermore, a linear increase in admission to ICU was observed with increasing BMI; this increase in ICU admission was independent of excess risks of related diseases.[82] The study conducted in Mexico utilised data from the National COVID-19 Epidemiological Surveillance Study. The cohort consists of 71,103 individuals and multivariate analysis showed that obesity, with and without comorbidities, was

associated with an increased risk of COVID-19 mortality.[83] The study conducted in the US used Veteran Affairs data; the cohort consisted of individuals who tested positive for COVID-19 (n=9,347).[84] When compared to those with a BMI<23kg/m^2, those with a BMI 30-39 kg/m^2 had an increased risk of hospitalisation, ICU admission, and mortality; conversely those with a BMI 23-30 kg/m^2 had a decreased risk of hospitalisation and mortality.[84] While formal data extraction and quality appraisal has not been undertaken of these four additional studies, their findings appear consistent with those of the 34 studies included in the review, that is of a relationship between obesity and poorer COVID-19 outcomes.

The overall impact of obesity on lung function is multifactorial, related to inflammatory and mechanical aspects of obesity. As such, the underlying mechanisms for the poorer COVID-19 outcomes in obese patients may be related to chronic inflammation that disrupts immune and thrombogenic responses to pathogens in addition to impaired lung function.[85] Obesity causes substantial changes to the mechanics of the lungs and chest wall, and changes in mediators produced by adipose tissue likely also contribute to altered lung function, though this is poorly understood.[86] The findings of this review generally support a dose-response relationship between increasing BMI and poorer COVID-19 outcomes.

4.2.2 Smoking

Twenty-five studies assessed the association between smoking and COVID-19 outcomes. Eleven studies reported that smoking was significantly associated with negative COVID-19 outcomes, eight studies reported mixed findings and seven studies reported no association between smoking and COVID-19 outcomes. Six studies reported that smoking was associated with a decreased risk of COVID-19 diagnosis,[15, 27, 40, 47] severity[27] and mortality.[25, 36] This was surprising given that COVID-19 is a respiratory disease. A rapid review on the topic was published by the EU Science Hub in 2020.[87] The authors noted the 'astonishingly low number of current smokers among patients suffering from symptomatic COVID-19 compared to the general population, leading to the conclusion that smoking and or nicotine uptake might have a preventive effect.' However, they concluded that specifically designed studies would be required to prove or disprove any hypothesis on the effect of nicotine on symptomatic COVID-19.

A BMJ Evidence-Based Medicine analysis discussed plausible biologic mechanisms by which smoking might be protective in COVID-19.[88] These include an anti-inflammatory effect of nicotine, a blunted immune response in smokers (reducing the risk of a cytokine storm in COVID-19) and increased nitric oxide in the respiratory tract (which may inhibit replication of SARS-CoV-2 and its entry into cells). However, the authors note that 'smoking may worsen susceptibility and

prognosis in COVID-19, in a manner similar to other respiratory infections' and that 'claims of a protective effect must be viewed with extreme caution by both the general population as well as clinicians.'[88]

A discussion within one of the studies included in this review may shed light upon the anomaly. Williamson et al.[48] reported that both current and former smoking were associated with a higher risk in mortality in models that were adjusted for age and sex only, but in the fully adjusted model current smoking was associated with a lower risk (fully adjusted HR 0.89, 95%CI 0.82–0.97).[48] This was investigated in more depth post hoc by adding covariates individually to the age, sex and smoking model. The change in hazard ratio was driven largely by adjustment for chronic respiratory disease (aHR 0.98, 95%CI 0.90–1.06) after adjustment. This and other comorbidities could be consequences of smoking, highlighting that the fully adjusted smoking HR cannot be interpreted causally owing to the inclusion of factors that are likely to mediate smoking effects. A model adjusted for demographic factors only (age, sex, deprivation and ethnicity) showed a non-significant positive HR for current smoking (aHR 1.07, 95%CI 0.98–1.18); this does not support a protective effect of nicotine.[48]

Eleven studies included in this evidence summary reported that smoking was significantly associated with poor COVID-19 outcomes. Compared to 'past-smokers' or 'never-smokers', 'current smokers' had an increased risk of COVID-19 infection, with adjusted odds ratios ranging from (aOR 1.24, 95%CI 1.17-1.31) to (aOR 1.76, 95%CI 1.09-1.05). Compared to 'never-smokers' or 'non-smokers', 'smokers' or 'past-smokers' had a higher risk of hospitalisation from COVID-19; increased risks ranged from (aOR 1.09, 95%CI 1.01-1.18) to (aOR 2.91, 95%CI 2.04–4.12). Compared to 'non-smokers', 'current smokers' also had an increased risk of mortality, with effect estimates ranging from (aHR 1.13, 95%CI 1.08-1.18) to (aOR 3.37, 95%CI 1.06-10.73). These findings would suggest that smoking is associated with poorer COVID-19 outcomes. This was also concluded in a systematic review and meta-analysis of 47 studies conducted in August 2020.[89]

4.2.3 Vitamin D

Ten studies included in this evidence summary estimated the association between vitamin D status (25(OH)D concentration) and COVID-19 outcomes. Four studies reported no association between 25(OH)D concentration and COVID-19 outcomes, three studies reported that 25(OH)D deficiency was significantly associated with negative COVID-19 outcomes, and two studies reported a protective effect of habitual vitamin D supplement use and higher circulating 25(OH)D levels. Additionally, one study reported mixed findings between 25(OH)D concentration and increased risk of COVID-19 outcomes.

The debate over the potential role of vitamin D in mediating respiratory infections is long standing in the research literature; however, a consensus has not yet been reached. In 2017, Martineau et al., conducted a systematic review and meta-analysis of individual participant data from 10,933 participants in 25 RCTs.[90] The authors concluded that there was an overall protective effect of vitamin D supplementation against acute respiratory tract infections, that is, vitamin D reduced the risk of acute respiratory tract infection (aOR 0.88, 95% CI 0.81-0.96). The beneficial effects were greater in those receiving daily or weekly vitamin D (without additional bolus doses), and the protective effects against acute respiratory tract infections were strongest in those with severe vitamin D deficiency at baseline.[90] Conversely, in a systematic review and meta-analysis of 15 RCTs of individual patient data from 7,053 individuals published in 2016, no statistically significant association was observed between vitamin D supplementation and risk of acute respiratory tract infection (relative risk 0.94, 95% CI 0.88-1.00).[91]

Owing to its potential to bolster the immune response and attenuate excessive inflammation, such as that observed in severe COVID-19 patients,[92] the possible role of vitamin D in the prevention of COVID-19 has received increased attention in the research literature.

In December 2020,[93] the National Institute for Health and Care Excellence published a rapid review of vitamin D in COVID-19. In short, the review aimed to address the effectiveness of vitamin D for treatment of COVID-19, prevention of COVID-19 and determine if susceptibility to COVID-19 is associated with vitamin D status. The authors concluded that there was a lack of evidence to support the use of vitamin D for treatment and or prevention of COVID-19, as well as a lack of evidence supporting an association between vitamin D status and susceptibility to COVID-19.[93]

In Ireland, McCartney and Byrne[94] have recommended that certain groups (for example, those with darker skin, vegetarians and vegans, those who are overweight or obese) should be supplemented with vitamin D at a daily dose of 20-50mcg (for adults), regardless of vitamin D status. The authors also propose that this should be extended to the rest of the population to mitigate COVID-19 infection.[94] However, this proposition has been countered by McKenna and Flynn[95] who report that there is a lack of evidence to support such an intervention. The authors also reported that some studies that aimed to prevent fractures and falls have shown that high dose vitamin D resulted in an increased risk of fractures and falls. Furthermore, in a trial of high dose vitamin D in infants, the rate of repeat pneumonia was significantly higher in the vitamin D therapy group.[95] The Irish Longitudinal Study on Ageing consists of a nationally representative population-based sample. In April 2020, Laird

and Kenny[96] reported that almost 50% of frail, older people and 18% of those who are middle-aged, are vitamin D deficient during winter; during summer months these deficiencies fall to 31% and 9%, respectively.[96] The authors recommend that frail older people who are housebound and those who are middle-aged, should supplement with 20mcg and 10mcg of vitamin D during the winter months, respectively;[96] these recommendations are in line with those from the Food Safety Authority of Ireland.[97]

One of the cohort studies on vitamin D, included in this evidence summary, used data from the UK Biobank to prospectively investigate the association between regular use of vitamin D supplements and risk of COVID-19 infection, and determine whether such an association differed according to different levels of circulating and or genetically predicted vitamin D.[32] Vitamin D supplement use was collected through the baseline questionnaire (2006–2010).[32] Whilst a significant association was reported between regular vitamin D use and lower risk of COVID-19 infection, the authors note a number of important limitations.[32] Firstly, outcome data were collected between 16 March and 29 June 2020. At this time, testing for COVID-19 was largely restricted to those with symptoms and in hospital settings. As such, this may not be representative of the UK population. Secondly, data relating to regular use of vitamin D supplementation was collected a median of 10 years before outcomes were measured and therefore the results may reflect the association between "ever" use of vitamin D supplements and the risk of COVID-19 infection. It should also be noted that whilst confounding variables were adjusted for in the analysis, residual confounding may exist. For example, when compared to those who do not use vitamin D supplementation, those who do might also have a healthier lifestyle and be from a higher socio-economic level.[32]

At the time of writing, evidence for the role of vitamin D in prevention of COVID-19 is lacking, however we have identified five ongoing trials registered in trial databases, and there may indeed be others either unregistered or not yet registered.

4.2.4 Physical activity

Four studies reported mixed findings between physical activity and risk of COVID-19 outcomes, two studies reported that decreased physical activity was significantly associated with negative COVID-19 outcomes, one study reported a protective effective of physical activity. Exercise is known to have physical and mental benefits and the benefits of engaging in regular physical activity are widely acknowledged. Indeed, it has been shown that physical inactivity is responsible for 6-10% of the major non-communicable diseases, as defined by the United Nations, (that is, coronary heart disease, type 2 diabetes, breast cancer and colon cancer), and 9% of premature mortality.[98] Additionally, regular physical activity has been reported to

be associated with reduced risk of community-acquired infectious diseases,[99, 100] and an improved immune response.[101]

In a systematic review and meta-analysis (published in March 2021 by Chastin et al.), higher levels of habitual physical activity was associated with a 31% risk reduction of community-acquired infectious disease and 37% risk reduction of infectious disease mortality.[102] Such findings pose the question, "Is there an association between regular physical activity and better COVID-19 outcomes?" The studies included in the review by Chastin et al. were all conducted before 2020 and therefore the outcomes were not specific to COVID-19. Yet, the authors concluded that, "regular physical activity should be promoted in the general population to decrease the risk of community-acquired infection and infectious disease mortality, strengthen the potency of immunisation programmes and help lessen the impact of pandemics such as the recent COVID-19."[102] Such findings have been disseminated in the mainstream media and can mislead the public into thinking these results originated from populations with COVID-19.

4.2.5 Alcohol consumption

Our review found no association between alcohol consumption, heavy alcohol consumption or current or former alcoholism and being diagnosed with COVID-19 in studies based on UK Biobank data.[16, 21, 24] However, the included VA study reported a significant reduction in infection in those with alcohol use disorder. In this study, currently a pre-print, the authors note that factors which generally increase the risk of pneumonia (current smoking, COPD and alcohol use disorder), were associated with decreased probability of testing positive. However, the authors also note several limitations within this study.[40] At the time of data collection, only a small proportion of veterans had been tested (3,789 out of over 2 million veterans) and there was much variation in the rates of testing across various sites.[40] The VA population is noted to be highly skewed, comprising an older population which is predominantly male with a higher prevalence of heavy alcohol consumption, chronic disease and mental health conditions.[103]

Two studies based on UK Biobank data (Hamer et al.[21] and Lassale et al.[30]) reported that those who rarely and or never consume alcohol had a significantly increased risk of hospitalisation due to COVID-19. However, Hamer et al.[21] also reported that those who consumed alcohol above the recommended UK guidance (≥14 units for women and ≥21 units for men) are also associated with an increased risk of hospitalisation for COVID-19; this finding was not reported by Lassale et al.[30]

Only one study considered the association between developing severe COVID-19 and alcohol consumption, finding that those who were obese and were heavy

drinkers had an increased risk of developing severe COVID-19 and dying compared with non-drinkers.[16] Obese patients who reported consuming alcohol weekly (compared with those drinking none or infrequently) also had an increased risk of dying. These associations were absent in those who were not obese. This may indicate an as yet unidentified physiological interaction between COVID-19 and obese frequent drinkers.

Both the Health Service Executive (HSE)[104] and WHO[105] have issued warnings regarding excess consumption of alcohol, which, they state may occur as people try to cope with the stress of the pandemic, restrictions of movement and social interactions. The WHO document states that in 'no way will consumption of alcohol protect you from COVID-19 or prevent you from being infected by it' and goes on to consider the negative impacts,[105] while the HSE advice also notes the negative impact of alcohol on the immune system.[104]

4.2.6 Processed meat intake

One study reported no association between processed meat intake and risk of COVID-19 infection. This finding should be viewed with caution as it came from one study. Data used to inform this finding came from the UK Biobank and was collected at baseline between 2006 and 2010. However, nutritional habits may have changed during the follow-up period. Nevertheless, good nutrition is important for a healthy immune system; as such, food and nutrition insecurity may increase the risk of poor COVID-19 outcomes.[106] More studies are needed to evaluate this hypothesis.

4.3 Limitations

This review is subject to a number of important limitations. These relate to the type of review conducted ('rapid review'), which was limited by the time constraints associated with the review, and the biases considered likely to be present in the studies included in this review. For example, screening of titles, abstracts and full texts were done by one reviewer as well as data extraction and quality appraisal; although data extraction and quality appraisal were checked by a second reviewer. Of the 51 studies included in this review, ten studies were pre-prints[8] and had not been formally peer-reviewed. This raises additional concerns about the overall quality and the potential for results to change prior to formal publication. This review included five controlled trials of pharmacological interventions to prevent COVID-19.

[8] It has come to the attention of the evaluation team that one of the RCTs (Elgazzar et al.) detailed in this report has been removed from preprint publication following additional scrutiny of the reported data.

Evidence from the five controlled trials was deemed to be of 'low' or 'very low' certainty and not suitable for informing changes in policy.[9]

Of the 46 cohort studies on modifiable health-related risk factors, 18 used UK Biobank data. As such, these studies are subject to the inherent limitations of the UK Biobank dataset, it is also likely that there is considerable overlap in the populations included in the cohort studies that used UK Biobank data. Exposure data were collected at baseline between 2006 and 2010 therefore, participants' health and self-reported exposures (such as smoking, engagement in physical activity, alcohol consumption and processed meat intake) may have changed. The UK Biobank cohort is not representative of the general UK population, and is subject to self-selection bias. The response rate to the baseline survey was 5.5%; it may be the case that this self-selected cohort is healthier and have a higher education level relative to the general population. In the UK, COVID-19 testing was almost entirely limited to hospital settings until 18 May 2020; after this date testing was extended to the community. Some of the studies included in this review used data collected before 18 May 2020, therefore the COVID-19 outcomes came from hospital records and may only reflect patients with severe disease. Alternatively, some cases may only have been identified because the patients were hospitalised for other reasons. Although studies reported associations between exposures and COVID-19 outcomes, this does not infer causality due to the possibility of residual confounding.

Finally, this review does not consider socioeconomic factors as these are largely non-modifiable. Research shows that the COVID-19 pandemic has disproportionately affected those from lower socioeconomic positions; whether that is financially or through increased exposure to the virus through, for example, poor and or crowded housing conditions or occupation. Identification of those at risk of poorer outcomes requires access to high-quality, rigorous socioeconomic data; as yet, this is lacking.(107)

5.0 Conclusion

The aim of this evidence summary was to report the evidence on the effectiveness of pharmacological and non-pharmacological interventions in the community, prior to a diagnosis of COVID-19, to prevent COVID-19 or minimise progression to severe COVID-19. An additional aim was to determine the evidence of associations between modifiable health-related factors and the risk of COVID-19 or progression to severe

[9] It has come to the attention of the evaluation team that one of the RCTs (Elgazzar et al.) detailed in this report has been removed from preprint publication following additional scrutiny of the reported data.

COVID-19. At the time of writing, and in line with other international reviews, there is no high quality evidence to support the use of pharmacological interventions to prevent COVID-19. No eligible studies of non-pharmacological interventions were identified for inclusion in this evidence summary. As such, with the exception of the COVID-19 vaccination, the most effective measures for prevention of COVID-19 continue to be, social distancing, hand hygiene, cough etiquette, mask wearing and avoidance of places where COVID-19 spreads more readily such as confined and enclosed spaces. While there are mixed results reported from the included cohort studies, in general those who are overweight or obese, who smoke, who have inadequate levels of Vitamin D, are physically inactive and consume excessive amounts of alcohol are more likely to contract COVID-19 or have poorer outcomes. This information can be used to inform clinical decision making around risk reduction. In general, maintaining a healthy weight, not smoking, engaging in physical activity, moderating alcohol consumption, good nutrition and being Vitamin D sufficient have beneficial effects on general health and should continue to be encouraged.

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Appendix 1: Data extraction table for randomised controlled trials

Study characteristics	PICO	Patient demographics Clinical characteristics	Primary outcome results
Author: Chahla (pre-print) *Country:* Argentina *DOI:* 10.1101/2021.03.26.21254398 *Study design:* RCT *Setting:* Tucumán State Health System	*Population:* n=117 (intervention group) and n=117 (control group) healthcare workers and administration staff who were PCR negative at baseline *Intervention:* Ivermectin orally (12 mg every 7 days) and iota-carrageenan nasal spray 6 sprays per day for 4 weeks plus standard biosecurity care and PPE *Comparator:* Standard biosecurity care and PPE only *Outcomes:* ▪ COVID-19 symptoms ▪ COVID-19 diagnosis	*Intervention group:* mean age (±SD), 39.6 (±9.4) years; female, 65%. *Control group:* mean age (±SD), 38.4 (±7.4) years; female, 61%.	*COVID-19 symptoms* Intervention group: 4 patients (mild) Control group: 15 patients (mild); 7 patients (moderate); 3 patients (severe). *COVID-19 diagnosis* Intervention group, 4/117 (3.4%) versus control group 25/117 (21.4%); ($p=1.10^{-5}$) (OR 0.13, 95%CI 0.03-0.40) and (aOR 0.11, 95%CI 0.03-0.33); adjusted for comorbidity, age, sex and designation (healthcare versus no healthcare).
Author: Elgazzar (pre-print)[10] *Country:* Egypt *DOI:* 10.21203/rs.3.rs-100956/v1 *Study design:* RCT	*Population:* n=100 (intervention group) and n=100 (control group) healthcare or household contacts of patients diagnosed with mild, moderate or severe COVID-19 infection. *Intervention:* Ivermectin 400mcgs/kg single oral dose,	*Intervention:* mean age, N/R; male, N/R. *Control:* mean age, N/R; male, N/R.	*COVID-19 diagnosis* Intervention group, 2% versus control group 10%.

[10] It has come to the attention of the evaluation team that one of the RCTs (Elgazzar et al.) detailed in this report has been removed from preprint publication following additional scrutiny of the reported data.

Study characteristics	PICO	Patient demographics Clinical characteristics	Primary outcome results
Setting: Main study is in two COVID-19 isolation hospitals but the two groups of relevance to this evidence summary are healthcare or household contacts of patients.	repeated after one week in addition to PPE (Group V). *Comparator:* PPE only (Group VI) *Outcome:* ▪ COVID-19 diagnosis		
Author: Shoumann *Country:* Egypt *DOI:* 10.7860/JCDR/2021/46795.14529 *Study design:* RCT *Setting:* Community	*Population:* n=203 (intervention group) and n=101 (control group) asymptomatic household family members in close contact with cases of COVID-19. *Intervention:* Ivermectin weight adjusted dose was 15mg per day for those with a body weight 40-60kg, 18mg per day for those with a body weight 60-80kg and 24mg per day for those with a body weight >80kg. *Comparator:* No treatment. *Outcomes:* ▪ Symptomatic COVID-19 (not all PCR-confirmed)	*Intervention:* mean age, 40 years; male, 52.2%. *Control:* mean age, 38 years; male, 49.5%.	*Symptomatic COVID-19:* ▪ Intervention group: 15 (7.4%) overall 8 (53.3%) mild 6 (40%) moderate 1 (6.7%) severe ▪ Control group: 59 (58.4%) overall 31 (52.5%) mild 21 (35.6%) moderate 7 (11.9%) severe (OR 12.53, 95%CI 7.41-21.21) p<0.001 (aOR* 11.45, 95%CI 4.44-29.48) p<0.001 *Adjusted for index case severity, age, sex, any comorbidity.
Author: Cohen *Country:* US *DOI:* 10.1001/jama.2021.8828	*Population:* n=966 participants (666 staff and 300 residents) of 74 skilled nursing and assisted living facilities with at least one confirmed SARS-CoV-2 index case.	*Intervention group (residents):* median age (range), 76 (31-104) years; female, n (%): n=95 (59.0%).	*COVID-19 diagnosis (overall)** Intervention group, 8.5% versus control group 15.2%). (aOR 0.43, 95%CI 0.28-0.68); p<0.001. *COVID-19 diagnosis (residents)**

Study characteristics	PICO	Patient demographics Clinical characteristics	Primary outcome results
Study design: RCT *Setting:* Skilled nursing and assisted living facilities	*Intervention:* bamlanivimab, 4200mg as a single intravenous infusion. *Comparator:* placebo *Outcomes:* ▪ COVID-19 diagnosis	*Control group (residents):* median age (range), 75 (41-96) years; female, n (%): n=84 (60.4%). *Intervention group (staff):* median age (range), 43 (18-82) years; female, n (%): n=260 (80.5%). *Control group (staff):* median age (range), 42 (18-74) years; female, n (%): n=283 (82.5%).	Intervention group, 8.8% versus control group 22.5%). (aOR 0.20, 95%CI 0.08-0.49); p<0.001. *COVID-19 diagnosis (staff)** Intervention group, 8.4% versus control group 12.2%). (aOR 0.58, 95%CI 0.33-1.02); p=0.6. *Adjusted for facility, sex and role (resident or staff).

Key: ADE, adverse drug effects; aOR, adjusted odds ratio; CI, confidence intervals; HCW, healthcare worker; OR, odds ratio; PCR, polymerase chain reaction; PPE, personal protective equipment; RCT, randomised controlled trial.

Appendix 2: Data extraction table for non-randomised controlled trial

Study characteristics	PICO	Patient demographics Clinical characteristics	Primary outcome results
Author: Hector *Country:* Argentina *DOI:* 10.31546/2633-8653.1007 *Study design:* non-RCT *Setting:* Four hospitals (data were collected from 1 June until 1 August 2020)	*Population:* n=788 (intervention group) and n=407 (control group) asymptomatic HCWs with negative PCR or rapid tests, involved in care of COVID-19 patients. *Intervention:* four sprays of Carrageenan (1 spray 0.17g carrageenan) followed by 1 drop ivermectin (0.6mg/ml). This was repeated five times daily for 2 weeks. *Comparator:* PPE only *Outcomes:* ▪ COVID-19 diagnosis	*Intervention:* mean age, N/R; male, N/R. *Control:* mean age, N/R; male, N/R.	*COVID-19 diagnosis* Intervention group, 0% versus control group 58.2%.

Key: HCW, healthcare worker; non-RCT, non-randomised controlled trial; NR, not reported; PCR, polymerase chain reaction; PPE, personal protective equipment.

Appendix 3: GRADE assessment of the certainty of the body of evidence per outcome

Ivermectin (alone or in combination with carrageenan or iota carrageen nasal spray) versus placebo for prevention of COVID-19 infection

Certainty of evidence question	Response	Downgrade?
1. Are the study designs used appropriate?	Yes (3 RCTs[11] and 1 nRCT)	No
2. Are there important limitations in the research design or execution of the research?	Yes 2 RCTs were non-blinded, 1 RCT and 1 nRCT didn't report blinding. Confounders were not appropriately adjusted for or were not reported. The high protective efficacy detected for ivermectin caused the researcher to stop prematurely the non-intervention arm of one RCT.	Yes – 2 levels

[11] It has come to the attention of the evaluation team that one of the RCTs (Elgazzar et al.) detailed in this report has been removed from preprint publication following additional scrutiny of the reported data.

3. Are the results consistent across studies when the settings, populations, interventions, comparators, and outcomes are reasonably similar?	Yes	No
4. How directly do the results apply to the population (including setting), intervention, comparator, and outcomes (PICO) of interest?	They are not applicable – trials conducted in Egypt and Argentina and may not be applicable to Irish context.	Yes – 1 level
5. Are the results precise enough or likely due to chance?	They are not precise enough The RCTs were small (ranged from 200-234 participants) and the nRCT had 788 participants. The follow-up time was either short (ranged from two weeks to three months) or not reported by one RCT.	Yes – 2 levels
6. Is this all the research that has been conducted on the PICO question of interest?	Yes (database search supplemented by grey literature search and search for preprints)	No
7. Is there anything, in particular very large effects of an intervention, dose response gradients, or unfavourable scenarios still leading to convincing effect that makes us more confident?	No	No
Overall result: Very low certainty		

Key: nRCT, non-randomised controlled trial; RCT, randomised controlled trial.

Bamlanivimab versus placebo for the prevention of COVID-19 infection

Certainty of evidence question	Response	Downgrade?
1. Are the study designs used appropriate?	Yes (1 RCT)	No
2. Are there important limitations in the research design or execution of the research?	Yes Nasal swabs alone were obtained for subsequent SARS-CoV-2 detection during the evaluation and follow-up period. Use of nasal swabs for detection of SARS-CoV-2 may have lower sensitivity than nasopharyngeal swabs.	Yes – 1 level
3. Are the results consistent across studies when the settings, populations, interventions, comparators, and outcomes are reasonably similar?	NA	No
4. How directly do the results apply to the population (including setting), intervention, comparator, and outcomes (PICO) of interest?	They are applicable	No
5. Are the results precise enough or likely due to chance?	They are not precise enough. One RCT of n=966 followed for 24 weeks.	Yes – 1 level
6. Is this all the research that has been conducted on the PICO question of interest?	Yes (database search supplemented by grey literature search and search for preprints)	No

7. Is there anything, in particular very large effects of an intervention, dose response gradients, or unfavourable scenarios still leading to convincing effect that makes us more confident?	No	No
Overall result: Low certainty		

Key: RCT, randomised controlled trial.

Appendix 4: Planned or ongoing trials of interventions to prevent COVID-19

Trial/protocol number	Intervention	Trial status 14 April 2021*
NCT04383548	Anti-corona VS2 immunoglobulins prepared from COVID-19 convalescent plasma	Not yet recruiting
NCT04323800	Anti-SARS-CoV-2 plasma and SARS-CoV-2 non-immune plasma	Recruiting
NCT04452318	Anti-Spike SARS CoV-2 Monoclonal Antibodies	Recruiting
NCT04625972	AZD7442	Recruiting
NCT04369365	Azithromycin	Recruiting cancer patients
NCT04420260	Blockace (oropharyngeal spray)+ acecovid (active principle immunostimulant)	Not yet recruiting
NCT04405999	Bromhexine hydrochloride	Completed, no results posted
NCT04535791	Cholecalciferol	Recruiting
NCT04721535	Camostat mesilate DWJ1248	Not yet recruiting
NCT04584567	Doxycycline and zinc	Recruiting
NCT04405271	Emtricitabine/tenofovir alafenamide	Not yet recruiting
NCT04448119	Favipiravir	Recruiting
PACTR202005599385499	Folic acid	Not yet recruiting
ChiCTR2000031944	Herbal tea	Recruiting
CTRI/2020/05/025049	Homoeopatic arsenicum album	Not yet recruiting
NCT04348435	Hope biosciences allogeneic mesenchymal stem cell therapy (HB-adMSCs)	Enrolling by invitation
NCT04505098	Icosapent ethyl	Recruiting
NCT04460651	Icosapent ethyl	Recruiting
NCT04521322	Iota-Carrageenan	Recruiting
NCT04527211	Ivermectin	Not yet recruiting
JRCTs031200150	Kampo medicines	Not reported
NCT04427865	Lactoferrin	Not yet recruiting
IRCT20200503047280N1	Laris-teucrium polium L. and laris-hyssop	Ongoing
NCT04360122	Levamisole and isoprinosine	Not yet recruiting
NCT04328285	Lopinavir and ritonavir vs placebo arm one; hydroxychloroquine vs placebo arm two	Ongoing
NCT04321174	Lopinavir/ritonavir	Recruiting
NCT04364022	Lopinavir/ritonavir	Recruiting
EUCTR2020-001194-69	Mefloquine	Ongoing
EUCTR2020-001530-35	Melatonin	Ongoing
NCT04353128	Melatonin	Recruiting

Trial/protocol number	Intervention	Trial status 14 April 2021*
NCT04353518	Mycobacterium	Recruiting
NCT04583410	Nicotine patch	Recruiting
NCT04343248	Nitazoxanide	Recruiting
NCT04435314	Nitazoxanide	Not yet recruiting
NCT04359680	Nitazoxanide and vitamin super B complex	Ongoing
NCT04312243	Nitric oxide	Recruiting
NCT04337918	Nitric oxide	Completed, no results posted
NCT04344600	Peginterferon lambda-1a	Recruiting
NCT04364802	Povidone-iodine nasal spray	Recruiting
NCT04478019	Povidone-iodine nasal decolonization swab plus 0.12% CHG oral rinse	Recruiting
NCT04366180	Probiotic lactobacillus coryniformis K8	Recruiting
NCT04313023	Pul 042 inhalation solution	Recruiting
NCT04421391	QuadraMune™	Recruiting
NCT04377789	Quercetin	Completed, no results posted
NCT04320238	Recombinant human interferon alpha-1b and thymosin alpha 1	Recruiting
ChiCTR2000029602	SC09/ritonavir and lopinavir/ritonavir	Status unknown
NCT04534725	Selinexor or lenzilumab	Recruiting cancer patients
NCT04684550	Stabilized hypochlorous acid	Not yet recruiting
NCT04334928	Tenofovir disoproxil fumarate/emtricitabine and hydroxychloroquine	Recruiting
NCT04519125	Tenofovir/emtricitabine and personal protective equipment	Not yet recruiting
ChiCTR2000029518	Traditional Chinese medicine	Status unknown
ChiCTR2000029517	Traditional Chinese medicine	Recruiting
ChiCTR2000029435	Traditional Chinese medicine	Recruitment pending
ChiCTR2000029479	Traditional Chinese medicine	Completed, no results posted
NCT04483635	Vitamin D	Recruiting
NCT04334005	Vitamin D	Not yet recruiting
NCT04579640	Vitamin D	Not yet recruiting
NCT04476680	Vitamin D	Not yet recruiting
10.1016/j.cct.2020.106176**	Vitamin D	Not registered
CTRI/2020/05/025093	Yastimadhu	Not yet recruiting

*Trial status is reported as per trial registry on 28 April 2021; however, the registries may not be up-to-date; **Trial not registered, DOI provided instead.

Appendix 5: Data extraction table for cohort studies using UK Biobank data

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
Author: Aung *Country:* UK *DOI:* 10.3389/fgene.2020.586308 *Study design:* Cohort study *Setting:* UK Biobank (a population-based cohort study of over 500,000 individuals aged 40-69 years at the time of initial recruitment (2006-2010) *Data date range:* 16 March to 31 May 2020	*Participants:* n=1,211 European participants with lab confirmed SARS-CoV-2 and n=387,079 participants who were untested and or tested negative. *Mean age (±SD) at recruitment:* total population 56.6 years (±8.0); untested/negative 56.6 years (±8.0); positive 57.1 years (±9.2). *Male, n (%):* total population n=175,535 (45%); untested/negative n=174,895 (45%); n=positive 640 (53%).	*Exposure(s) measured:* obesity (per SD increment in BMI and WC) *Outcome results*:* In observational analyses, higher BMI and WC were associated with higher odds of SARS-CoV-2 positivity (aOR 1.13, 95% CI 1.07–1.20 and aOR 1.15, 95% CI 1.08–1.23) for 1 SD increment in BMI and WC, respectively. *Adjusted for age at recruitment, sex, multiple deprivation index, smoking history, pre-existing cardiovascular disease, respiratory disease, renal disease and dementia, previous malignancy, hypertension, dyslipidaemia and diabetes. *Author conclusions:* "We identified causal associations between BMI, LDL cholesterol and susceptibility to COVID-19. In particular, individuals in higher genetic risk categories were predisposed to SARS-CoV-2 infection. These findings support the integration of BMI into the risk assessment of COVID-19 and allude to a potential role of lipid modification in the prevention and treatment."
Author: Cho (pre-print) *Country:* UK *DOI:* 10.1101/2020.05.05.20092445 *Study design:* Cohort study *Setting:* UK Biobank (a population-based cohort study of	*Participants:* n=2,237 participants were tested for COVID-19 infection, of which n=908 (40.6%) tested positive. Those who had developed vascular, respiratory or neoplastic diseases by March 2020 were excluded. Not tested, n=322,341; tested, n=1,331; tested positive for COVID-19, n=538. *Mean age:* NR	*Exposure(s) measured:* Smoking, obesity (BMI<27kg/m^2; BMI 27-29kg/m^2; BMI≥30kg/m^2) *Outcome results*:* While the point estimate suggests that current smokers were more likely to test positive for COVID-19 than never smokers, this was not statistically significant (men's aOR 1.12, 95%CI 0.75-1.68; women's aOR 1.38, 95%CI 0.89-2.15). Former smoking was not associated with a positive test.

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
over 500,000 individuals aged 40-69 years at the time of initial recruitment (2006-2010) *Data date range:* 16 March to 26 April 2020	*Male, n (%):* Not tested, n=145,555 (45%); tested, n=676 (51%); tested positive for COVID-19, n=301 (56%).	Compared with a BMI<27, having a BMI of 27-29 among men was significantly associated with a positive test (aOR1.64, 95%CI 1.12-2.39), as was a BMI of ≥30 among men (aOR 1.60, 95%CI 1.10-2.35). No variables were significantly associated with a positive test in women. *Adjusted for age, smoking status, BMI, and self-reported diabetes or hypertension. *Author conclusions:* "Further examination of smoking as a risk factor for COVID 19 in other prospective studies is required. This must take into account not only reverse causality, where smokers quit to avoid disease, but also prior diseases and co-morbidities including obesity, diabetes and hypertension, as each is associated with COVID-19 hospitalisation or mortality."
Author: Darling (pre-print) *Country:* UK *DOI:* 10.1101/2020.04.29.20084277 *Study design:* Cohort study *Setting:* UK Biobank (a population-based cohort study of over 500,000 individuals aged 40-69 years at the time of initial recruitment (2006-2010) *Data date range:* NR	*Participants:* n=580 individuals who tested positive for COVID-19; n=723 individuals who tested negative. *Mean age (±SD):* positive cases, 57.5 (±8.7); negative controls, 57.9 (±8.7). *Male, n (%):* n=713 (55%).	*Exposure(s) measured:* obesity (assumption that normal weight is BMI<25kg/m^2; overweight is BMI 25-30kg/m^2; obese is BMI>30kg/m^2 as not stated in study), smoking, vitamin D (25(OH)D concentration) *Outcome results:* Being overweight (compared to normal weight/underweight) was significantly associated with an increased risk of a positive COVID-19 test (OR, 1.51, 95%CI 1.13-2.02). Being obese (compared to normal weight/underweight) was significantly associated with an increased risk of a positive COVID-19 test (OR, 1.67 95%CI 1.24-2.26). Being a regular smoker (compared to a non-smoker) was significantly associated with reduced risk of a positive COVID-19 test (OR 0.58, 95%CI 0.39-0.86).

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
		However a key limitation of this is that there were only a small number of regular smokers (n=142) in the sample and larger populations will be required to confirm these results. Being an occasional smoker was not associated with a reduced risk of positive test. Vitamin D status was not associated with an increased risk of a COVID-19 positive test. *Author conclusions:* "As the number of reported cases increases in the UK Biobank, we will expand our model to control for additional factors such as blood pressure, use of statin medications, diagnoses of cardiovascular disease, respiratory disease, diabetes, COVID-19-attributed mortality and conditions affecting immune function, as well as genetics."
Author: Fan (pre-print) *Country:* UK *DOI:* 10.1101/2020.11.25.20238915 *Study design:* Cohort study *Setting:* UK Biobank (a population-based cohort study of over 500,000 individuals aged 40-69 years at the time of initial recruitment (2006-2010) *Data date range:* 16 March to 27 July 2020	*Participants:* n=12,937 individuals aged 50-83 who were tested for COVID-19 (and had data relating to alcohol consumption and genotype) were included in the analysis. Of this, n=1,570 (12.1%) tested positive for COVID-19 and n=11,367 (87.9%) tested negative. *Mean age (±SD):* NR *Male, n (%):* NR	*Exposure(s) measured:* alcohol consumption Participants classed as heavy drinkers (>7 drinks per week for women; >14 drinks per week for men), moderate drinkers (4-7 drinks per week for women; 4-14 drinks per week for men), light drinkers (3 drinks or fewer per week), and never or infrequent drinkers (special occasions only or 1-3 times a month). Heavy, moderate and light drinkers also classed as "frequent drinkers" and those who never or infrequently drink were classed as "non-drinkers". *Outcome results*:* Alcohol and risk of SARS-CoV-2 infection Logistic regression analysis showed that alcohol consumption within the four-level categorical variable of drinkers, the binary variable (non-drinkers and frequent drinkers), and the continuous variable of weekly alcohol intake in frequent drinkers were not associated with the risk of SARS-CoV-2 infection.

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
		No association with increased risk of COVID-19 positive test, was detected in white participants either with or without obesity. In addition, there was no association between average weekly alcohol consumption and the risk of SARS-CoV-2 infection in either obese (aOR 1.07, 95%CI 0.92-1.23) or non-obese (aOR 0.96, 95%CI 0.86-1.06) individuals. <u>Alcohol and risk of death in COVID-19 positive participants</u> COVID-19 positive patients who were heavy drinkers with obesity had a higher risk of death (aHR 2.07, 95%CI 1.24-3.47). COVID-19 positive patients with obesity who reported consuming alcohol weekly were more likely to die compared with those drinking none or infrequently. Cox regression (aHR 1.57, 95%CI 1.01-2.42). While frequent drinking, and especially heavy drinking, was associated with higher risk of death in obese patients, there was no increased risk in non-obese patients. Higher alcohol consumption in frequent drinkers (who were also obese) resulted in higher risk of death when analysed by Cox regression (aHR 1.46, 95%CI 1.05-2.03) This association did not exist in non-obese participants with COVID-19. Kaplan–Meier survival plots illustrated that heavy drinkers with obesity had a higher mortality than non-drinkers (Log rank P=0.03), which was not observed in non-obese patients with COVID-19 (Log rank P=0.05). <u>Alcohol and risk of severe outcomes in COVID-19 positive participants</u>

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
		Heavy drinkers with obesity had a higher likelihood of admission to ICU and death compared to non-drinkers (aOR 2.43, 95%CI 1.35-4.40). *Matching factors for PSM included age, sex, BMI categories, current smoking status, alcohol related diseases, asthma, emphysema, COPD, bronchitis/bronchiectasis, esophagitis, gastritis/duodenitis, peptic ulcer, GERD, hypertensive, chronic ischemic heart disease, heart failure, diabetes, dementia, renal failure, liver cirrhosis and/or liver failure, tumor and AIDS. *Author conclusions:* "Alcohol consumption, especially heavy drinking, is associated with a higher risk of suffering worse COVID-19 clinical outcomes in patients with obesity through both traditional regression analyses and Mendelian randomization analyses. In addition, alcohol consumption was not associated with either increased or decreased risk of SARS-CoV2-2 infection. Our findings could help people understand the relationship between alcohol consumption and COVID-19, especially those who may drink excessively in the mistaken belief that alcohol consumption reduces the risk of SARS-CoV-2 infection. Moreover, due to the possible interactions between alcohol consumption and obesity in the progression of COVID-19, physicians may need to adjust and develop appropriate management and treatment strategies for COVID-19 positive patients who consume alcohol and are obese."
Author: Hamer *Country:* UK *DOI:* 10.1016%2Fj.bbi.2020.05.059	*Participants:* n=387,109 participants, of which 760 COVID-19 cases *Mean age (±SD):* 56.4 years ±8.8 *Female (%):* 55.1%	*Exposure(s) measured:* smoking, physical activity (assessed using the International Physical Activity Questionnaire short form that measures duration and frequency of moderate-to-vigorous physical activity (MVPA) in the last week. Meeting activity guidelines was defined as ≥150 min/week MVPA or ≥75 min/week vigorous physical activity), alcohol consumption (heavy alcohol intake was defined as ≥14 units

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
Study design: Cohort study *Setting:* UK Biobank (a population-based cohort study of over 500,000 individuals aged 40-69 years at the time of initial recruitment (2006-2010) *Data date range:* 16 March to 27 July 2020		in women and ≥21 units in men), obesity (healthy weight BMI<25kg/m^2; overweight BMI 25 – <30kg/m^2; obese ≥30kg/m^2) *Outcome results:* After adjustment for age, sex and mutually for each lifestyle factor, physical inactivity (aRR 1.32, 95%CI 1.10-1.58), smoking (aRR 1.42, 95%CI 1.12-1.79) and obesity (aRR 2.05, 95%CI 1.68-2.49) but not heavy alcohol consumption (aRR 1.12, 95%CI 0.93-1.35) were all related to COVID-19. Compared to never smoking, past and current smokers were at an increased risk of hospitalisation due to COVID-19*, (aRR 1.36, 95%CI 1.15-1.59 and aRR 1.36, 95%CI 1.08-1.71), respectively. Compared to sufficient physical activity, those who do insufficient activity were not at an increased risk of hospitalisation due to COVID-19*, (aRR 0.99, 95%CI 0.84-1.18), whereas those who did no physical activity were at an increased risk of hospitalisation due to COVID-19*, (aRR 1.38, 95%CI 1.15-1.64). Compared to those whose alcohol consumption was below the current guidance, those who rarely/never consumed alcohol and those who consumed alcohol above the current guidance were at increased risk of hospitalisation due to COVID-19*, (aRR 1.57, 95%CI 1.31-1.88 and aRR 1.24, 95%CI 1.03-1.50). Compared to those at a healthy weight, those who were overweight and obese had an increased risk of hospitalisation due to COVID-19*, (aRR 1.32, 95%CI 1.09-1.60 and aRR 1.97, 95%CI 1.61-2.42), respectively.

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
		*Adjusted for age, sex, education, ethnicity, diabetes, hypertension, cardiovascular disease (heart attack, angina, or stroke). *Author conclusions:* "In conclusion, these data suggest that adopting simple lifestyle changes could lower the risk of severe COVID-19 infection."
Author: Hastie (a) *Country:* UK *DOI:* 10.1016/j.dsx.2020.04.050 *Study design:* Cohort study *Setting:* UK Biobank (a population-based cohort study of over 500,000 individuals aged 40-69 years at the time of initial recruitment (2006-2010) *Data date range:* 5 March to 25 April 2020.	*Participants:* 2,724 COVID-19 tests were conducted on n=1,474 individuals. Complete data on 25(OH)D concentration and covariates were available for n=348,598 UK Biobank participants. Of these, n=449 had a positive COVID-19 test. *Median age (IQR) at assessment:* Non-COVID-19 group, 57 years (49–63); COVID-19 group, 58 years (49–64). *Male, n (%):* Non-COVID-19 group, n=168,391 (48.37%); COVID-19 group, 265 (59.02%).	*Exposure(s) measured:* Vitamin D (25(OH)D concentration), obesity (underweight, BMI<18.5 kg/m^2; normal weight, BMI 18.5–24.9 kg/m^2; overweight, BMI≥25–29.9 kg/m^2 and obese BMI≥30 kg/m^2), smoking *Outcome results:* Median 25(OH)D concentration measured at recruitment was lower in patients who subsequently had confirmed COVID-19 infection (28.7 (IQR 10.0–43.8) nmol/L) than other participants (32.7 (IQR 10.0–47.2) nmol/L). When analysed as a continuous variable, increased vitamin D concentration predicted lower risk of COVID-19 infection in the univariate analysis (OR 0.99, 95%CI 0.99–0.999), but not after adjustment for covariates* (aOR 1.00, 95%CI 0.998–1.01). When analysed as a categorical variable, vitamin D deficient (<25 nmol/L) and not deficient, vitamin D deficiency was associated with increased risk of COVID-19 (OR 1.37, 95%CI 1.07–1.76) but not when adjusted for covariates* (aOR 0.92, 95%CI 0.71–1.21). When analysed as a categorical variable, vitamin D insufficient was not associated with increased risk of COVID-19 (OR 1.19, 95%CI 0.99–1.44), nor when adjusted for covariates* (aOR 0.88, 95%CI 0.72–1.08).

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
		Being overweight (aOR 1.34, 95%CI 1.04–1.72) or obese (aOR 1.62, 95%CI 1.23–2.14) was associated with an increased risk of COVID-19 infection in the multivariable logistic regression. An independent association between smoking and COVID-19 was not found (aOR 0.93, 95%CI 0.69-1.25). *Adjusted for ethnicity, sex, month of assessment, Townsend deprivation quintile, household income, self-reported health rating, smoking status, BMI category, age at assessment, diabetes, SBP, DBP, and long-standing illness, disability or infirmity. *Author conclusions:* "Our analyses of UK Biobank data provided no evidence to support a potential role for 25 (OH)D concentration to explain susceptibility to COVID-19 infection either overall or in explaining differences between ethnic groups."
Author: Hastie (b) *Country:* UK *DOI:* 10.1007/s00394-020-02372-4 *Study design:* Cohort study *Setting:* UK Biobank (a population-based cohort study of over 500,000 individuals aged 40-69 years at the time of initial recruitment (2006-2010)	*Participants:* n=341,484 UK Biobank participants with data on 25(OH)D concentration and covariates were linked to Death Register data. In the sample, n=656 had confirmed COVID-19 and n=203 participants died due to COVID-19. *Mean age (±SD):* NR *Male, n (%):* NR	*Exposure(s) measured:* Vitamin D (25(OH)D concentration) *Outcome results:* When analysed as a continuous variable, increased vitamin D concentration predicted lower risk of COVID-19 mortality in the univariate analysis (HR 0.92, 95%CI 0.86–0.98), but not after adjustment for covariates* (aHR 0.98, 95%CI 0.91–1.06). When analysed as a categorical variable, vitamin D deficient (<25 nmol/L) and not deficient, vitamin D deficiency was associated with increased risk of COVID-19 mortality (HR 1.61, 95%CI 1.14–2.27) but not when adjusted for covariates* (aHR 1.21, 95%CI 0.83–1.76).

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
Data date range: 5 March and 25 April 2020		When analysed as a categorical variable, vitamin D insufficiency was not associated with increased risk of COVID-19 mortality (HR 1.29, 95%CI 0.97–1.72), nor when adjusted for covariates* (aHR 1.02, 95%CI 0.75–1.38). When analysed as a continuous variable, increased vitamin D concentration predicted a lower risk of inpatient COVID-19 infection in the univariate analysis (IRR 0.93, 95%CI 0.90–0.97), but not after adjustment for covariates* (aIRR 1.00, 95%CI 0.96–1.06). When analysed as a categorical variable, vitamin D deficiency was associated with an increased risk of inpatient COVID-19 infection (IRR 1.56, 95%CI 1.28–1.90) but not when adjusted for covariates* (aIRR 1.10, 95%CI 0.88–1.37). When analysed as a categorical variable, vitamin D insufficiency was associated with an increased risk of inpatient COVID-19 infection (IRR 1.33, 95%CI 1.14–1.56), but not when adjusted for covariates* (aIRR 1.06, 95%CI 0.89–1.26). *Adjusted for ethnicity, sex, month of assessment, Townsend deprivation quintile, household income, self-reported health rating, smoking status, BMI category, age at assessment, diabetes, SBP, DBP, and long-standing illness, disability or infirmity. *Author conclusions:* "For now, recommendations for vitamin D supplementation to lessen COVID-19 risks appear premature and, although they may cause little harm, they could provide false reassurance leading to changes in behaviour that increase risk of infections." Vitamin D insufficiency or deficiency was not independently associated with either COVID-19 infection or linked mortality.

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
Author: Ho *Country:* UK *DOI:* 10.1136/bmjopen-2020-040402 *Study design:* Cohort study *Setting:* UK Biobank (a population-based cohort study of over 500,000 individuals aged 37-73 years at the time of initial recruitment (2006-2010) *Data date range:* 16 March to 3 May 2020	*Participants:* complete data on covariates were available for n=235,928 participants. Of these participants, n=1,525 received at least one COVID-19 test, and n=518 had confirmed SARS-CoV-2 infection, with n=397 positive results conducted in hospital or A&E (primary outcome). *Age range:* age range of eligible participants was 49–83 years. *Male, n (%):* NR	*Exposure(s) measured:* smoking (self-reported), alcohol consumption (self-reported), obesity (assumption that normal weight is BMI<25kg/m^2; overweight is BMI 25-30kg/m^2; obese is BMI>30kg/m^2 as not stated in study), walking pace (self-reported). *Outcome results: (multivariable models)* Compared to not smoking, current/former smoking was associated with an increased risk of COVID-19 in Model 1, (aOR 1.45, 95%CI 1.19-1.79) and Model 2, (aOR 1.39, 95%CI 1.13-1.71). Compared to having never consumed alcohol, former alcohol consumers and current alcohol consumers did not have an increased risk of COVID-19 in Model 1, (aOR 0.90, 95%CI 0.49-1.65) and (aOR 0.65, 95%CI 0.43-1.00), respectively. Every 1 SD increased in BMI, was associated with an increased risk in COVID-19 in Model 1, (aOR 1.36, 95%CI 1.25-1.48) and Model 2, (aOR 1.28, 95%CI 1.16-1.40). Compared to being of normal weight, being overweight or obese was associated with an increased risk of COVID-19 in Model 1, (aOR 1.43, 95%CI 1.10-1.87) and (aOR 2.08, 95%CI 1.58-2.74), respectively. Compared to average walking pace, those who walked slowly had an increased risk of COVID-19 in Model 1, (aOR 1.99, 95%CI 1.48-2.68) and Model 2, (aOR 1.53, 95%CI 1.12-2.08); for those who walked briskly, there was no association with increased risk of COVID-19 in Model 1, (aOR 0.80, 95%CI 0.64-1.00) or Model 2, (aOR 0.95, 95%CI 0.75-1.20). Model 1: Adjusted for age, sex, ethnicity and deprivation index.

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
		Model 2: As for Model 1, and additionally adjusted for behavioural (smoking and alcohol drinking) and physical (adiposity, blood pressure, spirometry and physical capability) factors that were found to be significant in Model 1. PAFs were calculated to determine the relative contribution of each risk factor to the overall number of confirmed COVID-19 cases within UK Biobank. Smoking accounted for 14.9% of COVID-19 cases that occurred within the UK Biobank population, obesity accounted for 6.3% and slow walking pace accounted for 4.0%. In contrast, none of these factors were large contributors to pneumonia cases within UK Biobank. *Author conclusions:* "In conclusion, these data from UK Biobank suggest risk factors for confirmed COVID-19 infection differ in some important ways from risk factors for pneumonia, being more common in men than women, in lower SES, and with stronger associations with ethnicity, CV risk markers, prior smoking and adiposity. Such findings suggest possible merit in advocating improvements in lifestyle as an additional measure to reduce the risk of COVID-19 alongside existing public health measures such as social distancing and shielding of high risk groups. They also have implications for health advice targeted at the public to lessen risks during this pandemic."
Author: Lassale *Country:* UK *DOI:* 10.1016/j.bbi.2020.05.074 *Study design:* Cohort study *Setting:* UK Biobank (a population-based cohort study of	*Participants:* ethnicity data were available for n=428,494 participants. The main analytical sample comprised n=340,966 participants (640 COVID-19 cases) with complete data on the covariates included in this analysis. *Mean age:* 56.2 years *Female, n (%):* 235,528 (55%)	*Exposure(s) measured:* physical activity (UK guidance for physical activity ≥150min/week moderate-to-vigorous physical activity or ≥75 min/week vigorous activity), alcohol consumption (UK guidance <14 units for women and <21 units for men), smoking, obesity (per SD increment in BMI) *Outcome results:* Compared to those who met current UK guidance for physical activity, those who were active but did not meet the guidance did not have an increased risk of hospitalisation with COVID-

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
over 500,000 individuals aged 40-69 years at the time of initial recruitment (2006-2010) *Data date range:* 16 March to 26 April 2020		19, (aOR 0.93, 95%CI 0.77–1.13); those who were inactive had an increased risk of hospitalisation with COVID-19, (aOR 1.22, 95%CI 1.00–1.48). Compared to those whose alcohol consumption was within the current guidance, those who rarely and or never consumed alcohol had an increased risk of hospitalisation with COVID-19, (aOR 1.30, 95%CI 1.07–1.59); those whose alcohol intake was above the current guidance did not have an increased risk of hospitalisation with COVID-19, (aOR 1.10, 95%CI 0.90–1.34). Compared to those who had never smoked, those who were past-smokers had an increased risk of hospitalisation with COVID-19, (aOR 1.30, 95%CI 1.10–1.55); current smokers did not (aOR 1.25, 95%CI 0.96–1.62). Each 1 unit increase in BMI was associated with an increased risk of hospitalisation with COVID-19, (aOR 1.03, 95%CI 1.02–1.05) and each 0.1 unit increase in waist-to-hip ratio (WHR) (aOR 1.25, 95%CI 1.09–1.42), respectively. *Adjusted for age, sex, socioeconomic factors, lifestyle factors, co-morbidities and biomarkers. *Author conclusions:* "In England, the observed ethnic disparities in hospitalisation for COVID-19 was strong, in particular comparing Black and White individuals, and to a lower extent for Asian individuals too, and not fully explained by an extensive set of factors spanning socioeconomic, lifestyle and inflammatory disease disparities. If replicated, this has implications for health policy, including the targeting of prevention advice and vaccination coverage. Further research is needed to better understand the

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
		underlying mechanisms driving the racial/ethnic disparities in hospitalisation for COVID-19 observed in our study."
Author: Li *Country:* UK *DOI:* 10.14336/AD.2020.1108 *Study design:* Cohort study *Setting:* UK Biobank (a population-based cohort study of over 500,000 individuals aged 40-69 years at the time of initial recruitment (2006-2010) *Data date range:* 16 March to 31 May 2020.	*Participants:* the total sample included n=353,299 3,502, 1,082, and 714 cases of COVID-19 hospitalization, confirmed COVID-19, and severe COVID-19 were determined, respectively. *Mean age (±SD):* 67.7 years (±8.1) *Female, n (%):* n=192,001 (54.4%)	*Exposure(s) measured:* obesity (normal weight, BMI 18.5–24.9kg/m^2; overweight, BMI 25.0–29.9kg/m^2; obese, BMI ≥30.0 kg/m^2), vitamin D (25(OH)D concentration). Metabolically healthy determined by metabolic disorders, hypertension, hypercholesterolemia and diabetes. Exposure compared with metabolically healthy normal weight. *Outcome results:* After adjusting for confounders*, MHO participants had an increased risk of hospitalisation with COVID-19, testing positive with COVID-19 and developing severe COVID-19 disease, (aOR 1.28, 95%CI 1.13–1.46), (aOR 1.42, 95%CI 1.14–1.76) and (aOR 1.50, 95%CI 1.14–1.98), respectively. After adjusting for confounders*, MUHO participants had an increased risk of hospitalisation with COVID-19, testing positive with COVID-19 and developing severe COVID-19 disease, (aOR 1.96, 95%CI 1.75–2.19), (aOR 1.83, 95%CI 1.49–2.25) and (aOR 1.94, 95%CI 1.50–2.50), respectively. *Adjusted for sex, age, Townsend deprivation index, qualifications, employment, ethnicity and smoking status. After adjusting for confounders*, vitamin D insufficiency (<50nmol/L) was significantly associated with an increased risk of hospitalisation with COVID-19, testing positive with COVID-19 and developing severe COVID-19 disease, (aOR 1.21, 95%CI 1.13-1.30), (aOR 1.20, 95%CI 1.06-1.37) and (aOR 1.21, 95%CI 1.03-1.41), respectively.

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
		Adjusted for sex, age, Townsend deprivation index, qualifications, employment, ethnicity, smoking status and metabolic/obesity phenotypes. After adjusting for confounders, those who were MUHO and vitamin D deficient had the highest risk of COVID-19 hospitalisation, testing positive with COVID-19 and developing severe COVID-19, (aOR 2.46, 95%CI 2.05–2.94), (aOR 2.34, 95%CI 1.69–3.23) and (aOR 2.48, 95%CI 1.66-3.70), respectively. After adjusting for confounders*, those who were MUHO and vitamin D insufficient also had a high risk of COVID-19 hospitalisation, testing positive with COVID-19 and developing severe COVID-19, (aOR 2.33, 95%CI 2.02–2.70), (aOR 2.06, 95%CI 1.58–2.70) and (aOR 2.06, 95%CI 1.47-2.87), respectively. *Adjusted for sex, age, Townsend deprivation index, qualifications, employment, ethnicity and smoking status. *Author conclusions:* "In conclusion, metabolic/obesity phenotypes and vitamin D status are differentially associated with the development of COVID-19 in adults. In addition, obesity with a combination of metabolic disorders and vitamin D insufficiency could highly increase the risk of detection and severe illness from COVID-19. Such indicators might be useful in a primary care setting and in a hospital setting to assess the risk of a complicated course of disease in patients with a positive SARS-CoV-2 test. Additional research will help us confirm if these are risk factors for severe COVID-19 illness and determine whether other factors increase a person's risk."
Author: Ma	*Participants:* n=8,297 participants included in the final analysis. Analyses restricted to participants with	*Exposure(s) measured:* Use of vitamin D supplements was the primary exposure of interest. In the analysis, circulating

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
Country: UK *DOI:* 10.1093/ajcn/nqaa381 *Study design:* Cohort study *Setting:* UK Biobank (a population-based cohort study of over 500,000 individuals aged 40-69 years at the time of initial recruitment (2006-2010) *Data date range:* 16 March to 29 June 2020	records of COVID-19 test results from 22 assessment centres. Excluded participants with incomplete data on the use of vitamin D supplements, serum vitamin D, and cigarettes. Vitamin D users, n=363; non-users, n=7,934. *Mean age (±SD):* Vitamin D users, 59.1 years (±8.1); non-users, 57.4 years (±8.6) *Male, n (%):* Vitamin D users, n=141 (38.8%); non-users, n=3964 (50.0%).	vitamin D levels was categorised (in nmol/L) into 3 categories: <25 nmol/L (deficiency); 25–50 nmol/L (insufficiency); >50 nmol/L (sufficiency). Other exposures measured included: vitamin A, vitamin B, vitamin C, vitamin E, folic acid, a multivitamin, calcium, zinc, iron, selenium, glucosamine, or fish oil. *Outcome results:* In 8,297 participants who had records of COVID-19 test results, 16.6% (1378/8297) of the total population tested positive for SARS-CoV-2. In the unadjusted model, vitamin D users did not have a significantly lower risk of COVID-19 infection as compared with nonusers (OR 0.78, 95%CI, 0.57–1.05). After adjustment for covariates*, the habitual use of vitamin D supplements was significantly associated with a 34% lower risk of COVID-19 infection (aOR 0.66, 95%CI 0.45–0.97). *Adjusted for age group, sex, race, research centres, laboratory, origin (outpatient or inpatient), blood-type haplotype, years of education, Townsend deprivation index, smoking, moderate drinking, physical activity, healthy diet score, any other supplements, obesity, diabetes, hypertension, high cholesterol, cardiovascular diseases, cancer, asthma, and chronic obstructive pulmonary disease. Circulating vitamin D levels at baseline or genetically predicted vitamin D levels were not associated with the risk of COVID-19 infection. No significant association between the use of other individual supplements and the risk of COVID-19 infection was observed.

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
		Author conclusions: "The findings suggest that habitual use of vitamin D supplements is related to a lower risk of COVID-19 infection, although the possibility that the inverse association is due to residual confounding or selection bias cannot be ruled out."
Author: McQueenie *Country:* UK *DOI:* 10.1371/journal.pone.0238091 *Study design:* Cohort study *Setting:* UK Biobank (a population-based cohort study of over 500,000 individuals aged 37–73years at the time of initial recruitment (2006-2010) *Data date range:* 16 March to 18 May 2020	*Participants:* Data presented are from participants recruited from 16 assessment centres located in England only (5 participants with COVID-19 test data were excluded as they attended baseline assessment centres in Scotland or Wales). Participants who had died prior to the last available mortality register extraction (14 February 2018) were also excluded. This resulted in a final eligible study population of n=428,199 participants, of which n=1,324 tested positive for COVID-19. *Mean age (±SD):* NR Age at COVID test: Not tested/negative: 48-59y: 22.2% 60-69y: 32.8% 70-86y: 45.1% COVID positive: 48-59y: 28.8% 60-69y: 23.2% 70-86y: 48% *Male, n (%):* Not tested/COVID-19 test negative, n=192,368 (45.1%); COVID-19 positive, n=696 (52.6%).	*Exposure(s) measured:* smoking, physical activity (UK guidelines are 150 minutes/week moderate or 75 minutes/ week vigorous physical activity), obesity (severely obese ≥40kg/m^2) *Outcome results*:* In those who had no long term conditions (LTCs), when compared to those who never smoked, those who were current/previous smokers had an increased risk of a positive COVID-19 test, (aOR 1.26, 95%CI 1.02–1.57). In those who had no LTCs, when compared to those who engaged in physical activity ≥guidelines, those who did not meet physical activity guidelines had an increased risk of a positive COVID-19 test, (aOR 1.44, 95%CI 1.09–1.91). In those who had no LTCs, when compared to those who had a BMI<40, those who had a BMI≥40 did not have an increased risk of a positive COVID-19 test, (aOR 1.30, 95%CI 0.49–3.50). *Adjusted for sex, age, ethnicity, Townsend score, smoking status, alcohol intake frequency, physical activity, BMI, and assessment centre location. *Author conclusions:* "This study suggests that multimorbidity, cardiometabolic disease, and polypharmacy are associated with COVID-19. Those with multimorbidity who were also of non-white

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
		ethnicity, from the most socioeconomically deprived backgrounds, those who were severely obese, or who had reduced renal function, had more than twice the risk of COVID-19 infection. More work is required to develop risk stratification for COVID-19 in people with different patterns of multimorbidity in order to better define those individuals who would benefit from enhanced preventive measures in public, work, and residential spaces."
Author: Peters *Country:* UK *DOI:* 10.1111/dom.14199 *Study design:* Cohort study *Setting:* UK Biobank (a population-based cohort study of over 500,000 individuals aged 40-69 years at the time of initial recruitment (2006-2010) *Data date range:* up to 30 June 2020	*Participants:* n=502,493 participants, of which n=410 died of COVID-19. *Mean age (±SD):* NR *Female (%):* 54% women	*Exposure(s) measured:* obesity (per SD increment in BMI; overweight BMI ≥25 to <30kg/m²; obesity ≥30kg/m²) *Outcome results*:* A 1-SD higher BMI was associated with a stronger risk of COVID-19 mortality in women than men; (aHR 1.51, 95%CI 1.34-1.71) in women and (aHR 1.26, 95%CI 1.11-1.44) in men. The association of higher values of WHR with COVID-19 mortality was greater for men than women (aHR 1.34, 95%CI 1.23-1.47) in women and (aHR 1.57, 95%CI 1.37-1.79) in men. The risk of COVID-19 mortality was significantly associated with obesity in non-white women (aHR 8.55, 95%CI 4.02-18.19) but not in non-white men (aHR 1.51, 95%CI 0.68-3.36). *Adjusted for age, smoking status (never/ex/current), socio-economic status (determined using the Townsend index of area deprivation) and ethnicity (white or not). *Author conclusions:* "These results indicate that, if causal, obesity prevention strategies aimed at reducing the burden of several chronic diseases should also lead to better outcomes among both women and men affected by COVID-19. Furthermore, the striking similarity in most of the observed effects of adiposity

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
		on COVID-19 and the other two respiratory diseases considered, both in sex-specific and sex-comparative terms, suggests that obesity is likely to be a key driver of mortality in any future viral epidemic, particularly amongst women."
Author: Raisi-Estabragh *Country:* UK *DOI:* 10.3389/fcvm.2020.00138 *Study design:* Cohort study *Setting:* UK Biobank (a population-based cohort study of over 500,000 individuals aged 40-69 years at the time of initial recruitment (2006-2010) *Data date range:* 16 March to 14 June 2020	*Participants:* n=7,099 participants from the UK Biobank who had been tested for COVID-19 in hospital; of which n=1,439 participants tested positive. *Mean age (±SD) of those who were tested:* 69.11 years (±8.65) *Male, n (%) of those who were tested:* n=3,525 (49.7%)	*Exposure(s) measured:* obesity (per SD increment in BMI), smoking *Outcome results:* Every 5kg/m^2 increase in BMI, was associated within an increased risk of a positive COVID-19 test in Comparison 1, (aOR 1.19, 95%CI 1.13-1.25), Comparison 2, (aOR 1.09, 95%CI 1.03-1.16) and Comparison 3, (aOR 1.09, 95%CI 1.06-1.12). Compared to those who have never smoked, those who were current/past smokers had an increased risk of a positive COVID-19 test in Comparison 1, (aOR 1.26, 95%CI 1.13-1.40), and Comparison 3, (aOR 1.24, 95%CI 1.17-1.31). In Comparison 2, current/past smokers did not have an increased risk of a positive COVID-19 test compared to those who never smoked, (aOR 1.02, 95%CI 0.90-1.15) Comparison 1: COVID-19 positive (n=1,439) vs tested negative plus untested cohort (n=494,838). Comparison 2: COVID-19 positive (n=1,439) vs COVID-19 test negative (n=5,660). Comparison 3: COVID-19 test negative (n=5,660) vs untested population (n=494,838). *Author conclusions:* "This work highlights specific associations of BAME ethnicity, male sex, and higher BMI with COVID-19 positive status, which were independent of other demographic or cardiometabolic factors. More detailed characterization of these associations in larger and more diverse cohorts is

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
		warranted, particularly with regards ethnicity. Investigation of potential biological pathways underlying these observed associations may provide insight into the mechanisms by which SARS-CoV-2 causes disease, enabling more informed pursuit of potential therapeutic targets."
Author: Raisi-Estabragh *Country:* UK *DOI:* 10.1093/pubmed/fdaa095 *Study design:* Cohort study *Setting:* UK Biobank (a population-based cohort study of over 500,000 individuals aged 40-69 years at the time of initial recruitment (2006-2010) *Data date range:* 16 March to 18 May 2020	*Participants:* test results for n=4510 participants were available (positive, n=1,326; negative, n=3,184). *Mean age (±SD):* tested positive, 68.11 years (±9.23); tested negative, 68.91 years (±8.72). *Male, n (%):* tested positive, n=696 (52.5%); tested negative, n=1,505 (47.3%).	*Exposure(s) measured:* obesity (per SD increment in BMI), smoking (self-reported), vitamin D (25(OH)D concentration), processed meat consumption (g/day). *Outcome results:* Compared with those who have never smoked, current/past smokers did not have an increased risk of a positive COVID-19 test, (aOR 1.02, 95%CI 0.89-1.16)*. Every 1kg/m^2 increase in BMI was associated with an increased risk of a positive COVID-19 test, (aOR 1.02, 95%CI 1.01-1.03)*. *Adjusted for sex, age, ethnicity, smoking, BMI, diabetes, hypertension, high cholesterol, prior MI. In multivariate logistic regression models incorporating sex, age and ethnicity, there was no significant association between season-adjusted 25(OH)-vitamin D status and COVID-19 positivity, (aOR 1.00, 95%CI 1.00-1.00). In a separate model, adjustment for sex, age and ethnicity demonstrated no statistically significant association between processed meat consumption and COVID-19 status, (aOR 1.26, 95%CI 0.81-1.94). *Author conclusions:* "This study is consistent with growing reports of higher risk of severe COVID-19 in men and BAME populations. The augmented risk in BAME populations is non-uniform and

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
		disproportionately affects Black and Asian ethnicities. Higher BMI, greater material deprivation and household overcrowding are independent risk factors for COVID-19. The sex and ethnicity differential pattern of COVID-19 is not adequately explained by variations in cardiometabolic factors, 25(OH)-vitamin D levels, socio-economic or behavioural factors. However, factors which underlie ethnic differences in COVID-19 may not be easily captured. Investigation of alternative biological and genetic susceptibilities as well as more comprehensive assessment of the complex economic, social and behavioural differences is warranted."
Author: Rowlands *Country:* UK *DOI:* 10.1016/j.mayocp.2020.10.032 *Study design:* Cohort study *Setting:* UK Biobank (a population-based cohort study of over 500,000 individuals aged 40-69 years at the time of initial recruitment (2006-2010) *Data date range:* 16 March to 19 July 2020	*Participants:* Data from n=91,248 UK Biobank participants with accelerometer data and complete covariate and linked COVID-19 data, were included; n=207 individuals had a positive test, of which n=124 were classified as severe. *Median age (IQR):* positive cases, 64.9 years (56.2-73.4); negative cases, 68.1 years (61.0-73.2). *Female, n (%):* positive cases, n=103 (49.8%); negative cases, n=51,908 years (57.0%).	*Exposure(s) measured:* timing and balance of physical activity and rest/sleep. *Outcome results:* Overall physical activity level and moderate-to-vigorous physical activity (MVPA) were not significantly associated with increased risk of developing severe COVID-19*, (aOR 0.85, 95%CI 0.70-1.04) and (aOR 0.81, 95%CI 0.66-1.01), respectively; or an increased risk of testing positive for SARS-CoV-2** (aOR 0.93, 95%CI 0.79-1.09) and (aOR 1.00, 95%CI 0.84-1.18), respectively. *Adjusted for age, sex and ethnicity. **Adjusted for age, sex, ethnicity, Townsend Deprivation Index, number of people in household, fruit/vegetable consumption, red meat consumption, smoking status, alcohol intake, number of self-reported cancers & non-cancer illnesses and number of treatments/medications. A good balance between activity and sleep/rest was associated with lower risk of severe COVID-19* (aOR per SD: 0.71, 95%CI 0.62-0.81). This finding was related to higher daytime activity being associated with lower risk of severe COVID-19* (aOR 0.75, 95%CI 0.61-0.93) but higher

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
		movement during sleep/rest being associated with higher risk of severe COVID-19* (aOR 1.26, 95%CI 1.12-1.42). *Adjusted for age, sex, ethnicity and sleep duration. Greater variability in timing of sleep/rest was also associated with increased risk of severe infection* (aOR 1.21, 95%CI 1.08-1.35). A good balance between activity and sleep/rest was associated with decreased risk of testing positive for COVID-19* (aOR per SD: 0.86, 95%CI 0.75-0.98). Greater variability in timing of sleep/rest was also associated with increased risk of testing positive for COVID-19* (aOR 1.17, 95%CI 1.04-1.35). *Adjusted for age, sex, ethnicity, Townsend Deprivation Index, number of people in household, fruit/vegetable consumption, red meat consumption, smoking status, alcohol intake, number of self-reported cancers & non-cancer illnesses, number of treatments/medications and sleep duration. *Author conclusions:* "This report provides evidence of an association between markers of sleep/rest and physical activity and the risk or severity of COVID-19 infection. Public health studies could incorporate such measures to better identify and protect individuals at high risk of COVID-19 or cardiometabolic disease."
Author: Shi (pre-print) *Country:* UK	*Participants:* n=7,661 participants had been tested for COVID-19 by 17 June 2020; n=1,521 had a diagnosis for one or more of 44 different types of cancer, of which n=256 were COVID-19 positive.	*Exposure(s) measured:* obesity (per SD increment in BMI), smoking (self-reported) *Outcome results*:*

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
DOI: 10.1101/2020.07.10.20151076 *Study design:* Cohort study *Setting:* UK Biobank (a population-based cohort study of over 500,000 individuals aged 40-69 years at the time of initial recruitment (2006-2010) *Data date range:* up to 17 June 2020	*Mean age (±SD) of cancer patients:* 61.62 years (58.5-66.5) for those who tested negative; 61.36 years (56.5-67.5) for those who tested positive. *Male, n (%):* n=673 (53.2%) for those who tested negative; n=150 (58.59%) for those who tested positive.	In cancer patients, higher BMI was associated with increased likelihood of testing positive for COVID-19, (aOR 1.02, 95%CI 1.00-1.04) and an increased risk of mortality from COVID-19, (aOR 1.05, 95%CI 1.00-1.10); neither were significant. In cancer patients, smoking was associated with increased likelihood of testing positive for COVID-19, (aOR 1.32, 95%CI 1.00-1.74); this was not significant. Smoking was not associated with an increased risk of mortality from COVID-19, (aOR 0.86, 95%CI 0.44-1.65). *Adjusted for age and gender. *Author conclusions:* "We also showed that a subset of cancer patients is more likely to die of COVID-19 after the infection. These results, if confirmed, may provide guidance for COVID-19 prevention and treatment among cancer patients. Stronger personal protection should be made for cancer patients, and more intensive surveillance and/or treatment should be considered when cancer patients are infected with COVID-19."
Author: Zhang *Country:* UK *DOI:* 10.7189/jogh-10-020514 *Study design:* Cohort study *Setting:* UK Biobank (a population-based cohort study of over 500,000 individuals aged 40-69 years at the time of initial recruitment (2006-2010)	*Participants:* n=1,596 participants were COVID-19 positive, of which n=1,020 were inpatients and n=576 were outpatients. *Mean age (±SD):* COVID-19 positive, 68.8 years (±9.2); COVID-19 positive inpatients, 69.4 years (±8.9), COVID-19 positive outpatients, 66.0 years (±9.4). *Male, n (%):* COVID-19 positive, n=924 (52.9%); COVID-19 positive inpatients, n=570 (55.9%); COVID-19 positive outpatients, n=264 (45.8%).	*Exposure(s) measured:* physical activity (acceleration vector magnitude physical activity [AMPA] and moderate to vigorous physical activity [MVPA]), smoking status *Outcome results:* In the multivariate logistic regression models, AMPA was associated with decreased risk of contracting COVID-19* and attending as an outpatient with a COVID-19 related health concern*, (aOR per SD increase of AMPA 0.80, 95%CI 0.69-0.93) and (aOR per SD increase of AMPA 0.74, 95%CI 0.58-0.95), respectively. *Adjusted for age, gender and measures of body fatness.

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
Data date range: 16 March to 29 June 2020		When adjusted for age, gender, measures of body fatness and smoking status, AMPA was also associated with decreased risk of contracting COVID-19, aOR per SD increase of AMPA 0.81, 95%CI 0.69-0.96). Self-reported MVPA was not associated with increased risk of contracting COVID-19, being an inpatient with COVID-19, attending as an outpatient with COVID-19 related health concerns or COVID-19 related death. Compared with those who never smoked, previous smokers and current smokers had higher odds of contracting COVID-19 – (aOR 1.38, 95%CI 1.01 to 1.40) and (aOR 1.76, 95%CI 1.09 to 1.05) respectively, whereas exposure to smoking at home was not associated with increased risk. Compared with those who never smoked, previous smokers and current smokers had higher odds of being hospitalised from COVID-19, (aOR 1.57, 95%CI 1.04-2.36) and (aOR 1.95, 95%CI 1.03-3.69) respectively, whereas exposure to smoking at home was not associated with increased risk. Compared with those who never smoked, current smokers had higher odds of dying from COVID-19, (aOR 3.37, 95%CI 1.06-10.73) whereas previously smoking (aOR 1.93, 95%CI 0.91-4.12) was not associated with increased risk; nor was exposure to smoking at home. *Author conclusions:* "This study supports a protective effect of objectively measured physical activity on COVID-19 outcomes after adjusting for age, sex, measures of obesity, and smoking status. Associations tend to be observed in patients with relatively mild symptoms (outpatient COVID-19 and overall COVID-19 instead of inpatient COVID-19 and COVID-19

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
		death). These results suggest that physically active people may have a lower chance to be diagnosed with COVID-19 in general.”

Key: AMPA, acceleration vector magnitude physical activity; aHR, adjusted hazard ratio; aOR, adjusted odds ratio; aRR, adjusted relative risk; BMI, body mass index; HR, hazard ratio; LTC, long term condition; MHO, metabolically healthy obesity; MI, myocardial infarction; MUHO, metabolically unhealthy obesity; MVPA, self-reported moderate-to-vigorous physical activity; OR, odds ratio; PAF, population attributable fraction; PSM, propensity score matching; RR, relative risk; SD, standard deviation; WC, waist circumference; 25(OH)D, vitamin D.

Appendix 6: Data extraction table for cohort studies using non-UK Biobank data

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
Author: Abumayyaleh *Country:* Various countries *DOI:* 10.1016/j.orcp.2021.02.008 *Study design:* Retrospective cohort study *Setting:* HOPE-COVID-19 (Health Outcome predictive Evaluation for COVID-19, NCT04334291) is an international project. *Data date range:* up to 31 May 2020.	*Participants:* 3635 hospitalised COVID-19 patients in three groups of BMI: 1. BMI<25kg/m^2; n=1110 2. BMI 25-30kg/m^2; n=1464 3. BMI>30kg/m^2; n=1061 *Median age (IQR):* 63 years (IQR 18-99) *Male (%):* 58.2%	*Exposure(s) measured:* obesity (normal weight, BMI<25kg/m^2; overweight, BMI 25−30kg/m^2; BMI>30kg/m^2) *Outcome results:* Respiratory insufficiency compared with BMI 25-30kg/m^2 (OR's by multivariate logistic regression) ▪ BMI<25kg/m^2 OR 0.73 (95%CI 0.538 to 1.004) ▪ BMI>30kg/m^2 OR 1.12 (95%CI 0.847 to 1.503) Sepsis compared with BMI 25-30kg/m^2 (ORs by multivariate logistic regression) ▪ BMI<25kg/m^2 OR 0.93 (95%CI 0.607 to 1.454) ▪ BMI>30kg/m^2 OR 0.96 (95%CI 0.641 to 1.458) Mortality compared with BMI 25-30kg/m^2 (HRs by multivariate Cox regression) ▪ BMI<25kg/m^2 HR 1.15 (95%CI 0.889 to 1.508) ▪ BMI>30kg/m^2 HR 1.15 (95%CI 0.893 to 1.479) *Author conclusions:* Obesity was associated with a higher rate of respiratory insufficiency and sepsis but was not determined as an independent predictor for a high mortality.

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
Author: Bennett *Country:* Ireland *DOI:* 10.1016/j.lanepe.2021.100097 *Study design:* Population-based cohort study *Setting:* Data from the Health Protection Surveillance Centre in Ireland and included confirmed cases of COVID-19 *Data date range:* March to July 2020	Cohort 1: all cases (community and hospital); health outcome data included mortality and hospitalisation. Cohort 2: hospital admissions only; health outcome data included mortality and ICU admission. *Participants:* n=19,789 confirmed COVID-19 cases included; n=2,811 were hospitalised; n=438 were admitted to ICU; n=1,476 died. Among those who had been admitted to ICU, n=90 died. *Mean age:* NR *Male:* NR	*Exposure(s) measured:* obesity (defined as BMI ≥40kg/m^2). *Outcome results:* Cohort 1 (n=19,789) Compared to those with a BMI<40kg/m^2, those with a BMI ≥40kg/m^2 had an increased risk of mortality, (aOR* 2.48, 95%CI 1.59-3.87) and (aOR** 2.89, 95%CI 1.80-4.64). Compared to those with a BMI<40kg/m^2, those with a BMI ≥40kg/m^2 had an increased risk of hospitalisation, (aOR* 5.82, 95%CI 4.50-7.51) and (aOR** 4.29, 95%CI 3.27-5.65). Cohort 2 (n=2,811) Compared to those with a BMI<40kg/m^2, those with a BMI ≥40kg/m^2 had an increased risk of ICU admission, (aOR* 7.91, 95%CI 5.39-11.59) and (aOR** 7.53, 95%CI 4.94-11.48). Compared to those with a BMI<40kg/m^2, those with a BMI ≥40kg/m^2 had an increased risk of mortality, (aOR* 1.81, 95%CI 1.14-2.86) and (aOR** 2.19, 95%CI 1.34-3.56). *Adjusted OR, adjusted for age (linear, quadratic, cubic) **Adjusted OR, adjusted for age (linear, quadratic, cubic), chronic heart disease, chronic neurological disease, chronic respiratory disease, chronic kidney disease, chronic liver disease, asthma (requiring meds), immunodeficiency, diabetes, cancer, other comorbidity, unknown comorbidity, community health

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
		office, residential care facility and route of transmission. *Author conclusions:* "In conclusion, in a nationally representative sample of COVID-19 confirmed cases from Ireland, this study identified patient level underlying conditions associated with disease severity including mortality, hospitalisation, and ICU admission."
Author: Burn (pre-print) *Country:* Catalonia, Spain *DOI:* ; 10.1101/2020.07.13.20152454 *Study design:* Population-based cohort study *Setting:* All individuals registered on Information System for Research in Primary Care (SIDIAP). Includes primary care records of 80% of Catalan population. *Data date range:* 1 March to 6 May 2020	*Participants:* n=5,627,520, of whom n=109,367 had an outpatient diagnosis of COVID-19. *Median age (IQR):* general population, 44 years (25-60); those diagnosed with COVID-19, 47 years (36-61). *Female (%):* general population, n=2,859,274 (50.8%); those diagnosed with COVID-19, n=64,473 (59.0%).	*Exposure(s) measured:* Obesity (BMI between 30 and 60 kg/m^2, or a recorded weight between 120-200kg within 5 years of the index date). *Outcome results:* Transition from general population to diagnosis with COVID-19, overall*: (aHR 1.17, 95%CI 1.15-1.18) Male ≤70 years**: (aHR 1.14, 95%CI 1.11-1.17) Female ≤70 years**: (aHR 1.22, 95%CI 1.19-1.24) Male >70 years**: (aHR 0.97, 95%CI 0.92-1.02) Female >70 years**: (aHR 0.94, 95%CI 0.91-0.98) Transition from general population to hospitalised with COVID-19, overall*: (aHR 1.74, 95%CI 1.66-1.82) Male ≤70 years**: (aHR 1.85, 95%CI 1.69-2.02) Female ≤70 years**: (aHR 2.67, 95%CI 2.42-2.94) Male >70 years**: (aHR 1.33, 95%CI 1.22-1.44) Female >70 years**: (aHR 1.57, 95%CI 1.44-1.71) Transition from diagnosed with COVID-19 to hospitalised with COVID-19, overall*: (aHR 1.59, 95%CI 1.52-1.66) Male ≤70 years**: (aHR 1.44, 95%CI 1.34-1.55) Female ≤70 years**: (aHR 2.10, 95%CI 1.95-2.27) Male >70 years**: (aHR 1.20, 95%CI 1.08-1.33)

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
		Female >70 years**: (aHR 1.46, 95%CI 1.32-1.62) Transition from diagnosed with COVID-19 to death, overall*: (aHR 0.98, 95%CI 0.90-1.07) Male ≤70 years**: (aHR 1.13, 95%CI 0.80-1.59) Female ≤70 years**: (aHR 1.79, 95%CI 1.12-2.84) Male >70 years**: (aHR 0.91, 95%CI 0.79-1.06) Female >70 years**: (aHR 0.97, 95%CI 0.87-1.09) Transition from hospitalised with COVID-19 to death, overall*: (aHR 1.10, (95%CI 1.02 to 1.18) Male ≤70 years**: (aHR 1.62, 95%CI 1.31-2.01) Female ≤70 years**: (aHR 1.36, 95%CI 0.99-1.87) Male >70 years**: (aHR 1.01, 95%CI 0.90-1.14) Female >70 years**: (aHR 1.01, 95%CI 0.89-1.15) *Adjusted for age and gender **Adjusted for age *Author conclusions:* "The aim was not prediction, nor was it causal inference. In particular, it should be noted that associations between specific comorbidities and outcomes do not necessarily reflect a causal relationship. Assessing whether a particular chronic condition is the cause worse outcomes in COVID-19 will require further consideration of, and accounting for, relevant confounding factors."
Author: Carillo-Vega (pre-print) *Country:* Mexico *DOI:* 10.1101/2020.05.11.20098145	*Participants:* n=10,544 COVID-19 positive cases *Mean age (±SD):* 46.47 years (±15.62)	*Exposure(s) measured:* obesity (assumption is that obese is BMI>30kg/m^2 as not stated in study). *Outcome results*:* Hospitalisation: (aOR 1.64, 95%CI 1.37-1.95)

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
Study design: Cohort study *Setting:* Publically available data from the Epidemiological Surveillance System of Viral Diseases from the Mexican Ministry of Health. *Data date range:* up to 23 April 2020	*Male, n (%):* n=6,082 (57.68%)	Mortality: (aOR 1.74, 95%CI 1.35-2.26) *Covariates not reported. *Author conclusions:* "From individuals requiring hospitalisation 62% had comorbidities, primarily hypertension (34%), diabetes (30%), and obesity (25%). In fact, the presence of these three diseases in the same person increases 85% of the risk of hospitalisation. For mortality, a similar pattern can be observed. In individuals who died, hypertension was present in 44%, diabetes in 38%, and obesity in 30%. The risk of dying in individuals presenting the combination of these three diseases was 2.10 times the risk compared with those without these diseases."
Author: Denova-Gutiérrez *Country:* Mexico *DOI:* 10.1002/oby.22946 *Study design:* Cohort study *Setting:* National Epidemiological Surveillance System data (SINAVE) *Data date range:* 27 February to 10 April 2020	*Participants:* COVID-19 positive, n-3,844; COVID-19 negative, n=18,443. *Mean age:* COVID-19 positive, 45.4 years (±15.8); COVID-19 negative, 38.8 years (±17.5). *Male:* COVID-19 positive, 58%; COVID-19 negative 45.5%.	*Exposure(s) measured:* obesity (assumption is that obese is BMI>30kg/m^2 as not stated in study). *Outcome results:* Severe COVID-19 on admission Overall: Age-adjusted model, (OR 1.76, 95%CI 1.39-2.23); multivariate model*, (OR 1.43, 95%CI 1.11-1.83). Men: Age-adjusted model, (OR 2.25, 95%CI 1.55-3.25); multivariate model* (OR 1.75, 95%CI 1.15-2.57). Women: Age-adjusted model, (OR 1.52, 95%CI 1.12-2.08); multivariate model*, (OR 1.30, 95%CI 1.03-1.81).

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
		*Adjusted for age, sex, smoking status, history of chronic diseases (diabetes, hyper-tension, cardiovascular disease, chronic kidney disease, immunosuppression), place of care, USMER unit, date of symptom onset, and drug treatment. *Author conclusions:* "In conclusion, obesity, diabetes, and hypertension—important public health problems in Mexico—were significantly associated with severe COVID-19 on admission. In addition, the association of obesity was stronger in patients ≤50 years of age. As previously suggested, this pandemic has shown us that more must be done to combat and prevent obesity in our societies in order to reduce the burden of chronic diseases and adverse outcomes to viral pandemics. Finally, our data suggest the need for studies that evaluate the mechanisms associated with increased severity of COVID-19 in patients with obesity, as well as the need for prevention strategies for these patients."
Author: Fillmore *Country:* US *DOI:* 10.1093/jnci/djaa159 *Study design:* Cohort study *Setting:* Electronic records from US VA healthcare system Data date range: up to 4 May 2020	*Participants:* 22,914 cancer patients; n=1,794 (7.8%) COVID-19 positive. *Age*: <50 years, 6.7%; 50-59 years, 10.9%; 60-64 years, 11.7%; 65-69 years, 14.6%; 70-79 years, 38%; ≥80 years 18.0%. *Male:* NR	*Exposure(s) measured:* smoking status *Outcome results:* Prevalence of COVID-19 infection: Lower in current smokers compared with former smokers or those who never smoked (5.3% vs 9.5%; p<.001). COVID-19 attributable mortality: Lower in current smokers compared with former smokers or those who never smoked (6.5% vs 12%; p=.002). *Author conclusions:*

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
		"In conclusion, the presence of cancer changes the susceptibility to COVID-19 infection and affects overall outcome. The overall disease behaviour is modulated by both patient-related and cancer-related factors, which needs to be considered in development of COVID-19 preventative strategies as well as modulation of cancer therapies to optimize the patient care. Importantly, having equal access to care is an important component to improving overall outcome."
Author: Fresán *Country:* Spain *DOI:* 10.1002/oby.23029 *Study design:* Population-based cohort study *Setting:* Navarra Health Services electronic data *Data date range:* March and April 2020	*Participants:* n=433,995, of these n=7,460 had class 3 obesity (defined as BMI ≥40 kg/m^2). *Age:* Range 25 to 79 years *Male:* in those with class 3 obesity, 38.6%; in those without class 3 obesity, 50.1%.	*Exposure(s) measured:* class 3 obesity (BMI≥40kg/m^2) *Outcome results*:* Risk of COVID-19 hospitalisation in total study population: (aRR 2.20, 95%CI 1.66-2.93). Age 25-49 years: (aRR 5.02, 95%CI 3.19-7.90). Age 50-64 years: (aRR 1.87, 95%CI 1.12-3.12). Age 65-79 years: (aRR 1.22, 95%CI 0.70-2.12). Risk of severe COVID-19 (admission to ICU or death) in total study population: (aRR 2.30, 95%CI 1.20-4.40). Age 25-49 years: (aRR 13.80, 95%CI 3.11-61.17). Age 50-64 years: (aRR 2.07, 95%CI 0.62-6.85). Age 65-79 years: (aRR 1.42, 95%CI 0.52-3.88). *Adjusted for sociodemographic characteristics: sex, age, country of origin, municipality size and annual taxable income level, health-related characteristics: primary health care visits in prior 12 months, hospitalisation in prior 12 months, smoking status, hypertension, and major chronic conditions. *Author conclusions:*

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
		"Our findings highlight that class 3 obesity is an independent and relevant risk factor for COVID-19 hospitalization and severe disease in the population. Class 3 obesity is associated with an increased risk for hospitalization and severe COVID-19 in young adults. Although the risk of severe obesity remains similar in older adults, the excess risk diminishes and disappears with aging, suggesting that the role of severe obesity in young people could have a magnitude similar to that of aging in the general population. Therefore, young people with class 3 obesity should be recognized as a population at risk of severe COVID-19, and they should be considered in preventive protocols and clinical guidelines for groups at high risk. In addition, further policies should be carried out to tackle the obesity pandemic in our society, which could have benefits for fighting both noncommunicable and infectious disease."
Author: Garassino *Country:* Eight countries (Italy, Spain, France, Switzerland, Netherlands, US, UK and China) from The Thoracic Cancers International COVID-19 Collaboration (TERAVOLT) global consortium. The aim of which is to characterise the effect of SARS-CoV2 infection on patients with thoracic cancers. *DOI:* 10.1016/S1470-2045(20)30314-4 *Study design:* Registry-based cohort study with two components:	*Participants:* n=200; n=152 hospitalised, 48 not hospitalised. *Age:* <50 years, 6%; 50-65 years, 33%; >65 years, 61%. *Male n, (%):* n=141, (70%).	*Exposure(s) measured:* smoking status *Outcome results:* Death: Current or former smoker vs. never smoked, (aOR* 3.18, 95%CI 1.11-9.06). *Covariates not reported. *Author conclusions:* "In multivariable analysis, only smoking habits maintained a significant association with death. Comorbidities such as hypertension or ischaemic heart disease, which are associated with increased risk of death in the general population, did not appear to be predictors for poor outcomes in our patient population. The question as to whether smoking exacerbated the

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
▪ a cross-sectional component describing patient/disease characteristics for cancer and COVID-19 ▪ a longitudinal component describing association between potential prognostic factors and outcomes. *Setting:* TERAVOLT registry. *Data date range:* 26 March to 12 April 2020		effect of other clinically associated variables (such as COPD and other comorbidities) or there is a net effect of smoking merits further investigation. However, these are preliminary data and we acknowledge that more events are needed to observe and confirm effects."
Author: Gianfrancesco *Country:* Global registry from 40 countries *DOI:* 10.1136/annrheumdis-2020-217871 *Study design:* Cohort study *Setting:* Global Rheumatology Alliance Registry data collected 24 March 2020 to 20 April 2020. *Data date range:* up to 20 April 2020	*Participants:* n=600 participants with rheumatic disease and COVID-19. *Median age (IQR):* 56 years (45-67). *Female, n (%):* n=423, (71%).	*Exposure(s) measured:* smoking status *Outcome results*:* Hospitalisation: Ever smoker vs never smoker, (OR 1.41, 95%CI 1.13-1.77); (aOR 1.18, 95%CI 0.90-1.53). *Adjusted for age group (<65 years vs >65 years), sex, rheumatic disease, systemic lupus erythematosus, psoriatic arthritis, axial spondyloarthritis or other spondyloarthritis, vasculitis, hypertension, lung disease, diabetes, cardiovascular disease, chronic renal insufficiency/end-stage renal disease, physician-reported disease activity (remission, minimal/low disease activity, moderate disease activity or severe/high disease activity), DMARD type, NSAIDs and prednisone-equivalent glucocorticoid use. *Author conclusions:* "Use of DMARDs did not increase the odds of hospitalisation. As in the general population, people with rheumatic diseases who are older and/or have comorbidities have a higher odds of COVID-19-related hospitalisation. Anti-TNF treatment was associated with

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
		reduced odds of hospitalisation while prednisone use ≥10 mg/day was associated with a higher odds of hospitalisation. There was no difference in antimalarials, such as hydroxychloroquine, or NSAID use between those who were or were not hospitalised."
Author: Holman *Country:* England *DOI:* 10.1016/S2213-8587(20)30271-0 *Study design:* Population-based cohort study *Setting:* National dataset linked with national civil death registrations (includes 98% GP practices in England). *Data date range:* 1 March to 11 May 2020	*Participants:* T1D, n=264,390; T2D, n=2,874,020. *Mean age:* T1D: <40 years, 38.1%; 40-49 years, 15.8%; 50-59 years, 18.6%; 60-69 years, 13.7%; 70-79 years, 9.2%; ≥80 years, 4.6%. T2D: <40 years, 2.4%; 40-49 years, 7.4%; 50-59 years, 18.1%; 60-69 years, 25.2%; 70-79 years, 26.8%; ≥80 years 20.1%. *Male n, (%):* T1D n=149,680 (56.6%); T2D n=1,606,430 (55.9%).	*Exposure(s) measured:* obesity (BMI categories <20, 20-24.9, 25-29.9, 30-34.9, 35-39.9, ≥40.0 kg/m^2) smoking status. *Outcome results:* COVID-19 related death, compared with T1D and BMI 25.0-29.9 kg/m^2*: T1D with a BMI <20 kg/m^2, (aHR 2.45, 95%CI 1.60-3.75) T1D with a BMI of 20-24.9 kg/m^2, (aHR 1.51, 95%CI 1.51-1.98) T1D with a BMI of 30-34.9 kg/m^2, (aHR 1.47, 95%CI 1.12-1.94) T1D with a BMI of 35-39.9 kg/m^2, (aHR 1.72, 95%CI 1.21-2.46) T1D with a BMI of ≥40.0 kg/m^2, (aHR 2.33, 95%CI 1.53-3.56) COVID-19 related death, compared with T2D and BMI 25.0-29.9 kg/m^2*: T2D with a BMI <20 kg/m^2, (aHR 2.33, 95%CI 2.11-2.56) T2D with a BMI of 20-24.9 kg/m^2, (aHR 1.34, 95%CI 1.27-1.42) T2D with BMI 30-34.9 kg/m^2, (aHR 1.04, 95%CI 0.98-1.10) T2D with a BMI of 35-39.9 kg/m^2, (aHR 1.17, 95%CI 1.08-1.26)

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
		T2D with BMI ≥40.0 kg/m^2, (aHR 1.60, 95%CI 1.47-1.75) COVID-19 related death, compared with T1D never smokers**: T1D current smokers, (aHR 0.88, 95%CI 0.62-1.25) T1D ex-smokers, (aHR 1.09, 95%CI 0.89-1.35) COVID-19 related death, compared with T2D never smokers**: T2D current smokers, (aHR 0.67, 95%CI 0.62-0.74) T2D ex-smokers, (aHR 1.13, 95%CI 1.08-1.18) *Adjusted for demographic characteristics (age, sex, socioeconomic deprivation, ethnicity, and region of residence), clinical characteristics (HbA1c, duration of diagnosed diabetes, systolic blood pressure, prescription for antihypertensive drugs, serum total cholesterol, prescription for statins, and smoking status), and history of cardiovascular or renal comorbidities (history of myocardial infarction, stroke, heart failure, and eGFR). **Adjusted for demographic characteristics (age, sex, socioeconomic deprivation, ethnicity, and region of residence), clinical characteristics (HbA1c, duration of diagnosed diabetes, BMI, systolic blood pressure, prescription for antihypertensive drugs, serum total cholesterol and prescription for statins), and history of cardiovascular or renal comorbidities (history of myocardial infarction, stroke, heart failure, and eGFR). *Author conclusions:*

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
		"BMI and COVID-19 related mortality was U-shaped. The higher risk seen in people with lower BMI might reflect confounding by factors that are associated with weight loss either not included in our analysis or for which we have only imperfectly adjusted. Although the association with obesity was more complex, particularly in the T2D population, bodyweight can also be affected by healthcare interventions. Improved achievement of standard diabetes care recommendations that target prevention of cardiovascular and microvascular complications would also serve to modify some of the risk factors that we have shown to be associated with COVID-19-related mortality. Current tobacco smoking, compared with having never smoked, was associated with a lower risk of COVID-19-related mortality in people with type 2 diabetes. This finding was seen across all BMI categories and all ethnicities. It is the reverse of what was found in non-COVID-19-related mortality over the same time period. Being an ex-smoker was associated with an increased risk of both COVID-19-related and non-COVID-19-related mortality. Another English population based study has reported similar associations with tobacco smoking. The unexpected finding with regard to current smoking status should not be taken to imply that tobacco smoking is protective of COVID-19 and might be the result of confounding by as yet unidentified factors or collider bias. Other studies have shown that, among people with diagnosed COVID-19, smokers have poorer outcomes. The need for more research into smoking and COVID-19 is indicated. Meanwhile, it should be emphasised that tobacco smoking increases the risk of non-communicable

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
		diseases, including cardiovascular and respiratory diseases, which are themselves risk factors for poor COVID-19 outcomes."
Author: Ioannou *Country:* US *DOI:* 10.1001/jamanetworkopen.2020.22310 *Study design:* Longitudinal cohort study *Setting:* VA electronic health records *Data date range:* 28 February to 14 May 2020, (follow-up to 20 June 2020)	*Participants:* n=88,747 veterans tested for COVID-19, of which n=10,131 were COVID-19 positive. *Age:* 18-49 years, 19.5%; 50-64 years, 28.8%; 65-79 years, 36.8%; ≥80 years 15.0%. *Male, n (%):* n=9,221 (91%).	*Exposure(s) measured:* obesity (BMI categories underweight, <18.5; normal weight, 18.5-24.9; overweight, 25-29.9; obesity I, 30-34.9; obesity II or III, ≥3), smoking status. *Outcome results:* Hospitalisation at the index date: Current vs never smoker*, (aHR 1.10, 95%CI 0.98-1.25) Former vs never smoker*, (aHR 1.01, 95%CI 0.94-1.10) BMI <18.5 vs BMI 18.5-24.9**, (aHR 1.19, 95%CI 1.00-1.42) BMI 25.0-29.9 vs BMI 18.5-24.9**, (aHR 0.84, 95%CI 0.77-0.93) BMI 30.0-34.9 vs BMI 18.5-24.9**, (aHR 0.80, 95%CI 0.72-0.98) BMI ≥35 vs 18.5-24.9**, (aHR 0.87, 95%CI 0.77-0.98) Mechanical ventilation at the index date: Current vs never smoker*, (aHR 0.94, 95%CI 0.69-1.28) Former vs never smoker*, (aHR 1.02, 95%CI 0.85-1.22) BMI <18.5 vs 18.5-24.9**, (aHR 0.90, 95%CI 0.56-1.46) BMI 25.0-29.9 vs 18.5-24.9**, (aHR 1.04, 95%CI 0.82-1.31) BMI 30.0-34.9 vs 18.5-24.9**, (aHR 1.03, 95%CI 0.80-1.33)

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
		BMI ≥35 vs 18.5-24.9**, (aHR 1.22, 95%CI 0.93-1.61) *Adjusted for age, sex, race, ethnicity, urban vs rural, BMI, diabetes, cancer, hypertension, coronary artery disease, congestive heart failure, cerebrovascular disease, dialysis, chronic kidney disease, cirrhosis, asthma, COPD, obstructive sleep apnoea, alcohol dependence, hyperlipidaemia, CCI. **Adjusted for age, sex, race, ethnicity, urban vs rural, smoking status, diabetes, cancer, hypertension, coronary artery disease, congestive heart failure, cerebrovascular disease, dialysis, chronic kidney disease, cirrhosis, asthma, COPD, obstructive sleep apnoea, alcohol dependence, hyperlipidaemia, CCI. *Author conclusions:* "Obesity and smoking were not significantly associated with mortality."
Author: Israel (pre-print) *Country:* Israel *DOI:* 10.1101/2020.06.01.20118877 *Study design:* Cohort study *Setting:* over 3,000,000 adult members of Clalit Health Services, the largest health provider in Israel. *Data date range:* up to 3 June 2020	*Participants:* n=128,427 participants with documented smoking status, underwent RT-PCR tests for SARS-CoV-2, n=4,235 (3.3%) of whom tested positive. For this study, cases and control within the population were matched in a 1:5 ratio to individuals tested negative, of the same sex, age, and ethnicity/religion. COVID-19 positive cases, n=4,151; COVID-1 negative controls, n=20,755. *Median age (IQR):* COVID-19 positive cases, 39.54 years (27.38-58.26); COVID-19 negative controls, 39.65 years (27.55-58.67).	*Exposure(s) measured:* smoking, obesity (defined by diagnosis in electronic medical record or last measured BMI>30kg/m^2). *Outcome results*:* Compared to those who never smoked, those who were current smokers, and those who were past smokers were at a reduced risk of COVID-19 infection, (aOR 0.45, 95%CI 0.41-0.51) and (aOR 0.77, 95%CI 0.69-0.86), respectively. Those who were obese had an increased risk of COVID-19 infection, (aOR1.17, 95%CI 1.08-1.27).

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
	Female, n (%): COVID-19 positive cases, n=1,998 (48.1%); COVID-19 negative controls, n=9,990 (48.1%). Male, n (%): COVID-19 positive cases, n=2,153 (51.9%); COVID-19 negative controls, n=10,765 (51.9%).	In those who tested positive for COVID-19, those who were current smokers, and those who were past smokers had a reduced risk of severe COVID-19, (aOR 0.59 95%CI 0.27-1.30) and (aOR 1.11, 95%CI 0.73-1.69), respectively. In those who tested positive for COVID-19, those who were obese did not have an increased risk of severe COVID-19, (aOR 1.13, 95%CI 0.79-1.62). *Adjusted for age, gender, ethnicity, COPD, asthma, hypertension, obesity, reported arrhythmia, peripheral vascular disease, ischemic heart disease and malignancy *Author conclusions:* "Acknowledging the destructive effects of smoking on health, the importance of smoking prevention and cessation to preserve health, and the highly addictive nature of nicotine, we strongly encourage all patients to refrain from smoking, as the long term effects of this hazardous habit far outweigh potential benefits in preventing SARS-CoV-2 infection. Nevertheless, the strong negative association demonstrated in this study between smoking and COVID-19 incidence may offer promising new directions for fighting this disease, based on a better understanding of the mechanisms by which smoking reduces the risk of SARS-CoV-2 infection."
Author: Katz *Country:* US *DOI:* 10.1016/j.nut.2020.111106	*Participants:* N=987,849 patients, of whom n=887 were positively diagnosed with COVID-19; 950 were diagnosed with vitamin D deficiency, and n=87 had both COVID-19 and vitamin D deficiency.	*Exposure(s) measured:* Vitamin D deficiency (defined by International classification of diseases-10 diagnosis codes).

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
Study design: Cohort study *Setting:* i2b2 patients' registry platform at the University of Florida Data date range: up to 30 June 2020	*Median age (IQR):* In those with COVID-19 <18 years 4%; 18-44 3.5%; 45-65 23.5%; >65 19.7%. In those with Vit D deficiency <18 years 3.4%; 18-44 26.5%; 45-65 31.9%; >65 38.2%. In those with COVID-19 and Vit D deficiency <18 years 2%; 18-44 31.3%; 45-65 37.4%; >65 29.3%. In those hospitalised <18 years 16%; 18-44 31.2%; 45-65 26.5%; >65 26.4%. *Female (%):* In those with COVID-19, 43.6%. In those with Vit D deficiency, 30.3%. In those with COVID-19 and Vit D deficiency, 28.7%. In those hospitalised, 53.9%.	*Outcome results:* Likelihood of COVID-19 infection in those with vitamin D deficiency compared with patients with no deficiency: 1. unadjusted (OR 4.6, 95%CI 3.71-5.78) 2. adjusted for sex (aOR 4.58, 95%CI 3.67-5.73) 3. adjusted for malabsorption (aOR 4.46, 95%CI 3.55-5.60) 4. adjusted for periapical abscesses (aOR 3.92, 95%CI 3.16-4.86) 5. adjusted for dental caries (aOR 3.76, 95%CI 3.03-4.69) 6. adjusted for race (aOR 3.76, 95%CI 2.98-4.55) 7. adjusted for diabetes (aOR 3.28, 95%CI 2.59-4.15) 8. adjusted for sex and obesity (aOR 2.27, 95%CI 1.79-2.87) 9. adjusted for age (aOR 5.16, 95%CI 3.97-6.69) *Author conclusions:* Vitamin D deficiency is significantly associated with increased risk for COVID-19.
Author: Kaufman *Country:* US *DOI:* 10.1371/journal.pone.0239252 *Study design:* Cohort study	*Participants:* n=191,779 participants from all 50 US states and the District of Columbia, 9.3% of whom were SAR-Cov-2 positive *Median age (IQR):* 54.0 years (40.4–64.7) *Female (%):* 68%	*Exposure(s) measured:* Vitamin D (25(OH)D concentration <20ng/mL=deficient; 20–29ng/mL=suboptimal; ≥30ng/mL=optimal). *Outcome results:* The SARS-CoV-2 positivity rate was lower in the 27,870 patients with "optimal" 25(OH)D (8.1%, 95%CI 7.8%–8.4%) than in the 39,190 patients with "deficient"

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
Setting: De-identified test results from a clinical laboratory, a Quest Diagnostics-wide unique patient identifier was used to match all results of SARS-CoV-2 testing performed 9 March to 19 June 2020, with 25(OH)D results from the preceding 12 months. Data date range: 9 March to 19 June 2020		25(OH)D (12.5%, 95%CI 12.2%–12.8%), (difference 35%; p<0.001). Similarly, the SARS-CoV-2 positivity rate was lower in the 12,321 patients with 25(OH)D values ≥55 ng/mL (5.9%, 95%CI 5.5%–6.4%) than in patients with adequate values (difference 27%; p<0.001). Lower SARS-CoV-2 positivity rates were significantly associated with higher circulating 25(OH)D levels, (aOR 0.98, 95%CI 0.98–0.99) per ng/mL increase; variables included in the multivariate analysis not reported. *Author conclusions:* "Our findings provide further rationale to explore the role of vitamin D supplementation in reducing the risk for SARS-CoV-2 infection and COVID-19 disease. If controlled trials find this relationship to be causative, the implications are vast and would present a cheap, readily-available method for helping prevent infection, especially for those with vitamin D deficiency."
Author: Kuderer *Country:* US, Canada, and Spain *DOI:* 10.1016/S0140-6736(20)31187-9 *Study design:* Cohort study *Setting:* COVID-19 and Cancer Consortium (CCC19) database for whom baseline data were added between 17 March to 16 April 2020	*Participants:* n=928 participants with COVID-19 and previous or active cancer. *Median age (IQR):* 66 years (57-76) *Male, n (%):* n=468 (50%)	*Exposure(s) measured:* smoking, obesity (assumption is BMI>30kg/m^2 as not defined by study). *Outcome results:* Compared to those who never smoked, former smokers had an increased risk of 30-day mortality, (aOR 1.60, 95%CI 1.03–2.47), adjusted for age, sex and obesity. The authors noted that no conclusions can be drawn about current smoking due to the small number of events. The multivariate analysis showed that current smokers did not have an increased risk of

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
Data date range: 17 March to 16 April 2020 (follow-up until 7 May 2020)		30-day mortality (aOR 1.34, 95%CI 0.49–3.67; adjusted for age, sex and obesity. Compared to those whose obesity status was not specified, those who were classified as obese did not have an increased risk of 30-day mortality, (aOR 0.99, 95%CI 0.58–1.71); adjusted for age, sex and smoking status (in patients with COVID-19 and previous or active cancer). *Author conclusions:* "In summary, this study of patients with cancer and COVID-19 reinforces several important considerations for clinical care, and emphasises the urgent need for more data. Longer-term follow-up and larger sample sizes are needed to more completely understand the effect of SARS-CoV-2 on outcomes in patients with cancer."
Author: McGurnaghan *Country:* Scotland *DOI:* 10.1016/S2213-8587(20)30405-8 *Study design:* Cohort study *Setting:* Population-based, using Electronic Communication of Surveillance in Scotland database, which captures all National Health Service (NHS) virology testing, the RAPID database of daily hospitalisations, the Scottish Morbidity Records-01 of hospital discharges, and the National Records of Scotland death registrations data.	*Participants:* Total population of Scotland (n=5,463,300), including all those with diabetes nationwide (n=319,349). *Median age (IQR):* 66.7 years (56.3–75.8) *Male, n (%):* NR	*Exposure(s) measured:* obesity (BMI categories <20kg/m^2, 20-25kg/m^2, >20-30kg/m^2, >30-35 kg/m^2, >35-40kg/m^2, >40kg/m^2), smoking status. *Outcome results*:* There was no significant linear relationship between BMI and requiring fatal or critical care unit treatment, (aOR 1.00, 95%CI 0.99-1.01). However, the multivariable fractional polynomials analysis revealed evidence for a statistically significant, non-linear, J-shaped relationship with BMI. BMI <20kg/m^2 (aOR 2.40, 95%CI 1.77-3.26) BMI 20-25kg/m^2 reference BMI >20-30kg/m^2 (aOR 0.80, 95%CI 0.67-0.96) BMI >30-35 kg/m^2 (aOR 0.93, 95%CI 0.77-1.12)

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
Data date range: 1 March to 31 July 2020		BMI >35-40kg/m^2 (aOR 0.97, 95%CI 0.76-1.23) BMI >40kg/m^2 (aOR 1.19, 95%CI 0.89-1.60) Compared with those who never smoked, ex-smokers had a higher risk of requiring fatal or critical care unit treatment, (aOR 1.30, 95%CI 1.13-1.49). Compared with those who never smoked, current smokers did not have statistically significant higher risk of requiring fatal or critical care unit treatment, (aOR 1.13, 95%CI 0.91-1.42). *Adjusted for age, sex, diabetes duration and type. *Author conclusions:* "We showed that, when adjusted for age, sex, and diabetes duration, people who developed fatal or critical care unit-treated COVID-19 on average had worse profiles for almost every clinical measure we examined. They were more likely to have smoked and there was a J shaped relationship with BMI."
Author: Merzon 2020 *Country:* Israel *DOI:* 10.1111/febs.15495 *Study design:* Cohort study *Setting:* Population-based, using Leumit Health Services (LHS) database, a large health maintenance organization in Israel that provides services to around 730,000 members nationwide	*Participants:* n=7,807 who had data on plasma 25(OH)D levels (out of 14,000 who had a COVID test). COVID-19 positive, n=782; COVID-19 negative, n=7,025. *Mean age:* COVID-19 positive, 35.58 (95% CI: 34.49-36.67); COVID-19 negative: 47.35 (95% CI: 46.87–47.85). *Male:* COVID-19 positive, 49%; COVID-19 negative, 41%.	*Exposure(s) measured:* Vitamin D (25(OH)D concentration <30ng/ml defined as 'suboptimal' or 'low'. *Outcome results:* Mean plasma vitamin D level was significantly lower among those who tested positive than negative for COVID-19 [19.00ng/mL 95%CI 18.41–19.59 vs 20.55 95%CI 20.32–20.78]. Univariate analysis demonstrated an association between the low plasma 25(OH)D level and increased likelihood of COVID-19 infection, (OR 1.58, 95%CI

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
Data date range: 1 February to 30 April 2020		1.24–2.01), and of hospitalization due to the SARS-CoV-2 virus, (OR 2.09, 95%CI 1.01–4.31). In multivariate analyses that controlled for demographic variables, and psychiatric and somatic disorders, the increased likelihood of COVID-19 infection was, (aOR 1.50, 95%CI 1.13–1.98) and of hospitalization due to the SARS-CoV-2 virus, (aOR 1.95, 95%CI 0.98–4.78). *Author conclusions:* Low plasma 25(OH)D levels appear to be an independent risk factor for COVID-19 infection and hospitalisation.
Author: Núñez-Gil *Country:* Spain, Ecuador, Germany and Italy *DOI:* 10.1007/s11739-020-02543-5 *Study design:* Retrospective cohort study *Setting:* HOPE-COVID-19 (Health Outcome predictive Evaluation for COVID-19, NCT04334291) is an international project *Data date range:* 8 February to 1 April 2020	*Participants:* 1021 discharged patients. of which 301 were dead and 607 alive. *Median age (SD)* 68 years (IQR 52-79) *Male, n (%)* 59.7%	*Exposure(s) measured:* Obesity (defined as BMI>30kg/m^2). *Outcome results*:* Mortality from logistic regression model: Whole cohort (aOR1.52, 95%CI 0.83-2.76) <70 years (aOR 4.93, 95%CI 1.77-13.74) >70 years (aOR 0.85, 95%CI 0.40-1.80) *Covariates not reported *Author conclusions:* Specifically we identified…obesity…as significant factors.
Author: Parra-Bracamonte *Country: Mexico* *DOI:* 10.1016/j.annepidem.2020.08.005 *Study design:* Cohort study	*Participants:* n=331,298 COVID-19 positive *Mean age:* 44 years (95% IQR, 33–56) *Male:* 54%	*Exposure(s) measured:* smoking status, obesity (coded as yes/no in database; obesity classed as BMI>30kg/m^2) *Outcome results:* Obesity was associated with higher mortality, (aOR 1.22 95%CI 1.17–1.28); adjusted for age, sex,

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
Setting: Population-based, using Epidemiologic Surveillance Source of Respiratory Viral Diseases (Sistema de Vigilancia Epidemiológica de Enfermedades Respiratorias Virales) that include information from 475 monitoring units all along the country from the public and private health sectors. *Data date range:* 13 January to 17 July 2020		smoking habits, patient hospitalisation, hypertension, pneumonia, COPD, asthma, immunosuppression, chronic renal disease. Smoking habit was not identified as a risk factor for death, (aOR 0.93, 95%CI 0.87-0.99); adjusted for age, sex, obesity, patient hospitalisation, hypertension, pneumonia, COPD, asthma, immunosuppression, chronic renal disease. *Author conclusions:* Obesity was associated with in a higher odds of death in COVID-19 patients.
Author: Rentsch (pre-print) *Country:* US *DOI:* 10.1101/2020.04.09.20059964 *Study design:* Retrospective cohort study *Setting:* VA birth cohort (aged 54-75 years) *Data date range:* 8 February to 30 March 2020	*Participants:* n=3,789 tested, of which n=585 COVID-19 positive. *Median age:* 65.7 years *Male:* 90.2%	*Exposure(s) measured:* smoking status and alcohol use disorder (defined by read codes). *Outcome results:* In unadjusted analyses: Smoking, COPD, and alcohol use disorder were associated with a lower probability of a positive test (all p<0.001). Based on multivariable analyses (C-statistic=0.806): Current smoking (aOR 0.45, 95%CI 0.35-0.57) was associated with decreased likelihood of COVID-19. Alcohol use disorder (aOR 0.58, 95%CI 0.41-0.83) was associated with decreased likelihood of COVID-19. Smoking and alcohol use were not associated with hospitalisation or ICU admission. *Adjusted for age, black race, ACE inhibitor and or ARB use and NSAID use.

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
		Author conclusions: No firm conclusions relating to alcohol/smoking were made.
Author: Sallis *Country:* US *DOI:* 10.1136/bjsports-2021-104080 *Study design:* Retrospective cohort study *Setting:* Kaiser Permanente Southern California (KPSC), which is an integrated healthcare system that serves approximately 4.7 million residents in Southern California at 15 medical centres. *Data date range:* 1 January to 21 October 2020	*Participants:* n=103,337 patients with a diagnosis of COVID-19 during the study period. Of these, n=84,377 were 18 years or older and continuously enrolled in the KPSC health plan during the 6 months prior to their COVID-19 diagnosis. Among these, n=48,440 patients had three or more exercise vital sign (EVS) measurements within the 2 years prior to the California pandemic lockdown on 18 March 2020, which comprised the analytical cohort for this study. *Mean age (±SD):* 47.5 years (±16.97) *Male, n (%):* n=18,447 (38.1%)	*Exposure measured:* physical activity (consistently meeting guidelines, >150min/week at all assessments during the study period; consistently inactive, 0-10min/week at all assessments; some activity, 11-149min/week or those with variability in their exercise vital signs), obesity (BMI categories <25kg/m^2, 25-29kg/m^2, 30-39kg/m^2, ≥40kg/m^2, smoking. *Outcome results*:* *Physical activity* Compared to those who were consistently active, those who were consistently inactive and inconsistently active, had an increased risk of hospitalisation with COVID-19, (aOR 2.26, 95%CI 1.81-2.83) and (aOR 1.89, 95%CI 1.53-2.33), respectively. • an increased risk of ICU admission with COVID-19, (aOR 1.73, 95%CI 1.18-2.55) and (aOR 1.58, 95%CI 1.10-2.27), respectively. • an increased risk of mortality from COVID-19, (aOR 2.49, 95%CI 1.33-4.67) and (aOR 1.88, 95%CI 1.02-3.47), respectively. *Obesity* Compared to those with a BMI<25, the risk of hospitalisation with COVID-19 in those with a BMI 25-29, BMI 30-39 and BMI≥40 was, (aOR 0.99, 95%CI 0.89-1.10), (aOR 1.12, 95%CI 1.01-1.24) and (aOR 1.77, 95%CI 1.55-2.02), respectively.

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
		Compared to those with a BMI<25, the risk of ICU admission with COVID-19 in those with a BMI 25-29, BMI 30-39 and BMI≥40 was, (aOR 0.98, 95%CI 0.81-1.19), (aOR 1.17, 95%CI 0.97-1.41) and (aOR 1.95, 95%CI 1.54-2.45), respectively. Compared to those with a BMI<25, the risk of mortality from COVID-19 in those with a BMI 25-29, BMI 30-39 and BMI≥40 was, (aOR 0.79, 95%CI 0.64-0.97), (aOR 0.89, 95%CI 0.72-1.10) and (aOR 1.90, 95%CI 1.43-2.54), respectively. *Smoking* Compared to those who never smoked, those who ever smoked had an increased risk of hospitalisation with COVID-19, (aOR 1.09, 95%CI 1.01-1.18). Compared to those who never smoked, those who ever smoked did not have an increased risk of ICU admission with COVID-19, (aOR 1.08, 95%CI 0.95-1.23). Compared to those who never smoked, those who ever smoked had an increased risk of mortality from COVID-19, (aOR 1.24, 95%CI 1.05-1.47). *Covariates included age, sex and race, along with underlying medical conditions associated with increased risk for severe illness from COVID-19 as defined by the CDC. *Author conclusions:* "We found that consistently meeting PA guidelines was strongly associated with a reduced odds for severe

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
		COVID-19 among infected adults. Specifically, when compared with those who reported being consistently inactive, those who were consistently meeting PA guidelines had lower odds of being hospitalised, requiring ICU admission and dying from COVID-19."
Author: Singh *Country:* US *DOI:* 10.1053/j.gastro.2020.08.028 *Study design:* Retrospective cohort study *Setting:* Based on electronic medical records of patients from multiple large member health care organizations in the United States. *Data date range:* 20 January to 31 May 2020	*Participants:* n=41,513 adult patients who were COVID-19 positive. Out of these patients with COVID-19, 8,641 patients were included in the obesity group (n=5,879 had a documented BMI≥30 kg/m^2 and n=2,762 had a diagnosis of obesity). In the control group, n=31,273 patients did not have a diagnosis of obesity, of which n=6,437 had a BMI<30 kg/m^2. *Mean age (SD):* obese patients, 49.68 years (±15.84); non-obese patients 49.87 years (±19.27). *Female, n (%):* obese patients, n=5,374 (62.19%); non-obese patients, n=16,469 (52.66%).	*Exposure measured:* obesity (defined by diagnosis in read codes or last measured BMI>30kg/m^2). *Outcome results:* Before propensity matching: Compared to those who were not obese, obese patients had an increased risk of mortality, (Risk ratio 1.38, 95%CI 1.23–1.54) intubation, (Risk ratio 2.61, 95%CI 2.38–2.86) and hospitalisation, (Risk ratio 1.80, 95%CI 1.72–1.88). After propensity matching: Compared to those who were not obese, obese patients had an increased risk of mortality, (Risk ratio 1.17, 95%CI 1.01–1.36) intubation, (Risk ratio 1.83, 95%CI 1.62–2.07) and hospitalisation, (Risk ratio 1.40, 95%CI 1.32–1.49). Compared to those who were not obese, patients with stage 2 obesity had an increased risk of mortality, (Risk ratio 1.31, 95%CI 1.02–1.67) intubation, (Risk ratio 1.54, 95%CI 1.25–1.90) and hospitalisation, (Risk ratio 1.36, 95%CI 1.23–1.51). Compared to those who were not obese, patients with stage 3 obesity had an increased risk of mortality, (Risk ratio 1.35, 95%CI 1.72–1.76) intubation, (Risk ratio 2.24, 95%CI 1.83–2.75) and hospitalisation, (Risk ratio 1.44, 95%CI 1.30–1.58).

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
		Author conclusions: Patients with COVID-19 with any degree of obesity had a significantly higher risk of hospitalization and intubation or death compared to patients without obesity.
Author: Soares Country: Brazil DOI: 10.4269/ajtmh.20-0483 Study design: Retrospective cohort study Setting: Electronic health records from Espirito Santo State (general population) *Data date range:* 29 February to 11 June 2020	*Participants:* n=10,713 COVID-19 positive patients. Only patients with complete data for predictive variables were included in the study to avoid confounding by missing data (total sample n=24,428). *Age:* non-hospitalised, 93.7% aged <60 years and 6.3% aged ≥60 years; hospitalised, 70.3% aged <60 years and 29.7% aged ≥60 years. *Male, n (%):* non-hospitalised, n=4,146 (86.3%); hospitalised, n=658 (13.7%).	*Exposure(s) measured:* obesity (assumption is BMI>30kg/m^2 as not defined by study), smoking. *Outcome results:* Obesity Compared to those who were not obese, those who were obese had an increased risk of hospitalisation with COVID-19 (OR 2.04, 95%CI 1.64–2.52), and adjusted for covariates (aOR 1.74, 95%CI 1.35–2.23); adjusted for age, sex, race, comorbidities (cardiovascular disease, diabetes, kidney diseases, pulmonary disease, smoking) and signs and symptoms (cough, diarrhoea, fever, headache, runny nose, shortness of breath, sore throat). Smoking Compared to those who didn't smoke, those who did had an increased risk of hospitalisation with COVID-19, (OR 5.12, 95%CI 3.82–6.81) and (aOR 2.91, 95%CI 2.04–4.12); adjusted for age, sex, race, comorbidities (cardiovascular disease, diabetes, kidney diseases, pulmonary disease, obesity) and signs and symptoms (cough, diarrhoea, fever, headache, runny nose, shortness of breath, sore throat). *Author conclusions:* Obesity and smoking increased the risk of hospitalisation.

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
Author: Subramanian *Country:* UK *DOI:* 10.1530/EJE-20-1163 *Study design:* Cohort study *Setting:* The Health Improvement Network (THIN) database. THIN is an anonymized longitudinal primary care electronic medical records database from 365 active general practices in the UK. *Data date range:* 31 January to 22 July 2020	*Participants:* n=21,292 participants with PCO/PCOS; n=78,310 without PCO/PCOS; N=618 COVID-19 positive *Mean (±SD):* participants with PCO/PCOS 39.3 years ±11.1; participants without PCO/PCOS 39.5 years ±11.3. *Female, n (%):* 100%	*Exposure(s) measured:* obesity (per SD increment in BMI), vitamin D deficiency (defined by read codes) *Outcome results*:* Every unit increase in BMI was associated with an increased risk of suspected/confirmed COVID-19, (aHR 1.02, 95%CI 1.01–1.03). Vitamin D deficiency was associated with an increased risk of suspected/confirmed COVID-19, (aHR 1.61, 95%CI 1.05–2.47). *Variables included in the multivariate analysis unclear. *Author conclusions:* "Our study shows that women with PCOS are at an increased risk of COVID-19 infection, and except for obesity the adjustment for potentially confounding factors did not mitigate this risk, pointing at inherent PCOS-specific factors."
Author: Tartof *Country:* US *DOI:* 10.7326/M20-3742 *Study design:* Retrospective cohort study *Setting:* Kaiser Permanente Health System *Data date range:* 13 February to 2 May 2020	*Participants:* n=6,916 patients COVID-19 positive *Mean age:* 49.1 years *Male, n (%):* n=3,111 (45%)	*Exposure(s) measured:* obesity. Categorized by National Institutes of Health subcategories of: <18.5kg/m^2 (underweight), 18.5-24 kg/m^2 (normal), 25-29 kg/m^2 (overweight), 30-34 kg/m^2 (obese class I), 35-39 kg/m^2 (obese class II), and ≥40 kg/m^2 (obese class III or extreme obesity). *Outcome results*:* Compared with patients with a BMI of 18.5-24 kg/m^2, those with BMI 40-44 kg/m^2 and greater than 45 kg/m^2 had increased risk of death at 21 days, (aRR 2.68, 95%CI 1.43-5.04) and (aRR4.18, 95%CI 2.12-8.26), respectively. There was a J-shaped association between BMI and risk of death.

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
		*Adjusted for covariates that included other lifestyle factors, such as smoking. Author conclusions: Obesity plays a profound role in risk for death from COVID-19.
Author: Vila-Córcoles *Country:* Spain (Tarragona) *DOI:* 10.1136/bmjopen-2020-041577 *Study design:* Retrospective cohort study *Setting:* Twelve primary care centres *Data date range:* 1 March to 23 May 2020	*Participants:* n=79,083 people (n=77,676 community-dwelling and n=1,407 nursing-home residents); n=2,324 cohort members were PCR-tested, with 1,944 negative and 380 positive results. *Age:* 54% aged 50–64 years; 46% aged ≥65 years. *Male, n (%):* n=37,626 (47.6%)	*Exposure(s) measured:* smoking, obesity (defined by International Classification of Diseases-10 codes). *Outcome results*:* Smoking was associated with a lower risk of COVID-19 diagnosis, (aHR 0.62, 95% CI 0.41-0.93); smoking was also inversely associated with diagnosis in the community-dwelling subgroup. Obesity was not associated with increased risk of COVID-19 diagnosis, (aHR 0.87, 95%CI 0.68-1.11). *Adjusted for age, sex, residence, vaccinations history, comorbidities/underlying conditions and medications use. *Author conclusions:* "Surprisingly, smoking was associated with a statistically significant decreased risk for suffering COVID-19 in both multivariable analyses assessing the total study cohort and the subgroup of community-dwelling individuals." Authors conclude that this merits further investigations.

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
Author: Williamson *Country:* UK *DOI:* 10.1038/s41586-020-2521-4 *Study design:* Retrospective cohort study *Setting:* OpenSAFELY—a secure health analytics platform that covers 40% of all patients in England. *Data date range:* 1 February to 6 May 2020	*Participants:* Primary care records of 17,278,392 adults were pseudonymously linked to 10,926 COVID-19-related deaths. *Age:* 18–39 years, 34.2%; 40–49years, 16.5%; 50–59 years, 17.7%; 60–69 years, 13.8%; 70–79 years, 11.2%; ≥80 years, 6.5%. *Male, n (%):* n=8,630,403 (49.9%)	*Exposure(s) measured:* obesity (no evidence of obesity, BMI< 30kg/m^2; obese class I, BMI 30–34.9kg/m^2; obese class II, BMI 35–39.9kg/m^2; and obese class III, BMI ≥40kg/m^2, smoking *Outcome results:* Compared to those who were not obese (that is BMI<30kg/m^2), those who had a BMI 30-34.9kg/m^2, a BMI 35-39.9kg/m^2 and a BMI≥40kg/m^2 had an increased risk of death in the fully adjusted model, (aHR 1.05, 95%CI 1.00–1.11), (aHR 1.40, 95%CI 1.30–1.52) and (aHR 1.92, 95%CI 1.72–2.13), respectively. Both current and former smoking were associated with a higher risk in models that were adjusted for age and sex only, (aHR 1.43, 95%CI 1.37-1.49) and (aHR 1.14, 95%CI 1.05-1.23), respectively. In the fully adjusted model (adjusted for age using a four-knot cubic spline for age, except for estimation of age-group hazard ratios), current smoking was associated with a lower risk (aHR 0.89, 95%CI 0.82–0.97); former smoking remained associated with a higher risk of death, (aHR 1.19, 95%CI 1.14-1.24). This anomaly was investigated in more depth post hoc by adding covariates individually to the age, sex and smoking model. The change in hazard ratio was driven largely by adjustment for chronic respiratory disease (HR 0.98, 95%CI 0.90–1.06 after adjustment). This and other comorbidities could be consequences of smoking, highlighting that the fully adjusted smoking hazard ratio cannot be interpreted causally owing to

Study characteristics	Patient demographics	Relevant exposure(s), outcomes and conclusions
		the inclusion of factors that are likely to mediate smoking effects. A model adjusted for demographic factors only (age, sex, deprivation and ethnicity) showed a non-significant positive hazard ratio for current smoking (aHR 1.07, 95%CI 0.98–1.18); this does not support a protective effect of nicotine. *Author conclusions:* Obesity associated with higher risk of COVID-19 death.
Author: Yanover Country: Israel DOI: 10.2196/20872 Study design: Retrospective cohort study Setting: Complete medical records of a nationally representative cohort of patients (Maccabi Health Services – 2.3 million participants) *Data date range:* up to 22 April 2020 (follow-up to 30 April 2020)	*Participants:* n=4,353 COVID-19 positive *Age:* <18 years, 15%; 18-50 years, 54.5%; 50-60 years, 14.1%; 60-70 years, 8.7%; 70-80 years, 5.4%; >80 years, 3.1%. *Male:* 55%	*Exposure(s) measured:* smoking, obesity (BMI≥30kg/m^2). *Outcome results:* Obesity in patients aged 18-50 years had an increased risk of serious complications (experienced moderate or severe symptoms of COVID-19, admitted to the intensive care unit, or died), (OR 11.09, 95%CI 4.15-32.67). Obesity in older groups (50-65 years and >65 years) not statistically significant. Smoking was not identified as a risk factor. *Author conclusions:* Obesity is a significant risk factor for COVID-19 complications. Smoking does not significantly increase the risk of complications.

Key: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; DMARD, disease-modifying antirheumatic drugs; EHR, electronic health record; NR, not reported; NSAID, non-steroidal anti-inflammatory drug; RR, relative risk; T1D, type 1 diabetes; T2D, type 2 diabetes; VA, Veterans Affairs.

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