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**Risk factors for developing COVID-19: a population-based longitudinal study (COVIDENCE UK)**

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## Abstract

**Background:** Risk factors for severe COVID-19 include older age, male sex, obesity, Black or Asian ethnicity and underlying medical conditions. Whether these factors also influence susceptibility to developing COVID-19 is uncertain.

**Methods:** We undertook a prospective, population-based cohort study (COVIDENCE UK) from 1st May 2020 to 5th February 2021. Baseline information on potential risk factors was captured by an online questionnaire. Monthly follow-up questionnaires captured incident COVID-19. We used logistic regression models to estimate multivariable-adjusted odds ratios (aORs) for associations between potential risk factors and risk of COVID-19.

**Results:** We recorded 446 incident cases of COVID-19 in 15,227 participants (2.9%). Increased risk of developing COVID-19 was independently associated with Asian/Asian British *vs*. White ethnicity (aOR 2.28, 95% CI 1.33-3.91), household overcrowding (aOR per additional 0.5 people/bedroom 1.26, 1.11-1.43), any *vs*. no visits to/from other households in previous week (aOR 1.31, 1.06-1.62), number of visits to indoor public places (aOR per extra visit per week 1.05, 1.01-1.09), frontline occupation excluding health/social care *vs.* no frontline occupation (aOR 1.49, 1.12-1.98), and raised body mass index (BMI) (aOR 1.50 [1.19-1.89] for BMI 25.0-30.0 kg/m$^2$ and 1.39 [1.06-1.84] for BMI >30.0 kg/m$^2$ *vs.* BMI <25.0 kg/m$^2$). Atopic disease was independently associated with decreased risk (aOR 0.75, 0.59-0.97). No independent associations were seen for age, sex, other medical conditions, diet, or micronutrient supplement use.

**Conclusions:** After rigorous adjustment for factors influencing exposure to SARS-CoV-2, Asian/Asian British ethnicity and raised BMI were associated with increased risk of developing COVID-19, while atopic disease was associated with decreased risk.

**Funding:** Barts Charity, Health Data Research UK

- *What is the key question?*

How do demographic, socio-economic, lifestyle, dietary, pharmacological and comorbidity factors relate to the risk of developing COVID-19 in the general adult population of the UK?

- *What is the bottom line?*

After rigorous adjustment for factors influencing exposure to SARS-CoV-2, Asian/Asian British ethnicity and raised body mass index were associated with increased risk of developing COVID-19, while atopic disease was associated with decreased risk; no associations were seen for age, sex, or other underlying medical conditions.

- *Why read on?*

This large, population-based prospective study shows that there is limited overlap between risk factors for developing COVID-19 vs. those for intensive care unit admission and death as reported in hospitalised cohorts.

## Introduction

COVID-19 has taken a heavy toll on the health of populations globally.[1-3] Risk factors for severe and fatal disease are well-recognised, and include male sex, Black or Asian ethnic origin, obesity, deprivation and a range of comorbidities including diabetes mellitus, cardiovascular disease, chronic obstructive pulmonary disease (COPD) and hypertension.[4,5] Characterisation of risks for milder disease has been relatively neglected, but is important, both from a public health perspective (since it drives transmission to individuals at risk of severe disease), and from a biological perspective (since understanding susceptibility factors can provide insights into pathogenesis).

There is growing evidence from population-based studies to suggest that at least some risk factors for developing COVID-19 - irrespective of severity - may be distinct from those which predispose to disease at the most severe end of the spectrum. For example, population-based studies in both the US and the UK have reported that risk of COVID-19 is higher in younger vs. older adults [6], a finding supported by serology studies in the UK and Switzerland reporting higher prevalence of antibodies to SARS-CoV-2 in younger vs older adults.[7,8] Again, in contrast to studies reporting that diabetes, heart disease and hypertension are risk factors for severe disease, the presence of pre-existing health conditions has been reported to associate with decreased, rather than increased, risk of SARS-CoV-2 sero-positivity in a population-based study conducted in the UK.[7]

These apparently paradoxical associations are potentially attributable to changes in behaviour in response to the pandemic, whereby people at greater risk of severe disease because of older age or presence of comorbidities may reduce social contact and visits to indoor public places in order to reduce their exposure to SARS-CoV-2. However, to our knowledge, studies to investigate whether behaviours influencing risk of such exposure might partly explain associations between older age, presence of comorbidities and lower risk of developing COVID-19 are lacking. Such studies could potentially shed light on other controversies relating to risk factors for developing COVID-19, such as the extent to which ethnic differences in disease susceptibility can be explained by behavioural, occupational and socio-

economic factors,[9] and whether lifestyle, diet, and use of micronutrient supplements may influence risk of developing COVID-19.[10,11]

In order to address this knowledge gap, we established a new longitudinal study (COVIDENCE UK) at the start of the pandemic, with the specific aim of capturing detailed information on a very wide range of potential risk factors for COVID-19. Sufficient incident cases of test-confirmed COVID-19 have now accumulated to allow us to evaluate how a comprehensive panel of demographic, socio-economic, lifestyle, dietary, pharmacological and comorbidity factors relate to the risk of developing COVID-19.

## Methods

*Study design, setting and participants*

COVIDENCE UK (Longitudinal population-based observational study of coronavirus disease in the UK population, www.qmul.ac.uk/covidence) is a prospective cohort study with four main objectives, namely to: i) determine risk factors for incident COVID-19 in the UK population; ii) characterise the natural history of COVID-19 in the UK population; iii) evaluate the impact of COVID-19 on the physical and mental health of the UK population; and iv) provide a resource from which to identify potential participants for future clinical trials of interventions to reduce incidence and/or severity of COVID-19 and other acute respiratory infections. Inclusion criteria were age 16 years or more and residence in the UK at the point of enrolment; there were no exclusion criteria. Participants were invited via a national media campaign to complete an on-line baseline questionnaire to capture information on potential symptoms of COVID-19 experienced since 1st February 2020, results of any COVID-19 tests, and details of a wide range of potential risk factors for COVID-19, as described below. Follow-up questionnaires were administered at monthly intervals to capture incident test-confirmed COVID-19 as well as potential symptoms of COVID-19. The study was launched on 1st May 2020, and this paper reports findings of analysis of data collected up to 5th February 2021.

*Sponsorship, registration, ethics and reporting*

The study was sponsored by Queen Mary University of London and approved by Leicester South Research Ethics Committee (ref 20/EM/0117). It is registered with ClinicalTrials.gov (NCT04330599).

*Outcomes*

The primary outcome was incidence of test-confirmed COVID-19, as defined by a self-reported positive result from PCR or lateral flow testing of eluate from a nose or throat swab for SARS-CoV-2. Those who were not tested were assumed to be test negative. The secondary outcome was incidence of symptom-defined probable COVID-19, with casehood defined using the algorithm described by Menni and colleagues,[12] based on age, sex and self-reported loss of smell/taste, significant/severe persistent cough, severe fatigue and skipped meals (see supplementary Appendix for further details). This outcome was included in order to address potential under-ascertainment of COVID-19 arising from use of test-confirmed COVID-19 as an outcome measure, which would not have captured episodes where testing was not done, potentially introducing collider bias.[13] Test-confirmed COVID-19 and symptom-defined probable COVID-19 were analysed as separate outcomes (i.e. they were not combined). In order to minimise the potential for reverse causality to explain associations observed, outcomes occurring within 30 days of enrolment were excluded. At enrolment, participants were asked to provide details of potential symptoms of COVID-19 experienced since 1st February 2020, and results of any PCR or lateral flow tests for SARS-CoV-2 performed on eluates from nose / throat swabs to date.

*Independent variables*

At enrolment, participants were asked to complete an on-line questionnaire capturing information about their socio-demographic characteristics, type of occupation, lifestyle, weight, height, longstanding medical conditions, medication use, vaccination status, diet and supplemental micronutrient intake (for baseline questionnaire, see Table S1, Supplementary Appendix). Monthly on-line follow-up questionnaires (Table

S2, Supplementary Appendix) captured incident test-confirmed COVID-19 and potential symptoms of COVID-19.

*Sample size*

The sample size required to detect an odds ratio of at least 1.08 (effect size) for a binary exposure variable with maximum variability (probability = 0.50 changing to 0.52) and correlated with other variables in the model ($R^2$ = 0.5), with a power of 90% using a one-sided test with 5% significance level was estimated as 10,721, using the 'powerlog' program in Stata 14.2 (College Station, TX). Assuming 10% censoring at baseline (prevalent COVID-19 and missing) and 20% loss to follow-up, we aimed to recruit a minimum of 14,890 participants. No upper limit for sample size was specified.

*Statistical methods*

Statistical analyses were performed using Stata 14.2. Putative risk factors for COVID-19 were selected *a priori* and classified into the following groups: socio-demographic, occupational and lifestyle factors; longstanding medical conditions, medication use and vaccination status; and diet and supplemental micronutrient intake. To produce patient-level covariates for each class of medications investigated, participant answers were mapped to drug classes listed on the British National Formulary (BNF) or the DrugBank and Electronic Medicines Compendium databases if not explicitly listed on the BNF; further details of the computational methods used to achieve this are presented in supplementary Appendix. Index of Multiple Deprivation (IMD) 2019 scores were assigned according to participants' postcodes, and categorised into quartiles.

Participants who reported definite COVID-19 prior to enrolment, or who were classified as having had symptom-defined probable COVID-19 prior to enrolment on the basis of self-reported symptoms, were excluded from prospective analyses. Logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for each individual factor, first in a crude model, then in 'minimally adjusted' models. For the primary outcome of test-confirmed COVID-19, the minimally adjusted model included age (six categories), sex (male/female), duration of

participation and frequency of COVID-19 testing. For the secondary outcome of symptom-defined probable COVID-19, the minimally adjusted model included age (six categories), sex and duration of participation only. Factors associating independently with each outcome at the 10% significance level were evaluated for collinearity using Cramer's V statistic[14] for all pairwise combinations of the covariates and clustering with average-linkage hierarchical clustering using 1 - V as a dissimilarity metric. The resultant heat-maps were reviewed, and where a cluster of highly correlated covariates was identified, one variable within each cluster that was deemed to relate most closely and plausibly to COVID-19 risk was selected for inclusion in the multivariable model. Age was included within the multivariable model regardless of collinearity, since all covariates investigated in the collinearity analysis exhibited a significant relationship with COVID-19 in the minimally-adjusted model that controlled for age. Variables that did not exhibit clustering in the heat-maps were all included in the final model, along with age, sex, IMD score quartile, duration of participation and frequency of COVID-19 testing. We also used restricted cubic spline analysis to examine the shape of relationships between BMI and age and incident test-defined COVID-19 in multivariable-adjusted models. We selected the number of knots based on the values of Akaike information criteria (AIC) to fit the best-approximating model, chose the first knot as reference (at 20.7 kg/m$^2$ and 32.4 years, respectively), and tested for linearity using the Wald test. The lowest AIC (i.e. the best-fitting model) was obtained by 3 knots for BMI and 5 knots for age. Correction for multiple comparisons was not applied, on the grounds that we were testing *a priori* hypotheses for all risk factors investigated.[15] We conducted sensitivity analysis for unmeasured confounding by estimating E-values[16] using the 'evalue' package in Stata.[17] Two other sensitivity analyses were also performed: one excluded participants who received one or more doses of COVID-19 vaccine, and the other excluded those who were randomised to receive vitamin D supplementation as part of a nested clinical trial that was initiated during follow-up. We also performed an exploratory analysis to determine whether COVID-19 risk differed for participants with atopic vs. non-atopic asthma endotypes; this was conducted on the basis of evidence suggesting that decreased expression of *ACE2*, the gene encoding the SARS-CoV-2 receptor, has been reported in people with asthma who have high levels of allergic sensitisation.[18]

*Role of the funding source*

Barts Charity and Health Data Research UK had no role in study design, data analysis, data interpretation, or writing of the report. MT, HH and MG had access to raw data. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

## Results

Of the 17,558 participants who completed the COVIDENCE UK baseline questionnaire on or before 2nd November 2020, we excluded those who were identified as already having had test-confirmed and/or symptom-defined probable COVID-19 (n=1,477). Of the remaining 16,081 participants, 15,227 completed at least one subsequent monthly follow-up questionnaire at least 30 days after enrolment and were included in this prospective analysis; 14,348 completed the final follow-up questionnaire on or before 5th February 2021, giving a retention rate of 89.2% (Figure S1, Supplementary Appendix). Selected baseline characteristics of participants included in the prospective analysis are presented in Table 1; their characteristics are compared with those who were excluded from this analysis in Table S3, Supplementary Appendix. Mean age of those contributing data to prospective analyses was 59.4 years (range 16.0 to 94.4 years), 69.8% were female, and 94.9% identified their ethnic origin as White. The geographical distribution of COVIDENCE UK participants aligned closely with that of incident COVID-19 in the UK (Figure S2, Supplementary Appendix).

A total of 446 participants experienced at least one episode of PCR- or lateral flow test-confirmed COVID-19 during 2,613,921 person-days of follow-up, of whom 32 were hospitalised. We calculated crude and minimally-adjusted ORs for associations between risk of test-confirmed COVID-19 and socio-demographic, occupational and lifestyle factors (Table 2); longstanding conditions, medication use and vaccination status (Table 3); and diet and supplemental micronutrient intake (Table 4). After adjustment for age, sex, duration of participation and testing frequency ('minimal adjustment'), the following factors were found to associate with increased risk of

COVID-19 with P <0.10: Asian / Asian British vs. White ethnic origin, housing type (paying mortgage and 'other' vs. owning own home), frontline vs. non-frontline worker status, household overcrowding (>0.5 vs. ≤0.5 people per bedroom), any visit vs. no visits to/from other households in the previous week, presence vs. absence of schoolchildren and working-age adults in the household, living with others vs. living alone, periodontitis, having vs. not having a dog at home, any vs. no travel to work or place of study in the week preceding questionnaire completion, number of visits to shops or other indoor public places per week (quartiles 2,3,4 vs quartile 1), alcohol consumption (15-21 vs 0 U/week); sleep duration (7 or ≥9 vs 8 hours per night); raised body mass index (BMI) (>25.0 vs ≤25.0 kg/$m^2$) and history vs. no history of BCG vaccination. The following factors associated with decreased risk of COVID-19 with P<0.10 after minimal adjustment: age ≥60 vs. 16-29.99 years, education to college or postgraduate level vs primary / secondary level, shielding vs. non-shielding, low-impact physical activity (≥2 vs 0 hours/week), presence vs. absence of asthma diagnosis, presence vs. absence of atopic disease (defined by atopic eczema/dermatitis and/or hayfever/allergic rhinitis), use vs. no use of systemic immunosuppressants, inhaled corticosteroids and bronchodilators (defined as β-2-adrenoreceptor agonists or anticholinergics), higher intake of fruit and vegetables (top vs bottom quartiles) and use vs. no use of vitamin D supplements.

All factors associating with test-confirmed COVID-19 with P <0.10 in the minimally-adjusted model were then assessed for collinearity: the resultant heat-map (Figure S3, Supplementary Appendix) revealed a high degree of collinearity between the number of working-age adults in the household, multi-generational households and number of people per bedroom. Since household over-crowding (as indicated by number of people per bedroom) was deemed to relate most closely to SARS-CoV-2 exposure risk from a clinical / epidemiological perspective, the other two independent variables were excluded from the multivariable model.

Table 5 presents fully-adjusted ORs for associations between potential risk factors for test-confirmed COVID-19. The final multivariable model adjusted mutually for age, sex, duration of participation, test frequency, ethnicity, highest educational level attained, IMD rank, household income, housing type, number of people per bedroom, presence of schoolchildren at home, presence of a dog in the household, shielding,

visits to/from other households, visits to shops and other indoor places, travel to work or study, frontline worker status, low-impact physical activity, alcohol intake, BMI, history of asthma, history of atopic disease, use of systemic immunosuppressants, use of inhaled corticosteroids, use of bronchodilators, BCG vaccination status, intake of fruit, vegetables and salads, and intake of supplemental vitamin D. Increased risk of developing COVID-19 was independently associated with Asian/Asian British *vs*. White ethnicity (aOR 2.28, 95% CI 1.33-3.91), household overcrowding (aOR per additional 0.5 people/bedroom 1.26, 1.11-1.43), any *vs*. no visits to/from other households in previous week (aOR 1.31, 1.06-1.62), number of visits to indoor public places (aOR per extra visit per week 1.05, 1.01-1.09), frontline occupation outside health/social care *vs.* no frontline occupation (aOR 1.49, 1.12-1.98), and raised BMI (aOR 1.50 [1.19-1.89] for BMI 25.0-30.0 kg/m$^2$ and 1.39 [1.06-1.84] for BMI >30.0 kg/m$^2$ *vs.* BMI <25.0 kg/m$^2$). Lower risk of test-confirmed COVID-19 was independently associated with history of atopic disease (aOR 0.75, 0.59-0.97) and taking systemic immunosuppressants (aOR 0.47, 0.22-0.99). Restricted cubic spline analysis showed non-linear associations between BMI (P for non-linearity 0.009) and age (P for non-linearity 0.02) and incident test-defined COVID-19 (Figure 1).

We performed two sensitivity analyses to explore the robustness of the multivariable results. The first (Table S4, Supplementary Appendix) excluded 3,202 participants who received one or more doses of COVID-19 vaccine before the date of the data download (5$^{th}$ February 2021). The second (Table S5, Supplementary Appendix) excluded 3,813 participants who commenced vitamin D supplements after enrolment in the cohort due to participation in a clinical trial. Both analyses yielded similar findings to those presented above. An exploratory analysis to determine whether COVID-19 risk differed for participants with atopic vs. non-atopic asthma endotypes (as defined by the presence or absence of atopic eczema/dermatitis and/or hayfever/allergic rhinitis) showed a reduced risk of COVID-19 for participants with atopic asthma (aOR 0.62, 0.41-0.93), but not for those with non-atopic asthma (aOR 0.88, 0.60-1.30), as compared to participants without atopic disease or asthma. These effect estimates did not materially change after further adjustment for inhaled corticosteroids (Table S6, Supplementary Appendix).

We then proceeded to investigate determinants of symptom-defined probable COVID-19, with casehood ascribed using an algorithm published by Menni et al.[12] In the

subset of 6,035 COVIDENCE UK participants entering the prospective analysis who had one or more tests for COVID-19 during the follow-up period, this case definition had sensitivity and specificity for test-confirmed COVID-19 of 0.47 and 0.97, respectively, with an area under the receiver operating characteristic curve of 0.72 (95% CI, 0.69 to 0.74; Table S7, Supplementary Appendix). Potential risk factors associating with probable symptom-defined COVID-19 with P<0.10 in a minimally-adjusted model (i.e. adjusting for age, sex and duration of participation) were included in the multivariable model presented in Table S8, Supplementary Appendix. Increased risk of probable symptom-defined COVID-19 was independently associated with Asian / Asian British vs. White ethnicity, housing type (having a mortgage vs. home-ownership), household overcrowding (>1.0 vs. ≤0.5 people per bedroom), health or social care occupation, use of cod liver oil supplements, poorer self-assessed general health, periodontitis and use of selective serotonin reuptake inhibitors, while lower risk of probable symptom-defined COVID-19 was independently associated with greater age (age ≥50 vs. 16-29.99 years).

## Discussion

In this large, prospective population-based study evaluating a diverse array of potential risk factors for developing COVID-19, we found that Asian/Asian British ethnicity, household overcrowding, indoor social mixing, employment as a frontline worker outside of health and social care, and being overweight or obese were all independently associated with an increased risk of test-confirmed COVID-19. Associations with household overcrowding and visits to indoor public places showed dose-response relationships, strengthening causal inference. History of atopic disease and use of systemic immunosuppressant medication were independently associated with decreased risk of test-positive disease. No statistically significant independent associations with disease risk were seen for other factors investigated, including age, sex, diet, supplemental micronutrient intake, and other longstanding conditions and medications.

This study sheds new light on the degree of overlap between risk factors for developing COVID-19 (irrespective of severity) *vs.* risk factors for developing severe or fatal disease specifically. Our finding that people of Asian/Asian British ethnic origin are at

increased risk of developing COVID-19 is consistent with reports of increased susceptibility and disease severity in this group.[4,7,19] One limitation of previous studies investigating ethnic variation in COVID-19 risk is that they did not adjust for behaviours influencing SARS-CoV-2 exposure, such as visits to other households and indoor public places. In our study, increased risk of developing COVID-19 in people of Asian/Asian British ethnic origin was not explained by such behaviours, nor by social deprivation, domestic overcrowding, occupation, BMI, or comorbidities. There is therefore an urgent need for further research to investigate social and biological factors that might explain ethnic disparities in risk of developing COVID-19, including vitamin D deficiency.[9] The association between raised BMI and increased susceptibility to COVID-19 that we found is consistent with studies identifying obesity as a risk factor for both susceptibility to, and severe outcomes of, COVID-19.[4,20,21] It would appear that immune dysregulation associated with obesity may increase susceptibility to infection as well as disease severity.

By contrast, a number of established risk factors for severe and fatal disease, including older age, male sex and underlying conditions such as diabetes, heart disease, COPD and hypertension, were not associated with risk of developing COVID-19 in our study, where cases were predominantly mild (93.1% non-hospitalised). Our finding of no association between kidney disease and susceptibility to COVID-19 contrasts with that of de Lusignan and colleagues,[22] who reported such an association in a study that was conducted earlier in the UK pandemic when testing was limited to those with more severe COVID-19 illness presenting to hospital. The bias resulting from focusing testing on more severe disease in that study may have contributed to the different findings in our study, which was conducted over a later period when testing was more widely available. In contrast with other studies,[23,24] we found no association between intake of micronutrient supplements and protection against COVID-19: this may reflect a false-negative result from our study (arising due to a relative lack of power to detect modest protective effects), or a false-positive result from other studies arising as a result of less rigorous adjustment for potential socio-economic confounding.

We also  In keeping with reports from the UK[7] and elsewhere,[8] we found younger age to be associated with increased risk of developing COVID-19 in crude and minimally-adjusted models. However, this association did not persist after adjustment for multiple potential confounders, including behaviours related to social mixing, suggesting that lower incidence of COVID-19 in older adults in our study may be explained by reductions in social contact. We did not see a difference in disease risk for people with diabetes, heart disease or hypertension. Whilst this contrasts with a study reporting lower prevalence of SARS-CoV-2 seropositivity among people with these underlying conditions, that study did not adjust, as we did, for behaviours influencing exposure to infection.[7] The only long-standing conditions associated with disease risk in our study were atopic diseases, which were associated with reduced risk of disease, particularly among those who also had asthma. This may reflect decreased expression of *ACE2*, the gene encoding the SARS-CoV-2 receptor, which has been reported in people with both high levels of allergic sensitisation and asthma.[18]

Our study has several strengths. COVIDENCE UK was set up with the specific purpose of investigating incident COVID-19, and consequently our questionnaires were specifically designed to capture contemporaneous and granular detail on potential risk factors, including behaviours influencing risk of exposure to SARS-CoV-2. Our finding that visits to other households and indoor public places were associated with increased risk of disease supports the case for restricting such activities as a public health strategy to control disease. Our low rates of loss to follow-up reflect the very high degree of participant engagement with the COVIDENCE UK study. Our ability to identify episodes of milder disease affords potential insights into susceptibility factors as well as severity factors, and sets our study apart from long-established cohort studies in which assessment of risk factors may be temporally remote, and capture of outcomes is limited to events that are fatal or that precipitate hospitalisation. Our prospective design, coupled with censoring events occurring within 30 days of enrolment minimises the potential for reverse causation to explain associations observed.

Our study also has limitations. Use of test-confirmed COVID-19 as our primary outcome may have resulted in under-ascertainment of disease, particularly early in the pandemic (when testing capacity was particularly limited) and among people with less access to testing services; this might introduce collider bias.[13] We addressed this

limitation by including a secondary outcome of symptom-defined probable COVID-19, which did not rely on access to testing. However, the lack of direct swabbing surveillance and reliance on results of routine testing that will usually have been prompted by incident symptoms may have led to under-ascertainment of asymptomatic SARS-CoV-2 infection. A second issue relates to the self-selected nature of the cohort participants. Ethnic minorities, particularly people of Black, African and Caribbean ethnic origin, were under-represented in the study; a lack of statistical power may explain why we did not confirm an increased risk of disease in these groups. People with limited internet access or with fewer digital skills are also less likely to have participated. However, lack of representativeness in a study population does not preclude identification of causal associations.[25] Third, as with any observational study, we cannot exclude the possibility that the associations we report may be explained by residual and/or unmeasured confounding. We sought to minimise this by capture of, and mutual adjustment for, a comprehensive panel of potential confounders. Calculation of E-values enabled us to determine how likely it was that our main findings might be 'explained away' by unmeasured/unknown confounding factors. For example, for an unknown confounder to fully explain the association between frequent visits to shops/indoor places and COVID-19 risk (OR 2.63 comparing top versus bottom quartile of exposure), it would need to be associated with both the outcome and the exposure (above and beyond the measured confounders) by an odds ratio of nearly 5 or more (Table 5); weaker confounding could not explain away the association. In contrast, for the association between >9 hours sleep and COVID-19 risk (OR 1.29) to be explained away, an unknown confounder would need to be associated with the exposure and outcome by an odds ratio of at least 1.90; this effect estimate is comparable to other risk factor associations we have found, hence, more plausible for an unknown confounder. Accordingly, evidence for an unconfounded, causal association is considerably stronger for frequent visits to shops/indoor places than it is for prolonged sleep duration.

In conclusion, this population-based longitudinal study conducted in UK adults found that increased risk of developing COVID-19 associated independently with Asian/Asian British ethnicity, household overcrowding, visits to other households and other indoor public places, frontline occupation outside of health or social care, and increased BMI, after rigorous adjustment for multiple confounders. Atopic diseases,

and especially atopic asthma, were associated with decreased risk. In contrast to studies investigating risk factors for severe disease, older age, male sex and other comorbidities were not associated with increased risk of developing COVID-19.

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## Author Contributions

ARM wrote the study protocol, with input from HH, MT, CR, GB and SOS. HH, MT, JS, CR, KY, MD, KT, SF, SI, AM, PP, GL-J, TD, IC, DM, GD, RL, CJG, FK, AS, GB, SAS and ARM contributed to questionnaire development and design. HH co-ordinated and managed the study, with input from ARM, MT, JS and SOS. HH, JS, ARM, SOS, NSH and BA supported recruitment. HH, MT, MG, MD, KT, SSR, AAK, SER, PJL and DAJ contributed to data management and coding medication data. Statistical analyses were done by MT, with input from SOS, ARM, MG and HH. ARM wrote the first draft of the report. All authors revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

## Transparency Declaration

ARM is the manuscript's guarantor and he affirms that this is an honest, accurate, and transparent account of the study.

**Table 1.** Selected cohort characteristics

| | Total | Test-confirmed COVID-19 | |
|---|---|---|---|
| | | No | Yes |
| **n (%)** | 15227 (86.7) | 14781 (97.1) | 446 (2.9) |
| **Age, n (%)** | | | |
| 16-29.99 y | 576 (3.8) | 550 (3.7) | 26 (5.8) |
| 30-39.99 y | 988 (6.5) | 941 (6.4) | 47 (10.5) |
| 40-49.99 y | 1787 (11.7) | 1693 (11.5) | 94 (21.1) |
| 50-59.99 y | 3361 (22.1) | 3226 (21.8) | 135 (30.3) |
| 60-69.99 y | 5105 (33.5) | 5008 (33.9) | 97 (21.7) |
| ≥70.00 y | 3410 (22.4) | 3363 (22.8) | 47 (10.5) |
| **Age, y** | 59.4 ± 13.4 | 59.5 ± 13.4 | 53.3 ± 13.2 |
| **Sex, n (%)** | | | |
| Female | 10630 (69.8) | 10301 (69.7) | 329 (73.8) |
| Male | 4597 (30.2) | 4480 (30.3) | 117 (26.2) |
| **Ethnicity, n (%)** | | | |
| White | 14449 (94.9) | 14046 (95.0) | 403 (90.4) |
| Mixed/Multiple/Other ethnic groups | 401 (2.6) | 382 (2.6) | 19 (4.3) |
| South Asian | 281 (1.8) | 263 (1.8) | 18 (4.0) |
| Black/African/Caribbean/Black British | 96 (0.6) | 90 (0.6) | 6 (1.3) |
| **Country of residence, n (%)** | | | |
| England | 13463 (88.4) | 13052 (88.3) | 411 (92.2) |
| Northern Ireland | 294 (1.9) | 281 (1.9) | 13 (2.9) |
| Scotland | 915 (6.0) | 910 (6.2) | 5 (1.1) |
| Wales | 555 (3.6) | 538 (3.6) | 17 (3.8) |
| **Household income sufficient for basic needs, n (%)** | | | |
| Yes | 14209 (93.3) | 13793 (93.3) | 416 (93.3) |
| Mostly / Sometimes / No | 1016 (6.7) | 986 (6.7) | 30 (6.7) |
| **Housing, n (%)** | | | |
| Owns own home | 9326 (61.3) | 9137 (61.8) | 189 (42.4) |
| Mortgage | 3743 (24.6) | 3570 (24.2) | 173 (38.8) |
| Privately Renting | 1069 (7.0) | 1029 (7.0) | 40 (9.0) |
| Renting from council | 477 (3.1) | 461 (3.1) | 16 (3.6) |
| Others | 610 (4.0) | 582 (3.9) | 28 (6.3) |
| **Number of people per bedroom, n (%)** | | | |
| ≤0.50 | 5836 (38.6) | 5738 (39.1) | 98 (22.3) |
| >0.50-0.99 | 4179 (27.6) | 4069 (27.7) | 110 (25.0) |
| 1.00-1.99 | 4766 (31.5) | 4553 (31.0) | 213 (48.4) |
| ≥2.00 | 333 (2.2) | 314 (2.1) | 19 (4.3) |
| **Highest educational level attained, n (%)** | | | |
| Primary/Secondary | 1649 (10.8) | 1598 (10.8) | 51 (11.4) |
| Higher/further (A levels) | 2233 (14.7) | 2164 (14.7) | 69 (15.5) |
| College | 6720 (44.2) | 6523 (44.2) | 197 (44.2) |
| Post-graduate | 4610 (30.3) | 4481 (30.3) | 129 (28.9) |
| **Occupational status, n (%)** | | | |
| Employed | 5349 (35.1) | 5091 (34.4) | 258 (57.8) |
| Self-employed | 1369 (9.0) | 1330 (9.0) | 39 (8.7) |
| Retired | 6951 (45.6) | 6856 (46.4) | 95 (21.3) |
| Furloughed | 365 (2.4) | 348 (2.4) | 17 (3.8) |
| Unemployed | 267 (1.8) | 254 (1.7) | 13 (2.9) |
| Other | 926 (6.1) | 902 (6.1) | 24 (5.4) |
| **Frontline worker, n (%)** | | | |
| No | 12474 (82.0) | 12198 (82.6) | 276 (61.9) |
| Other frontline worker | 1572 (10.3) | 1492 (10.1) | 80 (17.9) |
| Health or social care worker | 1167 (7.7) | 1077 (7.3) | 90 (20.2) |
| **Body mass index, n (%)** | | | |
| <25, kg/m2 | 7431 (48.9) | 7254 (49.2) | 177 (39.8) |
| 25-30, kg/m2 | 4829 (31.8) | 4661 (31.6) | 168 (37.8) |
| >30, kg/m2 | 2929 (19.3) | 2829 (19.2) | 100 (22.5) |
| **Self-reported general health, n (%)** | | | |

| | | | |
|---|---|---|---|
| Excellent | 3071 (20.2) | 2982 (20.2) | 89 (20.0) |
| Very good | 6024 (39.6) | 5850 (39.6) | 174 (39.0) |
| Good | 4048 (26.6) | 3928 (26.6) | 120 (26.9) |
| Fair | 1633 (10.7) | 1581 (10.7) | 52 (11.7) |
| Poor | 449 (2.9) | 438 (3.0) | 11 (2.5) |
| **Tobacco smoking history, n (%)** | | | |
| Never-smoker | 8529 (56.0) | 8282 (56.0) | 247 (55.4) |
| Ex-smoker | 5862 (38.5) | 5697 (38.5) | 165 (37.0) |
| Current smoker | 836 (5.5) | 802 (5.4) | 34 (7.6) |
| **Alcohol consumption in week prior to questionnaire completion, n (%)** | | | |
| None | 4271 (28.1) | 4152 (28.1) | 119 (26.7) |
| 1-7 units | 5406 (35.5) | 5244 (35.5) | 162 (36.3) |
| 8-14 units | 2961 (19.4) | 2876 (19.5) | 85 (19.1) |
| 15-21 units | 1417 (9.3) | 1366 (9.2) | 51 (11.4) |
| 22-28 units | 657 (4.3) | 640 (4.3) | 17 (3.8) |
| >28 units | 513 (3.4) | 501 (3.4) | 12 (2.7) |
| **COVID-19 vaccine during follow-up, n (%)** | | | |
| No | 14529 (85.7) | 12675 (85.8) | 365 (81.8) |
| Yes | 2416 (14.3) | 2106 (14.2) | 81 (18.2) |

**Table 2.** Socio-demographic, occupational and lifestyle factors and risk of test-confirmed COVID-19: crude and minimally-adjusted odds ratios

| | | Number (%) with incident test-confirmed COVID-19 | Total number | Crude odds ratio (95% CI) | Minimally adjusted odd ratio (95% CI)[1] |
|---|---|---|---|---|---|
| Age, years | 16-29.99 | 26 (4.5) | 15227 | 1.00 | 1.00 |
| | 30-39.99 | 47 (4.8) | | 1.06 (0.65-1.73) | 1.08 (0.65-1.78) |
| | 40-49.99 | 94 (5.3) | | 1.17 (0.75-1.83) | 1.24 (0.79-1.95) |
| | 50-59.99 | 135 (4.0) | | 0.89 (0.58-1.36) | 0.96 (0.62-1.49) |
| | 60-69.99 | 97 (1.9) | | 0.41 (0.26-0.64) | **0.49 (0.31-0.77)** |
| | ≥70.00 | 47 (1.4) | | 0.30 (0.18-0.48) | **0.39 (0.24-0.64)** |
| Sex | Female | 329 (3.1) | 15227 | 1.00 | 1.00 |
| | Male | 117 (2.5) | | 0.82 (0.66-1.01) | 1.08 (0.86-1.34) |
| Ethnicity | Asian/Asian British | 18 (6.4) | 15227 | 2.39 (1.46-3.88) | **1.99 (1.20-3.30)** |
| | Black/African/Caribbean/Black British | 6 (6.3) | | 2.32 (1.01-5.34) | 1.98 (0.84-4.65) |
| | Mixed/Multiple/other ethnic groups | 19 (4.7) | | 1.73 (1.08-2.78) | 1.40 (0.86-2.28) |
| | White | 403 (2.8) | | 1.00 | 1.00 |
| Highest educational level attained | Primary/Secondary | 51 (3.1) | 15212 | 1.00 | 1.00 |
| | Higher/further (A levels) | 69 (3.1) | | 1.00 (0.69-1.44) | 0.86 (0.59-1.25) |
| | College | 197 (2.9) | | 0.95 (0.69-1.29) | **0.75 (0.54-1.03)** |
| | Post-graduate | 129 (2.8) | | 0.90 (0.65-1.25) | **0.62 (0.44-0.87)** |
| Index of multiple deprivation (IMD) rank, quartiles | Q1 (most deprived) | 131 (3.6) | 15152 | 1.30 (1.01-1.69) | 1.22 (0.93-1.60) |
| | Q2 | 108 (2.8) | | 1.02 (0.78-1.34) | 0.97 (0.73-1.28) |
| | Q3 | 97 (2.5) | | 0.90 (0.68-1.19) | 0.89 (0.67-1.19) |
| | Q4 (least deprived) | 107 (2.8) | | 1.00 | 1.00 |
| Household income sufficient for basic needs | Yes | 416 (2.9) | 15225 | 1.00 | 1.00 |
| | Mostly / Sometimes / No | 30 (3.0) | | 1.01 (0.69-1.47) | 0.85 (0.58-1.25) |
| Claiming universal credit | No | 425 (2.9) | 15178 | 1.00 | 1.00 |
| | Yes | 19 (4.7) | | 1.65 (1.03-2.64) | 1.25 (0.77-2.03) |
| Housing | Owns own home | 189 (2.0) | 15225 | 1.00 | 1.00 |
| | Mortgage | 173 (4.6) | | 2.34 (1.90-2.89) | **1.34 (1.04-1.74)** |
| | Privately Renting | 40 (3.7) | | 1.88 (1.33-2.66) | 1.17 (0.79-1.73) |
| | Renting from council | 16 (3.4) | | 1.68 (1.00-2.82) | 1.20 (0.70-2.07) |
| | Others | 28 (4.6) | | 2.33 (1.55-3.49) | **1.54 (0.95-2.49)** |
| Frontline worker | No | 276 (2.2) | 15213 | 1.00 | 1.00 |
| | Health or social care worker | 90 (7.7) | | 3.69 (2.89-4.72) | **1.68 (1.28-2.21)** |
| | Other frontline worker | 80 (5.1) | | 2.37 (1.84-3.06) | **1.85 (1.42-2.42)** |
| Shielding | No | 423 (3.0) | 15171 | 1.00 | 1.00 |
| | Yes | 23 (2.0) | | 0.64 (0.42-0.98) | **0.63 (0.41-0.97)** |
| Number of people per bedroom | ≥0.50 | 98 (1.7) | 15114 | 1.00 | 1.00 |
| | >0.50-0.99 | 110 (2.6) | | 1.58 (1.20-2.08) | **1.34 (1.01-1.78)** |
| | 1-1.99 | 213 (4.5) | | 2.74 (2.15-3.49) | **1.91 (1.46-2.50)** |
| | ≥2.00 | 19 (5.7) | | 3.54 (2.14-5.87) | **2.41 (1.40-4.13)** |
| Any visits to/from other households in week prior to questionnaire completion | No | 202 (2.7) | 15217 | 1.00 | 1.00 |
| | Yes | 244 (3.2) | | 1.21 (1.00-1.46) | **1.46 (1.19-1.80)** |
| Pre-school children (0-4 years old) at home with participant | No | 416 (2.8) | 15191 | 1.00 | 1.00 |
| | Yes | 30 (5.9) | | 2.15 (1.47-3.15) | 1.19 (0.77-1.84) |
| Schoolchildren (5-15 years old) at home with participant | No | 351 (2.6) | 15182 | 1.00 | 1.00 |
| | Yes | 95 (5.5) | | 2.18 (1.73-2.75) | **1.42 (1.08-1.87)** |
| Working-age adult (16-64 years old) at home with participant | No | 117 (1.6) | 15183 | 1.00 | 1.00 |
| | Yes | 329 (4.2) | | 2.74 (2.21-3.39) | **1.86 (1.45-2.41)** |
| Number of different generations in household | Living alone | 46 (1.6) | 15227 | 1.00 | 1.00 |
| | Single generation | 230 (2.8) | | 1.78 (1.29-2.45) | **1.66 (1.19-2.30)** |
| | Two generations | 164 (4.1) | | 2.62 (1.88-3.64) | **2.08 (1.48-2.94)** |
| | Three generations | 6 (5.0) | | 3.27 (1.37-7.83) | **2.54 (1.04-6.23)** |
| Cat at home | No | 344 (2.9) | 15215 | 1.00 | 1.00 |
| | Yes | 102 (3.1) | | 1.06 (0.85-1.33) | 0.88 (0.70-1.12) |
| Dog at home | No | 317 (2.7) | 15215 | 1.00 | 1.00 |
| | Yes | 129 (3.6) | | 1.33 (1.08-1.64) | **1.21 (0.97-1.50)** |
| Number of public transport journeys in week prior to questionnaire completion | 0 | 393 (2.9) | 15175 | 1.00 | 1.00 |
| | 1-5 | 35 (3.0) | | 1.02 (0.72-1.45) | 1.12 (0.78-1.61) |
| | ≥6 | 17 (3.7) | | 1.29 (0.79-2.12) | 1.37 (0.82-2.28) |
| Travel to work/study in week prior to questionnaire completion | No | 37 (2.5) | 15,042 | 1.00 | 1.00 |
| | Yes | 318 (3.8) | | 1.54 (1.09-2.18) | **1.71 (1.20-2.44)** |

| | | Number (%) with incident test-confirmed COVID-19 | Total number | Crude odds ratio (95% CI) | Minimally adjusted odd ratio (95% CI)[1] |
|---|---|---|---|---|---|
| | Not currently working or studying | 88 (1.7) | | 0.68 (0.46-1.00) | 1.20 (0.79-1.81) |
| Number of visits to shops and other indoor public places in week prior to questionnaire completion, quartiles | Q1 | 33 (1.5) | 15207 | 1.00 | 1.00 |
| | Q2 | 151 (3.0) | | 2.05 (1.40-2.99) | **2.23 (1.51-3.29)** |
| | Q3 | 118 (3.3) | | 2.25 (1.52-3.32) | **2.77 (1.85-4.14)** |
| | Q4 | 144 (3.2) | | 2.16 (1.48-3.17) | **3.38 (2.25-5.07)** |
| Tobacco smoking status | Never-smoker | 247 (2.9) | 15227 | 1.00 | 1.00 |
| | Ex-smoker | 165 (2.8) | | 0.97 (0.80-1.19) | 1.09 (0.89-1.35) |
| | Current smoker | 34 (4.1) | | 1.42 (0.99-2.05) | 1.24 (0.85-1.82) |
| Regular exposure to environmental tobacco smoke at home or in car | No | 433 (2.9) | 15226 | 1.00 | 1.00 |
| | Yes | 13 (3.9) | | 1.35 (0.77-2.37) | 1.17 (0.66-2.09) |
| Vaping status | Never-vaper | 410 (2.9) | 15185 | 1.00 | 1.00 |
| | Ex-vaper | 16 (3.2) | | 1.12 (0.67-1.86) | 0.89 (0.53-1.50) |
| | Current vaper | 19 (4.0) | | 1.40 (0.88-2.24) | 1.04 (0.64-1.69) |
| Alcohol consumption in week prior to questionnaire completion, units | None | 119 (2.8) | 15225 | 1.00 | 1.00 |
| | 1-7 | 162 (3.0) | | 1.08 (0.85-1.37) | 1.08 (0.85-1.38) |
| | 8-14 | 85 (2.9) | | 1.03 (0.78-1.37) | 1.07 (0.80-1.43) |
| | 15-21 | 51 (3.6) | | 1.30 (0.93-1.82) | **1.40 (0.99-1.98)** |
| | 22-28 | 17 (2.6) | | 0.93 (0.55-1.55) | 1.10 (0.65-1.87) |
| | >28 | 12 (2.3) | | 0.84 (0.46-1.52) | 0.95 (0.52-1.76) |
| Hours of vigorous physical exercise in week prior to questionnaire completion[2] | 0 | 171 (2.9) | 15176 | 1.00 | 1.00 |
| | 1-3 | 163 (2.9) | | 0.98 (0.79-1.22) | 0.95 (0.75-1.18) |
| | ≥4 | 109 (2.9) | | 0.99 (0.78-1.27) | 1.03 (0.80-1.32) |
| Hours of light physical exercise in week prior to questionnaire completion[3] | 0-4 | 189 (3.6) | 15192 | 1.00 | 1.00 |
| | 5-9 | 140 (2.8) | | 0.76 (0.61-0.95) | 0.87 (0.69-1.10) |
| | ≥10 | 117 (2.4) | | 0.64 (0.51-0.81) | 0.89 (0.70-1.14) |
| Hours of lower-impact physical activity in week prior to questionnaire completion[4] | 0 | 274 (3.1) | 15176 | 1.00 | 1.00 |
| | 1 | 88 (3.1) | | 0.97 (0.76-1.24) | 0.90 (0.70-1.16) |
| | ≥2 | 83 (2.3) | | 0.73 (0.57-0.94) | **0.76 (0.59-0.98)** |
| Estimated average hours of sleep per night in month prior to questionnaire completion[5] | ≤6 | 41 (3.1) | 15223 | 1.22 (0.86-1.73) | 1.15 (0.80-1.64) |
| | 7 | 113 (3.1) | | 1.20 (0.94-1.53) | **1.24 (0.97-1.59)** |
| | 8 | 159 (2.6) | | 1.00 | 1.00 |
| | ≥9 | 133 (3.3) | | 1.28 (1.02-1.62) | **1.26 (0.99-1.60)** |

Minimally adjusted odd ratios (95% CI) with a P-value <0.10 are emboldened.

1, adjusted for age, sex, duration of participation and test frequency

2, defined as exercise of sufficient intensity to make the participant breathless or to raise their heart rate significantly, such as heavy physical work, strenuous gardening (e.g. vigorous digging, landscaping) swimming, jogging, aerobics, football, tennis, cycling, gym workout, reported to the nearest hour

3, defined as exercise that did not make the participant breathless, such as light gardening, walking, including walking for pleasure or exercise, walking to the shops, walking to work, reported to the nearest hour

4, defined as exercise to improve flexibility or core strength such as yoga, tai chi or pilates, reported to the nearest hour

5, reported to the nearest hour

**Table 3.** Underlying conditions, medication use, vaccination status and risk of test-confirmed COVID-19: crude and minimally-adjusted odds ratios

| | | Number (%) with incident test-confirmed COVID-19 | Total number | Crude odds ratio (95% CI) | Minimally adjusted odds ratio (95% CI)[1] |
|---|---|---|---|---|---|
| **Underlying conditions** | | | | | |
| Self-rated general health | Excellent | 89 (2.9) | 15225 | 1.00 | 1.00 |
| | Very good | 174 (2.9) | | 1.00 (0.77-1.29) | 1.06 (0.81-1.38) |
| | Good | 120 (3.0) | | 1.02 (0.77-1.35) | 1.03 (0.77-1.37) |
| | Fair | 52 (3.2) | | 1.10 (0.78-1.56) | 0.99 (0.70-1.42) |
| | Poor | 11 (2.4) | | 0.84 (0.45-1.59) | 0.75 (0.40-1.43) |
| Self-rated anxiety or depression | No | 316 (2.8) | 15216 | 1.00 | 1.00 |
| | Yes | 130 (3.2) | | 1.13 (0.92-1.39) | 0.91 (0.73-1.12) |
| Body mass index, kg/m$^2$ | <25 | 177 (2.4) | 15189 | 1.00 | 1.00 |
| | 25-30 | 168 (3.5) | | 1.48 (1.19-1.83) | **1.58 (1.27-1.97)** |
| | >30 | 100 (3.4) | | 1.45 (1.13-1.86) | **1.37 (1.06-1.77)** |
| Asthma | No | 384 (3.0) | 15227 | 1.00 | 1.00 |
| | Yes | 62 (2.5) | | 0.82 (0.62-1.07) | **0.67 (0.51-0.88)** |
| Atopic disease[2] | No | 349 (3.1) | 15227 | 1.00 | 1.00 |
| | Yes | 97 (2.5) | | 0.80 (0.64-1.01) | **0.65 (0.51-0.82)** |
| COPD | No | 438 (2.9) | 15227 | 1.00 | 1.00 |
| | Yes | 8 (2.5) | | 0.84 (0.41-1.70) | 1.14 (0.55-2.34) |
| Diabetic status | No diabetes | 415 (3.0) | 15206 | 1.00 | 1.00 |
| | Pre-diabetes | 14 (3.1) | | 1.06 (0.62-1.82) | 1.38 (0.79-2.41) |
| | Type 1 diabetes | 3 (2.8) | | 0.96 (0.30-3.02) | 0.81 (0.25-2.62) |
| | Type 2 diabetes | 13 (2.1) | | 0.70 (0.40-1.22) | 0.92 (0.52-1.62) |
| Heart disease[3] | No | 432 (3.0) | 15227 | 1.00 | 1.00 |
| | Yes | 14 (2.4) | | 0.80 (0.47-1.38) | 1.28 (0.73-2.25) |
| Arterial disease[4] | No | 431 (3.0) | 15227 | 1.00 | 1.00 |
| | Yes | 15 (1.9) | | 0.63 (0.38-1.07) | 0.91 (0.53-1.57) |
| Hypertension | No | 378 (3.2) | 15227 | 1.00 | 1.00 |
| | Yes | 68 (2.1) | | 0.64 (0.50-0.84) | 0.88 (0.67-1.17) |
| Kidney disease | No | 441 (3.0) | 15227 | 1.00 | 1.00 |
| | Yes | 5 (1.6) | | 0.54 (0.22-1.31) | 0.62 (0.25-1.52) |
| Major neurological conditions[5] | No | 440 (3.0) | 15227 | 1.00 | 1.00 |
| | Yes | 6 (1.5) | | 0.50 (0.22-1.12) | 0.62 (0.27-1.41) |
| Cancer | Never | 410 (3.0) | 15227 | 1.00 | 1.00 |
| | Past (cured or in remission) | 33 (2.6) | | 0.87 (0.61-1.25) | 1.12 (0.77-1.63) |
| | Present (active treatment in progress) | 3 (2.2) | | 0.72 (0.23-2.27) | 0.89 (0.28-2.87) |
| Immunodeficiency[6] | No | 446 (2.9) | 15140 | 1.00 | 1.00 |
| | Yes | 0 (0.0) | | NA | NA |
| Periodontitis[7] | No | 240 (2.7) | 15227 | 1.00 | 1.00 |
| | Yes | 129 (3.3) | | 1.20 (0.96-1.49) | 1.30 (1.04-1.62) |
| | Missing | 77 (3.05) | | 1.12 (0.86-1.45) | 1.13 (0.86-1.49) |
| **Medications** | | | | | |
| Statins | No | 398 (3.2) | 15227 | 1.00 | 1.00 |
| | Yes | 48 (1.8) | | 0.57 (0.42-0.77) | 0.93 (0.67-1.29) |
| ACE inhibitors | No | 415 (3.0) | 15227 | 1.00 | 1.00 |
| | Yes | 31 (2.1) | | 0.68 (0.47-0.99) | 0.90 (0.62-1.32) |
| Proton pump inhibitors | No | 395 (3.0) | 15227 | 1.00 | 1.00 |
| | Yes | 51 (2.4) | | 0.80 (0.60-1.08) | 0.88 (0.65-1.20) |
| Inhaled corticosteroids | No | 410 (3.0) | 15227 | 1.00 | 1.00 |
| | Yes | 36 (2.5) | | 0.83 (0.59-1.18) | **0.68 (0.48-0.97)** |
| Systemic Immunosuppressants | No | 437 (3.0) | 15227 | 1.00 | 1.00 |
| | Yes | 9 (1.3) | | 0.43 (0.22-0.84) | **0.39 (0.20-0.77)** |
| Selective serotonin re-uptake inhibitors (SSRIs) | No | 401 (2.8) | 15227 | 1.00 | 1.00 |
| | Yes | 45 (4.2) | | 1.50 (1.09-2.05) | 1.19 (0.86-1.64) |
| Non-SSRI antidepressants | No | 424 (2.9) | 15227 | 1.00 | 1.00 |
| | Yes | 22 (3.4) | | 1.19 (0.77-1.84) | 1.17 (0.75-1.83) |
| Angiotensin receptor blockers | No | 427 (3.0) | 15227 | 1.00 | 1.00 |
| | Yes | 19 (2.2) | | 0.74 (0.46-1.17) | 1.01 (0.62-1.63) |
| Vitamin K antagonists | No | 444 (2.9) | 15227 | 1.00 | 1.00 |
| | Yes | 2 (1.8) | | 0.61 (0.15-2.46) | 0.73 (0.18-3.06) |
| Beta-blockers | No | 424 (3.0) | 15227 | 1.00 | 1.00 |
| | Yes | 22 (2.0) | | 0.67 (0.43-1.03) | 0.91 (0.59-1.43) |
| Thiazides | No | 437 (3.0) | 15227 | 1.00 | 1.00 |
| | Yes | 9 (1.8) | | 0.61 (0.31-1.19) | 0.81 (0.41-1.60) |

| | | Number (%) with incident test-confirmed COVID-19 | Total number | Crude odds ratio (95% CI) | Minimally adjusted odds ratio (95% CI)[1] |
|---|---|---|---|---|---|
| H2-receptor antagonists | No | 442 (2.9) | 15227 | 1.00 | 1.00 |
| | Yes | 4 (4.6) | | 1.60 (0.59-4.39) | 1.36 (0.48-3.83) |
| Calcium channel blockers | No | 417 (3.0) | 15227 | 1.00 | 1.00 |
| | Yes | 29 (2.0) | | 0.64 (0.44-0.93) | 0.91 (0.61-1.36) |
| Inhaled bronchodilators[8] | No | 14 (2.0) | 15227 | 1.00 | 1.00 |
| | Yes | 411 (3.0) | | 0.84 (0.59-1.20) | **0.54 (0.31-0.94)** |
| Non-steroidal anti-inflammatory drugs | No | 421 (3.0) | 15227 | 1.00 | 1.00 |
| | Yes | 25 (2.0) | | 0.66 (0.44-0.99) | 0.84 (0.55-1.28) |
| Sodium-glucose co-transporter-2 (SGLT2) inhibitors | No | 444 (2.9) | 15227 | 1.00 | 1.00 |
| | Yes | 2 (2.5) | | 0.86 (0.21-3.51) | 0.95 (0.23-4.00) |
| Anti-platelet drugs | No | 422 (3.0) | 15227 | 1.00 | 1.00 |
| | Yes | 24 (2.5) | | 0.83 (0.55-1.26) | 1.29 (0.83-1.99) |
| Sex hormone therapy | No | 401 (2.8) | 15227 | 1.00 | 1.00 |
| | Yes | 45 (4.0) | | 1.44 (1.05-1.97) | 1.19 (0.85-1.65) |
| Paracetamol | No | 430 (2.9) | 15227 | 1.00 | 1.00 |
| | Yes | 16 (2.5) | | 0.84 (0.51-1.39) | 0.89 (0.53-1.50) |
| Metformin | No | 434 (2.9) | 15227 | 1.00 | 1.00 |
| | Yes | 12 (2.8) | | 0.94 (0.52-1.67) | 1.28 (0.71-2.31) |
| Bisphosphonates | No | 441 (2.9) | 15227 | 1.00 | 1.00 |
| | Yes | 5 (1.9) | | 0.65 (0.27-1.58) | 0.76 (0.31-1.90) |
| **Vaccinations** | | | | | |
| BCG-vaccinated | No | 40 (2.0) | 15197 | 1.00 | 1.00 |
| | Yes | 366 (3.1) | | 1.55 (1.12-2.16) | 1.36 (0.97-1.90) |
| | Unsure | 38 (2.5) | | 1.23 (0.79-1.93) | 1.26 (0.80-2.00) |
| MMR-vaccinated | No | 131 (2.6) | 11451 | 1.00 | 1.00 |
| | Yes | 226 (3.5) | | 1.38 (1.11-1.71) | 1.04 (0.81-1.32) |

BCG, *M. bovis* Bacille Calmette Guérin; MMR, measles mumps and rubella

Minimally adjusted odd ratios (95% CI) with a P-value <0.10 are bold.

1, adjusted for age, sex, duration of participation and test frequency

2, defined by atopic eczema/dermatitis and/or hayfever/allergic rhinitis

3, defined as coronary artery disease or heart failure

4, defined as ischaemic heart disease, peripheral vascular disease or cerebrovascular disease

5, defined as stroke, transient ischaemic attack, dementia, Parkinson's disease, multiple sclerosis or motor neurone disease

6, defined as HIV, primary immune deficiency or other immunodeficiency

7, defined as being present if participant answered 'yes' to any of the three questions relating to gum disease / dental health listed in Table S1

8, defined as β-2-adrenoceptor agonists or anticholinergics

**Table 4.** Diet, supplemental micronutrient intake and risk of test-confirmed COVID-19: crude and minimally-adjusted odds ratios

| | | Number (%) with incident test-confirmed COVID-19 | Total number | Crude odds ratio (95% CI) | Minimally adjusted odds ratio (95% CI)[1] |
|---|---|---|---|---|---|
| **Diet** | | | | | |
| Dietary restrictions | None | 419 (2.9) | 15227 | 1.00 | 1.00 |
| | Vegetarian[2] | 22 (3.2) | | 1.11 (0.72-1.72) | 0.89 (0.57-1.40) |
| | Vegan[3] | 5 (2.2) | | 0.75 (0.31-1.83) | 0.60 (0.24-1.49) |
| Number of portions of fruit, vegetables, and salad intake per day in week prior to questionnaire completion, quartiles | Q1 | 78 (3.5) | 15188 | 1.00 | 1.00 |
| | Q2 | 158 (3.1) | | 0.88 (0.67-1.17) | 0.90 (0.68-1.20) |
| | Q3 | 87 (3.0) | | 0.85 (0.62-1.16) | 0.89 (0.64-1.22) |
| | Q4 | 120 (2.4) | | 0.66 (0.49-0.88) | **0.73 (0.54-0.99)** |
| Number of portions of dairy products per day in week prior to questionnaire completion | 0-1 | 114 (2.8) | 15183 | 1.00 | 1.00 |
| | 2 | 142 (3.2) | | 1.15 (0.90-1.48) | 1.18 (0.91-1.53) |
| | 3-5 | 99 (2.7) | | 0.96 (0.73-1.27) | 1.06 (0.80-1.41) |
| | ≥6 | 91 (2.9) | | 1.03 (0.78-1.37) | 1.24 (0.93-1.65) |
| Total number of portions of fish (oily or white) intake in the week prior to questionnaire completion | Q1 | 94 (3.8) | 15213 | 1.00 | 1.00 |
| | Q2 | 79 (3.2) | | 0.85 (0.63-1.15) | 0.99 (0.73-1.36) |
| | Q3 | 111 (2.7) | | 0.71 (0.53-0.93) | 0.88 (0.66-1.18) |
| | Q4 | 162 (2.6) | | 0.70 (0.54-0.90) | 0.95 (0.72-1.25) |
| Portions of oily fish intake in the week prior to questionnaire completion | 0 | 210 (3.7) | 15220 | 1.00 | 1.00 |
| | 1 | 133 (2.7) | | 0.72 (0.58-0.90) | 0.86 (0.69-1.08) |
| | 2 | 71 (2.4) | | 0.64 (0.49-0.85) | 0.80 (0.60-1.06) |
| | ≥3 | 32 (2.1) | | 0.57 (0.39-0.83) | 0.76 (0.52-1.13) |
| Portions of white fish intake in the week prior to questionnaire completion | 0 | 131 (3.3) | 15216 | 1.00 | 1.00 |
| | 1 | 170 (2.8) | | 0.83 (0.66-1.04) | 0.99 (0.78-1.26) |
| | 2 | 92 (2.6) | | 0.76 (0.58-1.00) | 0.95 (0.72-1.26) |
| | ≥3 | 53 (3.3) | | 0.98 (0.71-1.35) | 1.16 (0.83-1.61) |
| Number of cups of non-alcoholic fluids per day in the week prior to questionnaire completion, quartiles | Q1 | 104 (3.0) | 15177 | 1.00 | 1.00 |
| | Q2 | 75 (2.9) | | 0.98 (0.73-1.32) | 1.03 (0.76-1.41) |
| | Q3 | 116 (2.5) | | 0.84 (0.64-1.10) | 0.81 (0.62-1.07) |
| | Q4 | 149 (3.4) | | 1.14 (0.88-1.47) | 0.99 (0.76-1.29) |
| **Micronutrient supplement use** | | | | | |
| Multivitamin supplement | No | 331 (2.7) | 15227 | 1.00 | 1.00 |
| | Yes | 115 (3.6) | | 1.33 (1.07-1.65) | 1.12 (0.89-1.40) |
| Vitamin A supplement | No | 445 (2.9) | 15227 | 1.00 | 1.00 |
| | Yes | 1 (1.1) | | 0.38 (0.05-2.73) | 0.43 (0.06-3.15) |
| Vitamin C supplement | No | 397 (2.9) | 15227 | 1.00 | 1.00 |
| | Yes | 49 (3.1) | | 1.09 (0.80-1.47) | 1.03 (0.76-1.41) |
| Vitamin D supplement | No | 305 (3.2) | 15227 | 1.00 | 1.00 |
| | Yes | 141 (2.5) | | 0.80 (0.65-0.98) | **0.80 (0.65-0.99)** |
| Zinc supplement | No | 425 (2.9) | 15227 | 1.00 | 1.00 |
| | Yes | 21 (2.8) | | 0.97 (0.62-1.51) | 0.93 (0.58-1.46) |
| Iron supplement | No | 423 (2.9) | 15227 | 1.00 | 1.00 |
| | Yes | 23 (4.6) | | 1.63 (1.06-2.51) | 1.27 (0.82-1.98) |
| Probiotic supplement | No | 426 (3.0) | 15227 | 1.00 | 1.00 |
| | Yes | 20 (2.2) | | 0.72 (0.46-1.13) | 0.69 (0.44-1.10) |
| Fish oil, krill oil or other omega-3 supplements | No | 400 (3.0) | 15227 | 1.00 | 1.00 |
| | Yes | 46 (2.7) | | 0.91 (0.67-1.25) | 0.98 (0.71-1.35) |
| Cod liver oil supplement | No | 409 (2.9) | 15227 | 1.00 | 1.00 |
| | Yes | 37 (3.0) | | 1.03 (0.73-1.45) | 1.29 (0.91-1.84) |
| Garlic or garlic powder (allicin) supplement | No | 439 (2.9) | 15227 | 1.00 | 1.00 |
| | Yes | 7 (2.3) | | 0.77 (0.36-1.63) | 0.93 (0.43-2.02) |
| Selenium supplement | No | 445 (3.0) | 15227 | 1.00 | 1.00 |
| | Yes | 1 (0.6) | | 0.21 (0.03-1.47) | 0.20 (0.03-1.46) |

Minimally adjusted odd ratios (95% CI) with a P-value <0.10 are emboldened.

1, adjusted for age, sex, duration of participation and test frequency

2, defined as excluding meat and fish, but not eggs or cow's milk, from the diet

3, defined as excluding meat, fish, eggs and cow's milk from the diet

**Table 5.** Independent risk factors for test-confirmed COVID-19: final multivariable model (n=14,556)

| Characteristic | Categories | Fully-adjusted odds ratio (95% CI)[1] | P for trend | E value (upper or lower bound of 95% CI)[10] |
|---|---|---|---|---|
| Age, years | 16-29.99 | 1.00 | 0.08 | |
| | 30-39.99 | 1.20 (0.68-2.12) | | |
| | 40-49.99 | 1.20 (0.69-2.10) | | |
| | 50-59.99 | 1.12 (0.65-1.93) | | |
| | 60-69.99 | 0.80 (0.44-1.44) | | |
| | ≥70.00 | 0.74 (0.39-1.41) | | |
| Sex | Female | 1.00 | -- | |
| | Male | 0.97 (0.76-1.23) | | |
| Ethnicity | Asian/Asian British | 2.28 (1.33-3.91) | -- | 3.99 (1.99) |
| | Black/African/Caribbean/Black British | 1.84 (0.70-4.82) | | |
| | Mixed/Multiple/other ethnic groups | 1.53 (0.92-2.53) | | |
| | White | 1.00 | | |
| Highest educational level attained | Primary/Secondary | 1.00 | 0.08 | |
| | Higher/Further (A levels) | 0.90 (0.61-1.33) | | |
| | College | 0.82 (0.58-1.15) | | |
| | Post-graduate | 0.74 (0.51-1.07) | | |
| Index of multiple deprivation (IMD) rank, quartiles | Q1 (most deprived) | 1.11 (0.84-1.48) | 0.44 | |
| | Q2 | 0.90 (0.67-1.20) | | |
| | Q3 | 0.87 (0.65-1.16) | | |
| | Q4 (least deprived) | 1.00 | | |
| Housing | Owns own home | 1.00 | -- | |
| | Mortgage | 1.19 (0.91-1.56) | | |
| | Privately renting | 0.96 (0.63-1.46) | | |
| | Renting from council | 0.96 (0.53-1.74) | | |
| | Others | 1.34 (0.81-2.21) | | |
| Number of people per bedroom[2] | ≤0.50 | 1.00 | <0.001 | |
| | >0.50-0.99 | 1.24 (0.93-1.66) | | |
| | 1.00-1.99 | 1.67 (1.25-2.23) | | 2.73 (1.81) |
| | ≥2.00 | 2.04 (1.15-3.60) | | 3.52 (1.43) |
| Schoolchildren (aged 5-15 years) at home with participant | No | 1.00 | -- | |
| | Yes | 1.16 (0.86-1.56) | | |
| Dog at home | No | 1.00 | -- | |
| | Yes | 1.17 (0.93-1.47) | | |
| Shielding | No | 1.00 | -- | |
| | Yes | 1.04 (0.64-1.68) | | |
| Any visits to/from other households in week prior to questionnaire completion | No | 1.00 | -- | |
| | Yes | 1.31 (1.06-1.62) | | 1.95 (1.31) |
| Number of visits to shops and other indoor public places in week prior to questionnaire completion[3] | Q1 | 1.00 | <0.001 | |
| | Q2 | 1.96 (1.29-2.98) | | 3.33 (1.90) |
| | Q3 | 2.21 (1.43-3.43) | | 3.84 (2.21) |
| | Q4 | 2.63 (1.69-4.10) | | 4.70 (2.77) |
| Travel to work/study in week prior to questionnaire completion | No | 1.00 | -- | |
| | Yes | 1.36 (0.93-1.99) | | |
| | Not currently working or studying | 1.27 (0.82-1.95) | | |
| Frontline worker | No | 1.00 | -- | |
| | Health or social care worker | 1.35 (1.00-1.82) | | 2.04 (1.02) |
| | Other frontline worker | 1.49 (1.12-1.98) | | 2.34 (1.49) |
| Number of portions of fruit, vegetables, and salad intake per day in week prior to questionnaire completion, quartiles | Q1 | 1.00 | 0.31 | |
| | Q2 | 1.00 (0.75-1.35) | | |
| | Q3 | 1.04 (0.74-1.45) | | |
| | Q4 | 0.86 (0.63-1.19) | | |
| Taking vitamin D supplement | No | 1.00 | | |
| | Yes | 0.93 (0.75-1.16) | | |
| Hours of lower-impact physical activity in week prior to questionnaire completion[4] | 0 | 1.00 | 0.22 | |
| | 1 | 1.01 (0.78-1.31) | | |
| | ≥2 | 0.83 (0.63-1.09) | | |
| Estimated average hours of sleep per night in month prior to questionnaire completion[5] | ≤6 | 1.14 (0.79-1.65) | 0.31[6] | |
| | 7 | 1.14 (0.88-1.48) | | |
| | 8 | 1.00 | | |
| | ≥9 | 1.29 (1.01-1.66) | | 1.90 (1.11) |
| Alcohol consumption in week prior to questionnaire completion, units | None | 1.00 | 0.39 | |
| | 1-7 | 1.11 (0.85-1.44) | | |
| | 8-14 | 1.08 (0.79-1.47) | | |

| Characteristic | Categories | Fully-adjusted odds ratio (95% CI)[1] | P for trend | E value (upper or lower bound of 95% CI)[10] |
|---|---|---|---|---|
| | 15-21 | 1.45 (1.01-2.08) | | |
| | 22-28 | 1.23 (0.72-2.11) | | |
| | >28 | 0.83 (0.43-1.60) | | |
| Body mass index, kg/m$^2$ | <25 | 1.00 | | |
| | 25-30 | 1.50 (1.19-1.89) | 0.004 | 2.37 (1.67) |
| | >30 | 1.39 (1.06-1.84) | | 2.13 (1.31) |
| Asthma | No | 1.00 | -- | |
| | Yes | 0.82 (0.55-1.24) | | |
| Atopic disease[7] | No | 1.00 | -- | |
| | Yes | 0.75 (0.59-0.97) | | 2.00 (1.21) |
| Periodontitis[8] | No | 1.00 | | |
| | Yes | 1.20 (0.95-1.52) | -- | |
| | Missing | 1.03 (0.77-1.37) | | |
| Systemic immunosuppressants | No | 1.00 | -- | |
| | Yes | 0.47 (0.22-0.99) | | 3.68 (1.11) |
| Inhaled corticosteroids | No | 1.00 | -- | |
| | Yes | 1.01 (0.55-1.84) | | |
| Inhaled bronchodilators[9] | No | 1.00 | -- | |
| | Yes | 1.07 (0.61-1.88) | | |
| BCG-vaccinated | No | 1.00 | | |
| | Yes | 1.38 (0.97-1.96) | -- | |
| | Unsure | 1.24 (0.78-1.99) | | |
| Duration of participation, days | | 1.00 (1.00-1.00) | -- | |
| Swab test frequency | | 1.62 (1.52-1.72) | -- | |

Abbreviation: BCG, *M. bovis* Bacillus Calmette Guérin

1, adjusted for age, sex, duration of participation, test frequency, ethnicity, highest educational level attained, IMD rank, hours of sleep per night, housing, number of people per bedroom, presence of schoolchildren at home, dog at home, shielding, visits to/from other households, visits to shops and other indoor places, travel to work or study, frontline worker status, fruit, vegetable and salad intake, supplemental vitamin D intake, low-impact physical activity, alcohol intake, body mass index, history of asthma, history of atopic disease, use of systemic immunosuppressants, use of inhaled corticosteroids, use of inhaled bronchodilators and BCG vaccination status.

2, adjusted odds ratio per additional 0.5 people per bedroom 1.26 (95% CI 1.11 to 1.43)

3, adjusted odds ratio per extra visit per week 1.05 (95% CI 1.01 to 1.09)

4, defined as exercise to improve flexibility or core strength such as yoga, tai chi or pilates, reported to the nearest hour

5, reported to nearest hour

6, only applies to sleeping categories below 8 hours

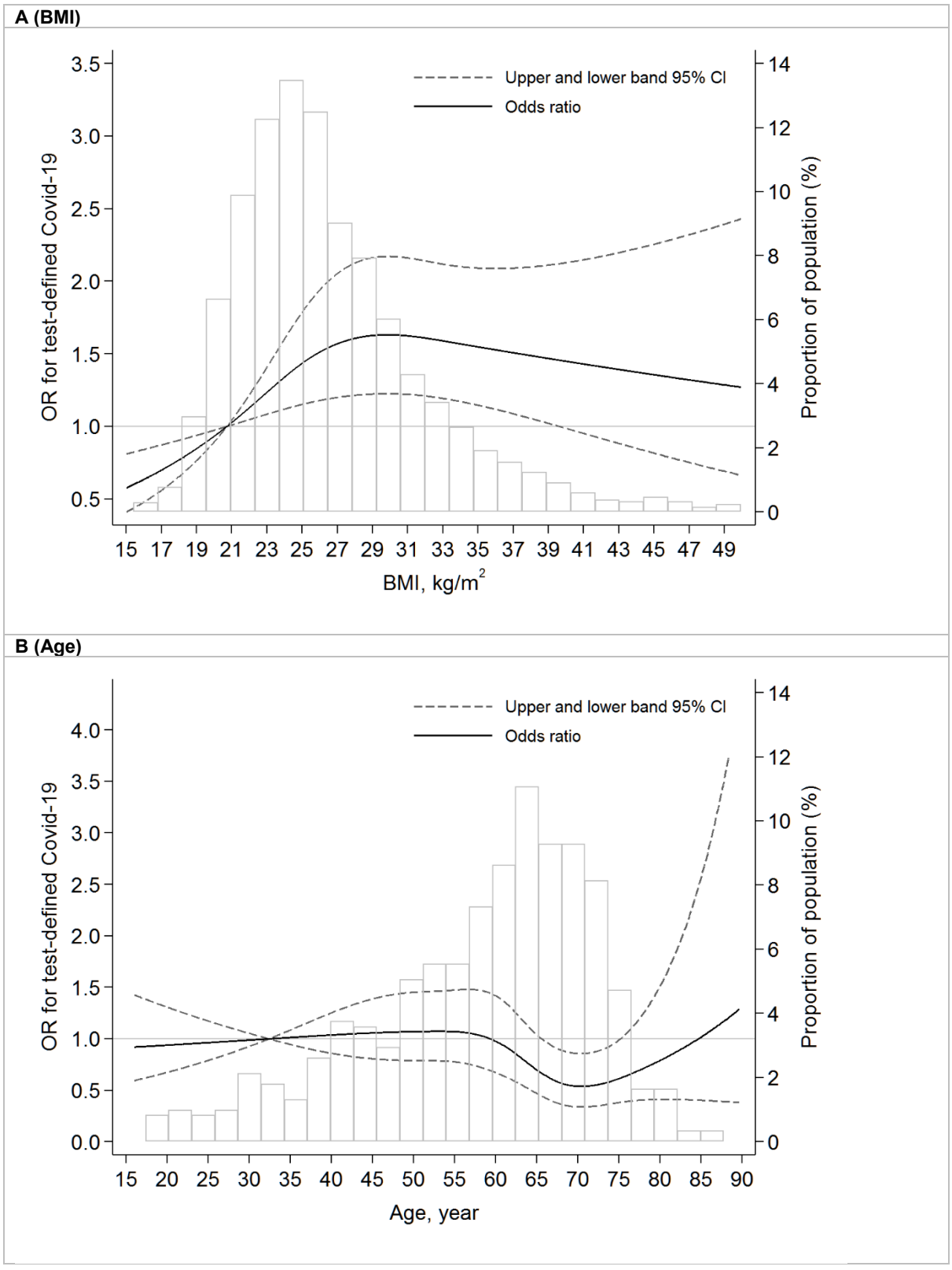
7, defined by atopic eczema/dermatitis and/or hayfever/allergic rhinitis

8, defined as being present if participant answered 'yes' to any of the three questions relating to gum disease / dental health listed in Table S1

9, defined as β-2-adrenoceptor agonists or anticholinergics

10, E-values are presented for associations which are significant with P<0.05. For protective associations, the upper bound of the 95% confidence interval for the E-value is presented. For non-protective associations, the lower bound of the 95% confidence interval for the E-value is presented.

**Figure 1.** Dose-response relationship between body mass index (A) and age (B) and risk of incident test-defined COVID-19 using restricted cubic spline analysis. The multivariable models were mutually adjusted for all factors presented in Table 5.



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