Determinants of pre-vaccination antibody responses to SARS-CoV-2: a population-based longitudinal study (COVIDENCE UK)

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Abstract

Background: Prospective population-based studies investigating multiple determinants of pre-vaccination antibody responses to SARS-CoV-2 are lacking.

Methods: We did a prospective population-based study in SARS-CoV-2 vaccine-naive UK adults between May 1 and Nov 2, 2020. Information on 88 potential risk factors was obtained through online questionnaires, and combined IgG/IgA/IgM responses to SARS-CoV-2 spike glycoprotein were determined in dried blood spots. We used logistic and linear regression to estimate adjusted odds ratios (aORs) and adjusted geometric mean ratios (aGMRs) for potential determinants of SARS-CoV-2 seropositivity (all participants) and antibody titres (seropositive participants only), respectively.

Findings: 1696 (15.2%) of 11,130 participants were seropositive. Factors independently associated with increased risk included frontline health/care occupation (aOR 1.86, 95% CI 1.49–2.33), international travel (1.22, 1.08–1.37), BMI >30 *vs* <25 kg/m² (1.22, 1.05–1.42), Asian/Asian British *vs* White ethnicity (1.65, 1.10–2.47), and alcohol consumption ≥15 *vs* 0 units/week (1.26, 1.06–1.49). Light physical exercise associated with decreased risk (0.80, 0.69–0.93, for ≥10 *vs* 0–4 h/week). Higher titres associated with frontline health/care occupation (aGMR 1.26, 95% CI 1.13–1.41), international travel (1.10, 1.04–1.16), BMI >30 *vs* <25 kg/m² (1.09, 1.01–1.17), and Asian/Asian British *vs* White ethnicity (1.23, 1.03–1.46); these associations were not substantially attenuated by adjustment for disease severity.

Interpretation: Higher alcohol consumption and reduced physical exercise represent new modifiable risk factors for SARS-CoV-2 infection. Recognised associations between Asian/Asian British ethnic origin and obesity and increased risk of SARS-CoV-2 seropositivity were independent of other sociodemographic, clinical, or behavioural factors investigated.

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Research in context

Evidence before this study

We searched PubMed, medRxiv, and Google Scholar for papers published from Jan 1, 2020, to Aug 1, 2021, using the search terms (risk factor OR determinant OR predictor) AND (SARS-CoV-2 OR coronavirus OR COVID) AND (antibod* OR serop* OR (test AND positiv*)), with no language restrictions. Several studies have investigated determinants of SARS-CoV-2 infection, suggesting associations with sex, race/ethnicity, socioeconomic deprivation, household size and composition, and frontline worker status; however, studies have predominantly been done in small populations or groups with specific occupational or environmental risk factors, such as healthcare workers or homeless people. The few large-scale population-based studies have explored a wide range of sociodemographic and clinical risk factors, but detailed individual behaviours such as diet, use of vitamin supplements, levels of physical activity, and sleep quality have rarely been included. Far fewer studies have been done on determinants of SARS-CoV-2 antibody titres, with findings suggesting associations with age, race/ethnicity, and disease severity, but the evidence is inconclusive.

Added value of this study

This study is among the first to provide a detailed analysis of determinants of SARS-CoV-2 seropositivity and antibody titres for a large population-based sample. We included more than 80 individual-level risk factors, covering sociodemographic, occupational, and lifestyle factors; longstanding medical conditions, prescribed medication use, and vaccination status; and diet and supplemental micronutrient intake. To our knowledge, no existing studies of SARS-CoV-2 antibody titres have used such granular data to capture such a wide range of determinants.

Implications of all the available evidence

We highlight new, modifiable risk factors for SARS-CoV-2 seropositivity, including alcohol consumption and physical exercise, and show that recognised associations between increased infection risk and Asian/Asian British ethnicity and obesity are independent of a much wider range of sociodemographic, clinical and behavioural factors than has previously been investigated. We also report that frontline health/care occupation, international travel, obesity and Asian/Asian British ethnicity associate with higher antibody titres: these associations were not substantially attenuated by adjustment for disease severity, raising the possibility that they relate to increased intensity of exposure to SARS-CoV-2 or greater immune reactivity in these groups.

Introduction

The COVID-19 pandemic has caused more than 220 million recorded infections and over 4.5 million recorded deaths,[1] with these figures representing only a portion of the true burden.[2] Large, population-based studies have identified various risk factors for SARS-CoV-2 infection, including non-White ethnicity and lower educational attainment.[3-5] However, the vast majority of studies have been based on routine real-time reverse transcription PCR (RT-PCR) testing in healthcare settings or in the community; consequently, they are potentially open to collider bias, as the probability of being tested for infection can itself depend on the risk factors under investigation.[6] Access to testing has also changed across the course of the pandemic,[7] meaning earlier studies were more likely to focus on people with symptomatic disease or a history of travel, or on specific populations such as healthcare workers.

Serological population-based studies offer a different approach by testing members of a population uniformly, including people who might not be captured by routine testing. This approach not only reduces the risk of collider bias, but also can uncover previously undetected asymptomatic infections. Inclusion of asymptomatic SARS-CoV-2 infections in the analysis of risk factors is crucial, as asymptomatic individuals have been found to be as infectious as those with symptoms.[8] Serology studies also offer the opportunity to identify determinants of anti-SARS-CoV-2 antibody titres, which are a recognised correlate of protection against future infection.[9,10]

The largest population-based serology studies done to date have explored several sociodemographic and clinical risk factors, but have not considered risk factors related to lifestyle, diet, or levels of physical activity.[3-5,11,12] These studies have focused on IgG antibodies alone[11,12] or relied on immunoassays with low sensitivity,[12] potentially missing infections. They have also tended to be cross-sectional in design, so that reverse causality could potentially explain associations between symptomatic seropositivity and modifiable risk factors. Additionally, studies investigating determinants of antibody titres have focused on specific populations such as healthcare workers,[13,14] limiting the generalisability of their findings.

We therefore undertook a prospective population-based study to uncover determinants of SARS-CoV-2 seropositivity and antibody titres, combining high statistical power with detailed assessment of sociodemographic, clinical, and behavioural risk factors, and supported by an assay with proven sensitivity for detection of SARS-CoV-2 antibodies in non-hospitalised adults with mild or moderate COVID-19.[15]

Methods

Study design and participants

COVIDENCE UK is a prospective, longitudinal, population-based observational study of COVID-19 in the UK population (www.qmul.ac.uk/covidence).[16] Inclusion criteria were age 16 years or older and UK residence at enrolment, with no exclusion criteria. Participants were invited via a national media campaign to complete an online baseline questionnaire to capture: information on potential symptoms of COVID-19 experienced since Feb 1, 2020; results of any COVID-19 tests; and details of a wide range of potential risk factors for COVID-19 (appendix table S1). Online monthly follow-up questionnaires captured incident test-confirmed COVID-19 and symptoms of acute respiratory infection (appendix table S2). The study was launched on May 1, 2020.

The antibody study described here was introduced as an approved protocol amendment (amendment 3; November, 2020). Participants enrolled before the amendment were invited via email to participate in the antibody study and to give additional consent. As part of the antibody study, participants were invited to participate in serology testing from November, 2020. For this analysis, we included all participants enrolled in the study by Nov 2, 2020, partaking in serology testing who were not vaccinated against COVID-19 or who provided their dried blood spot sample on or before the date of their first COVID-19 vaccination. This paper reports findings from analysis of data collected up to April 18, 2021.

COVIDENCE UK 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).

Procedures

Antibody study participants were sent a kit containing instructions, lancets, and blood spot collection cards, to be posted back to the study team. Once returned, the samples were logged by the study team and sent in batches to the Clinical Immunology Service at the Institute of Immunology and Immunotherapy of the University of Birmingham (Birmingham, UK). Up to two more test kits were offered to participants whose initial samples were found to be insufficient for testing. Samples were taken from Nov 6, 2020, to April 18, 2021.

Semi-quantitative determination of antibody titres was done using a commercially available ELISA that measures combined IgG, IgA, and IgM (IgGAM) responses to the SARS-CoV-2 trimeric spike glycoprotein (product code MK654; The Binding Site [TBS], Birmingham, UK). The SARS-CoV-2 spike used is a soluble, stabilised, trimeric glycoprotein truncated at the transmembrane region.[17,18] This assay has been CE-marked with 98.3% (95% CI 96.4–99.4) specificity and 98.6% (92.6–100.0) sensitivity following RT-PCR-confirmed mild-to-moderate

COVID-19 that did not result in hospitalisation.[15] A cut-off ratio relative to the TBS cut-off calibrators was determined by plotting 624 pre-2019 negatives in a frequency histogram. A cut-off coefficient was then established for IgGAM (1.31), with ratio values classed as positive (≥1) or negative (<1). Dried blood spots were pre-diluted at a 1:40 dilution with 0.05% PBS-Tween using a Dynex Revelation automated absorbance microplate reader (Dynex Technologies; Chantilly, VA, USA). Plates were developed after 10 min using 3,3′,5,5′-tetramethylbenzidine core, and orthophosphoric acid used as a stop solution (both TBS). Optical densities at 450 nm were measured using the Dynex Revelation.

Outcomes

Study outcomes were presence versus absence of antibodies against SARS-CoV-2 (binary outcome assessed in all participants who did not report having tested positive for SARS-CoV-2 infection via RT-PCR or lateral flow test before enrolment), and antibody titres (continuous outcome considered in all seropositive participants).

Independent variables

88 putative risk factors for SARS-CoV-2 infection were selected *a priori*, covering sociodemographic, occupational, and lifestyle factors; longstanding medical conditions and prescribed medication use; Bacille Calmette Guérin and measles, mumps, and rubella vaccine status; and diet and supplemental micronutrient intake (appendix tables S1, S2). These factors, which were obtained from the baseline questionnaire, were included as independent variables in our models. To produce patient-level covariates for each class of medications investigated, participant responses were mapped to drug classes listed in the British National Formulary or the DrugBank and Electronic Medicines Compendium databases if not explicitly listed in the British National Formulary, as previously described.[16] Index of Multiple Deprivation (IMD) 2019 scores were assigned according to participants' postcodes, and categorised into quartiles.

Statistical analysis

The sample size required to obtain an odds ratio (OR) of at least 1.08 for a binary exposure with maximum variability (probability 0.50 changing to 0.52) and correlated with other variables in the model (R^2=0.4), using a two-sided test with 90% power and 5% significance, was estimated as 10,964, using Stata's powerlog program. Assuming 10% censoring at baseline (i.e., participants with missing data or previous SARS-CoV-2 infection) and 20% loss to follow-up, we aimed to recruit a minimum of 15,228 participants into COVIDENCE UK, with no upper limit. The antibody study was a pragmatic study including all participants meeting the inclusion criteria, with no sample size specified.

Logistic regression models were used to estimate ORs and 95% CIs for potential determinants of SARS-CoV-2 seropositivity. Linear regression models with robust standard errors were used to estimate geometric mean ratios (GMRs) and 95% CIs for potential determinants of log-transformed antibody titres in seropositive participants. We first estimated ORs and GMRs in minimally adjusted models, and included factors independently associated with each outcome at the 10% significance level in fully adjusted models. Both the minimally adjusted and fully adjusted models were controlled for age (<30 years, 30 to <40 years, 40 to <50 years, 50 to <60 years, 60 to <70 years, and ≥70 years), sex (male *vs* female), and duration of follow-up (days). We calculated p for trend for ordinal variables by re-running the regressions treating each ordinal variable in turn as continuous. Analyses were done for all participants with available data; missing data were not imputed. Correction for multiple comparisons was not applied, on the grounds that we were testing *a priori* hypotheses for all risk factors investigated.[19]

In a sensitivity analysis, we excluded participants from the seropositivity analysis who were classified as having had probable COVID-19 before enrolment on the basis of self-reported symptoms, using the symptom algorithm described and validated by Menni and colleagues.[20]

As antibody titres have been found to be associated with disease severity,[13,21] we did an exploratory analysis to investigate the extent to which COVID-19 severity might explain associations between independent variables and antibody titres, by including this as an explanatory variable in the titre analysis. COVID-19 severity was classified into three groups: 'asymptomatic' (non-hospitalised seropositive participants, who either did not report any symptoms of acute respiratory infection or whose symptoms were classified as having <50% probability of being due to COVID-19, using the symptom algorithm by Menni and colleagues[20]); 'symptomatic non-hospitalised' (non-hospitalised seropositive participants who reported symptoms of acute respiratory infection that were classified as having ≥50% probability of being due to COVID-19, using the symptom algorithm[20]); and 'hospitalised' (seropositive participants who were hospitalised for treatment of COVID-19).

We present descriptive statistics as n (%), mean (SD), or median (IQR). Statistical analyses were done using Stata (version 14.2; StataCorp, College Station, TX, USA).

Role of the funding source

The study funders had no role in the study design, data analysis, data interpretation, or writing of the report.

Results

Serology data were available for 12,294 of the 15,853 participants who consented to participate in the antibody study. We excluded data from 1074 participants who had been vaccinated against SARS-CoV-2 before providing their dried blood spot sample (figure 1). Of the 11,220 participants included, 1774 (15.8%) tested positive for SARS-CoV-2 antibodies. For the analysis of determinants of seropositivity, we excluded 90 (0.8%) participants who reported a positive RT-PCR or lateral flow test result for SARS-CoV-2 infection before enrolment, leaving a sample size of 11,130 participants with 1696 seropositive cases (figure 1). Selected baseline characteristics of included participants are shown in table 1. 70.1% of participants were female, and 95.7% identified their ethnicity as White, with median age of 62.3 years (IQR 52.9–68.7; table 1).

After adjustment for age, sex, and duration of follow-up, 28 factors were independently associated with risk of SARS-CoV-2 seropositivity with $p<0.10$ (table 2). When these factors were included together in a fully adjusted model, we observed that Asian/Asian British ethnicity (*vs* White), working as a frontline worker in a health or care setting (*vs* not working as a frontline worker), recent travel to a place of work or study, travel outside of the UK, high levels of alcohol consumption (≥15 units per week), high body-mass index (BMI; ≥25 kg/m^2), sex hormone therapy (i.e. hormone replacement therapy and hormonal contraception), and use of vitamin D supplements were independently associated with increased risk of SARS-CoV-2 infection as indicated by antibody seropositivity (table 2). By contrast, postgraduate education (*vs* primary or secondary), passive smoking, high levels of light physical exercise (walking ≥10 h per week), and prescribed paracetamol use were independently associated with reduced risk of SARS-CoV-2 infection. We also found weak evidence for positive associations with frequency of visits to the shops and ages 30 to less than 50 years (*vs* <30 years). In the fully adjusted model, the associations originally observed in minimally adjusted models for generational composition of households and living with a working-age adult were attenuated and no longer achieved conventional significance (table 2). Excluding the 796 participants with symptom-defined probable COVID-19, who did not have a positive PCR or lateral flow test result before enrolment, had little effect on our findings (appendix table S3).

When investigating associations with antibody titres, analysed as a continuous outcome in the subset of seropositive participants only, we found that 33 factors were independently associated with antibody titres with $p<0.10$ after adjustment for age, sex, and duration of follow-up (table 3). The distribution of titres for three of these factors—ethnicity, frontline worker status, and COVID-19 severity—are shown in figure 2, with higher medians for non-White ethnicities, health or social care frontline workers, and participants who were hospitalised for treatment of COVID-19. When the 33 factors were included together in a fully

adjusted model, we found that Asian/Asian British ethnicity (*vs* White), having a mortgage (*vs* owning own home), working as a frontline worker in a health or care setting, being an ex-smoker (*vs* a never-smoker), travel outside of the UK, taking multivitamin supplements, consuming at least two portions of dairy products or calcium-fortified alternatives (*vs* 0–1 portions), high BMI, and use of beta blockers were associated with higher antibody titres, whereas high levels of fruit, vegetable, or salad consumption and reporting feeling anxious or depressed at baseline were associated with lower antibody titres (table 3). p-for-trend analyses suggested higher antibody titres with increasing intake of dairy or calcium-fortified alternatives and increasing BMI (table 3). The associations in minimally adjusted models with chronic obstructive pulmonary disease, poor self-reported general health, and use of metformin or statins were attenuated in the fully adjusted model and were no longer statistically significant (table 3).

The addition of COVID-19 severity to our model of determinants of antibody titres in seropositive participants attenuated the associations observed for BMI and smoking status, but significant associations remained for all other variables (table 3). Inclusion of the severity variable also led to weak associations between antibody titres and male sex (GMR 0.95 [95% CI 0.90–1.00]; p=0.045) and use of H2-receptor antagonists (1.29 [1.00–1.66]; p=0.052; table 3). p-for-trend analyses suggested lower antibody titres with increasing fruit, vegetable, and salad intake, and higher titres with increasing intake of dairy or calcium-fortified alternatives and increasing age (table 3).

Discussion

In this large, prospective, population-based serological study, we explored determinants of SARS-CoV-2 seropositivity and antibody titres, evaluating more than 80 sociodemographic, clinical, and behavioural risk factors. We found that four factors—Asian/Asian British ethnicity, frontline occupation in health or social care, international travel, and high BMI—were strongly associated both with increased risk of SARS-CoV-2 seropositivity and with higher antibody titres in the subset of seropositive participants. Lower levels of educational attainment and light physical exercise and higher levels of alcohol consumption were found to associated with increased risk of SARS-CoV-2 seropositivity, as was use of vitamin D supplements. Low intake of dairy or calcium-fortified alternatives and high intake of fruit, vegetables, and salad were associated with lower antibody titres, as was reporting anxiety or depression. Importantly, most factors associated with antibody titres in seropositive participants retained significance after adjusting for disease severity.

Our results support previous studies that have found increased risk of SARS-CoV-2 seropositivity for healthcare workers,[3,4,12] people of Asian ethnicity,[3,5,12] and people with lower

educational attainment.[3,4] Non-White race/ethnicity has previously been highlighted as a determinant of both SARS-CoV-2 seropositivity[22-24] and antibody titres,[25] but questions remained over residual confounding.[22] Despite including a wide range of potential confounders, point estimates for all non-White participants remained higher in both our seropositivity and titre analyses, and significantly so for Asian/Asian British participants, emphasising the need to investigate the underlying biological or social factors driving this disparity. While we did not confirm increased seropositivity for Black participants, we lacked statistical power, as they represented only 0.4% of the cohort.

We identified two modifiable lifestyle factors associated with SARS-CoV-2 seropositivity: alcohol consumption and light physical exercise. High levels of alcohol intake are known to negatively affect immune response through several mechanisms,[26] which supports our finding of increased risk among participants consuming more than 15 units of alcohol a week. By contrast, we observed reduced risk among participants doing more than 10 hours of light physical exercise per week. It has been speculated that there is a J-shaped relationship between exercise load and susceptibility to infection, whereby moderate exercise can improve immune response, but prolonged, high-intensity exercise can increase susceptibility to infection.[27] This curve might explain why we did not see similar benefits for vigorous physical activity.

Our finding that use of vitamin D supplements was associated with increased risk of seropositivity contrasts with a previous study, which found lower risk in a univariable model and no association after adjusting for confounders;[23] randomised controlled trials are needed to resolve questions around potential effects of vitamin D supplements on susceptibility to SARS-CoV-2. We found no associations for frontline workers not based in health or social care, at odds with previous findings.[11,12] We also did not observe associations between seropositivity and age or sex, unlike other studies.[5,23,24,28,29] This may reflect the fact that we adjusted for more potential confounders than most of these studies, and included behaviours that reflect social mixing and influence exposure to infected individuals.

After adjustment for disease severity, we uncovered six factors associated with higher titres (Asian/Asian British ethnicity, working as a frontline worker in the health or care setting, international travel, taking multivitamin supplements, increased consumption of dairy products or calcium-fortified alternatives, and use of beta blockers) and four associated with lower titres (male sex; IMD quartile; high levels of fruit, vegetable, or salad consumption; and reporting feeling anxious or depressed at baseline). Different mechanisms may explain these associations. High intensity and frequency of exposure could be a cause of elevated antibody titres in participants who travelled abroad and in frontline health and social care workers,[30]

supported by previous findings of higher titres in healthcare workers.[14] Alternatively, greater immune reactivity could be a cause of higher titres, as seen in female participants, who generally have stronger innate and adaptive immune responses than males.[31] Diet and nutrition are known to affect immune responses[32] and thus might explain the higher titres observed with use of multivitamin supplements and higher levels of dairy intake (potentially reflecting higher calcium intakes).[33] However, little evidence is available for the effect of vitamin supplementation in suboptimal rather than micronutrient-deficient diets,[32] and after adjustment, we found no associations between intake of any individual vitamin supplements and antibody titres. The negative association with fruit, vegetable, and salad consumption was observed for the highest level of intake only (≥6 portions a day); however, despite 40% of vegan or vegetarian participants being included in that category, neither diet type was found to be associated with antibody titres, suggesting it is not the result of a restricted diet. We observed a significant positive dose–response relationship with age, supporting findings from other studies.[13,34,35] This association was not attenuated by adjustment for disease severity, suggesting that other mechanisms relating to the effects of age on host responses might be responsible.[36]

This study has several strengths. Use of serology to measure SARS-CoV-2 infection reduces collider bias, as serology testing was offered to all participants enrolled in COVIDENCE UK, in contrast to results from external routine testing that had limited availability, particularly at the start of the pandemic. Serology testing has also allowed us to better quantify the risk of SARS-CoV-2 infection by capturing previous infections that were asymptomatic or unconfirmed. A further strength is the use of an assay with high sensitivity and specificity that targets three different types of antibody,[37] increasing the probability of identifying a past infection. Additionally, we used dried blood spots for our sampling, which have been found to reduce processing failures compared with microtubes,[38] which are currently used by large seroprevalence surveys.[39] The prospective nature of our study reduces the potential for reverse causation explaining our findings, and the granularity of our questionnaire allowed us to explore potential determinants and confounders that other studies have not investigated.

Our study also has some limitations. First, COVIDENCE UK is a self-selected cohort, and thus several groups—such as people younger than 30 years, people of lower socioeconomic status, and non-White ethnic groups—are under-represented. This particularly affected our power to investigate outcomes for Black participants, who have been found to be at higher risk of SARS-CoV-2 infection[4,5,12] and adverse outcomes[22] than White people. However, insufficient representativeness in a cohort does not preclude identification of causal associations, and self-selection may result in better response to follow-up.[40] Second, as we included asymptomatic infections in our titre analysis, we were not able to adjust for timing of

infection onset, preventing us from capturing the effects of temporal changes in antibody responses. As 40% of our seropositive participants did not experience symptoms suggestive of COVID-19 or provide a symptom onset date, excluding them would have greatly reduced the power and generalisability of our analysis. Third, as with any observational study, we cannot exclude the possibility that some of the associations we report might be explained by residual or unmeasured confounding. For example, the finding that passive smoking but not active smoking reduces the risk of seropositivity compared with never-smokers should be treated with caution, unless a plausible protective mechanism can be found. However, we have minimised the risk of confounding by adjusting for a comprehensive list of putative risk factors, and hope that future studies can investigate the robustness of the associations found.

In conclusion, this prospective serological study shows that people of Asian/Asian British ethnicity, frontline workers in health or social care, people with high BMI, and those who had travelled abroad were at higher risk of SARS-CoV-2 seropositivity, after robust adjustment for confounders, and shows that these factors are also determinants of antibody titres, regardless of disease severity. We additionally show that alcohol consumption and physical exercise, both modifiable lifestyle factors, are associated with risk of seropositivity. Future research should focus on modifiable risk factors for seropositivity, as well as determinants of antibody titres and other correlates of protection after SARS-CoV-2 infection, to better understand which groups are most at risk of reinfection and what preventive measures can be taken.

Contributors

ARM wrote the study protocol, with input from HH, MT, and SOS. HH, MT, JS, SF, GAD, RAL, CJG, FK, AS, and ARM contributed to questionnaire development and design. HH co-ordinated and managed the study, with input from ARM, DAJ, MT, JS, SOS, NP and SM. HH, JS, ARM, and SOS supported recruitment. SF and AGR developed, validated, and performed laboratory assays. MT, HH, MG, and DAJ contributed to data management and coding medication data. MT and GV directly accessed and verified the data. Statistical analyses were done by MT, with input from SOS, ARM, MG, HH, and GV. GV, MT and 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. MT, HH, DAJ, SOS, ARM, and GV had full access to all data in the study, and ARM had final responsibility for the decision to submit for publication.

Declaration of interests

JS declares receipt of payments from Reach plc for news stories written about recruitment to, and findings of, the COVIDENCE UK study. AS is a member of the Scottish Government Chief Medical Officer's COVID-19 Advisory Group and its Standing Committee on Pandemics. He is also a member of the UK Government's NERVTAG's Risk Stratification Subgroup. ARM declares receipt of funding in the last 36 months to support vitamin D research from the following companies who manufacture or sell vitamin D supplements: Pharma Nord Ltd, DSM Nutritional Products Ltd, Thornton & Ross Ltd and Hyphens Pharma Ltd. ARM also declares support for attending meetings from the following companies who manufacture or sell vitamin D supplements: Pharma Nord Ltd and Abiogen Pharma Ltd. ARM also declares participation on the Data and Safety Monitoring Board for the Chair, DSMB, VITALITY trial (Vitamin D for Adolescents with HIV to reduce musculoskeletal morbidity and immunopathology). ARM also declares unpaid work as a Programme Committee member for the Vitamin D Workshop. ARM also declares receipt of vitamin D capsules for clinical trial use from Pharma Nord Ltd, Synergy Biologics Ltd and Cytoplan Ltd.

Data sharing

De-identified participant data will be made available upon reasonable request to the corresponding author.

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Tables, figures, and panels

Table 1: Baseline characteristics of participants included in seropositivity analysis

	Characteristics (N=11,130)
Sociodemographic, occupational, and lifestyle factors	
Age (years)	62.3 (52.9–68.7)
<30	323 (2.9%)
30 to <40	651 (5.8%)
40 to <50	1246 (11.2%)
50 to <60	2545 (22.9%)
60 to <70	4098 (36.8%)
≥70	2267 (20.4%)
Sex	
Female	7806 (70.1%)
Male	3324 (29.9%)
Ethnicity	
Black, African, Caribbean, or Black British	49 (0.4%)
Asian/Asian British	145 (1.3%)
Mixed, multiple, or other ethnic groups	285 (2.6%)
White	10,651 (95.7%)
Country of residence	
England	9835/11,129 (88.4%)
Northern Ireland	188/11,129 (1.7%)
Scotland	694/11,129 (6.2%)
Wales	412/11,129 (3.7%)
Housing	
Owns own home	7059/11,129 (63.4%)
Mortgage	2716/11,129 (24.4%)
Privately renting	654/11,129 (5.9%)
Renting from council	318/11,129 (2.9%)
Other	382/11,129 (3.4%)
Number of people per bedroom	
≤0.5	4382/11,059 (39.6%)
>0.5 to <1	3085/11,059 (27.9%)
1 to <2	3355/11,059 (30.3%)
≥2	237/11,059 (2.1%)
Shares home with	
Pre-school children (0–4 years)	362/11,106 (3.3%)
Schoolchildren (5–15 years)	1227/11,101 (11.1%)
Working-age adult (16–64 years)	5748/11,101 (51.8%)
Household income sufficient for basic needs	
Yes	10,409/11,129 (93.5%)
Mostly	390/11,129 (3.5%)
Sometimes	80/11,129 (0.7%)
No	250/11,129 (2.2%)
Claiming Universal Credit	275/11,098 (2.5%)

IMD decile	7 (5–9)
Occupational status	
Employed	3662 (32.9%)
Self-employed	1048 (9.4%)
Retired	5284 (47.5%)
Furloughed	282 (2.5%)
Unemployed	186 (1.7%)
Student	174 (1.6%)
Other	494 (4.4%)
Frontline worker	1700/11,112 (15.3%)
Health or social care	499/11,112 (4.5%)
Other	1201/11,112 (10.8%)
Highest educational level attained	
Primary or secondary	1194/11,123 (10.7%)
Higher or further education (A levels or BTEC)	1600/11,123 (14.4%)
College or university	4961/11,123 (44.6%)
Postgraduate degree	3368/11,123 (30.3%)
Tobacco smoking status	
Never-smoker	6281 (56.4%)
Ex-smoker	4325 (38.9%)
Current smoker	524 (4.7%)
Regular environmental tobacco smoke exposure	203/11,128 (1.8%)
Vaping status	
Never-vaper	10,463/11,099 (94.3%)
Ex-vaper	339/11,099 (3.1%)
Current vaper	297/11,099 (2.7%)
Alcohol (units per week)	
None	2986/11,129 (26.8%)
1–7	3932/11,129 (35.3%)
8–14	2249/11,129 (20.2%)
≥15	1962/11,129 (17.6%)
Does any vigorous physical exercise	7001/11,102 (63.1%)
1–3 hours per week	4142/11,102 (37.3%)
≥4 hours per week	2859/11,102 (25.8%)
Duration of follow-up (days)	172 (72)
Medical conditions and prescribed medication use	
Self-reported general health	
Excellent	2291/11,129 (20.6%)
Very good	4435/11,129 (39.9%)
Good	2939/11,129 (26.4%)
Fair	1147/11,129 (10.3%)
Poor	317/11,129 (2.8%)
BMI, kg/m²	26.2 (5.3)
<25	5424/11,106 (48.8%)
25–30	3586/11,106 (32.3%)
>30	2096/11,106 (18.9%)

Comorbidities	
Arterial disease*	552 (5.0%)
Asthma	1800 (16.2%)
Atopy**	2861 (25.7%)
Autoimmune disease†	965 (8.7%)
Cancer	1036 (9.3%)
Past (cured or in remission)	945 (8.5%)
Present (active treatment)	91 (0.8%)
COPD	213 (1.9%)
Diabetes or pre-diabetes	858 (7.7%)
Pre-diabetes	332/11,118 (3.0%)
Type 1	80/11,118 (0.7%)
Type 2	434/11,118 (3.9%)
Heart disease‡	408 (3.7%)
Hypertension	2379 (21.4%)
Immunodeficiency§	64 (0.6%)
Kidney disease	214 (1.9%)
Major neurological conditions¶	287 (2.6%)

Data are n (%), n/N (%), mean (SD), or median (IQR). BTEC=Business and Technology Education Council. BMI=body-mass index. COPD=chronic obstructive pulmonary disease. IMD=Index of Multiple Deprivation. *Ischaemic heart disease, peripheral vascular disease, or cerebrovascular disease. ** Hayfever/allergic rhinitis or atopic eczema/dermatitis. †Including rheumatoid arthritis, multiple sclerosis, lupus, Crohn's disease, ulcerative colitis, and psoriasis. ‡Coronary artery disease or heart failure. §HIV, primary immunodeficiency disorder, or other immunodeficiency. ¶Stroke, transient ischaemic attack, dementia, Parkinson's disease, multiple sclerosis, or motor neuron disease.

Table 2: **Minimally adjusted and fully adjusted odds of seropositivity**

	Seropositive participants	Minimally adjusted model*		Fully adjusted model†	
		OR (95% CI)	p value	OR (95% CI)	p value
Sociodemographic, occupational, and lifestyle factors					
Age (years)					
<30	45/323 (13.9%)	1.00		1.00	
30 to <40	116/651 (17.8%)	1.34 (0.92–1.95)	0.123	1.42 (0.94–2.15)	0.092
40 to <50	241/1246 (19.3%)	1.47 (1.04–2.08)	0.028	1.47 (0.99–2.19)	0.056
50 to <60	419/2545 (16.5%)	1.20 (0.86–1.68)	0.272	1.28 (0.87–1.88)	0.211
60 to <70	557/4098 (13.6%)	0.96 (0.69–1.33)	0.808	1.18 (0.79–1.76)	0.420
≥70	318/2267 (14.0%)	0.99 (0.71–1.39)	0.954	1.35 (0.88–2.05)	0.168
p for trend	..	..	<0.001	..	0.862
Sex					
Female	1177/7806 (15.1%)	1.00		1.00	
Male	519/3324 (15.6%)	1.09 (0.97–1.23)	0.129	1.06 (0.94–1.21)	0.332
Ethnicity					
White	1598/10,651 (15.0%)	1.00		1.00	
Black, African, Caribbean, or Black British	10/49 (20.4%)	1.36 (0.67–2.73)	0.393	1.12 (0.51–2.44)	0.783
Asian/Asian British	34/145 (23.4%)	1.64 (1.11–2.43)	0.013	1.65 (1.10–2.47)	0.017
Mixed, multiple, or other ethnic groups	54/285 (18.9%)	1.28 (0.95–1.74)	0.109	1.26 (0.92–1.73)	0.158
Housing					
Owns own home	991/7059 (14.0%)	1.00		1.00	
Mortgage	481/2716 (17.7%)	1.15 (0.99–1.33)	0.063	1.09 (0.94–1.26)	0.276
Privately renting	108/654 (16.5%)	1.12 (0.88–1.42)	0.354	1.20 (0.93–1.54)	0.159
Renting from council	56/318 (17.6%)	1.21 (0.89–1.63)	0.221	1.31 (0.93–1.85)	0.121
Other	60/382 (15.7%)	1.11 (0.80–1.52)	0.535	1.12 (0.80–1.56)	0.509
Claiming Universal Credit					
No	1654/10,823 (15.3%)	1.00		1.00	
Yes	35/275 (12.7%)	0.72 (0.50–1.04)	0.081	0.71 (0.48–1.04)	0.080
Number of people per bedroom					
≤0.5	590/4382 (13.5%)	1.00		1.00	
>0.5 to <1	499/3085 (16.2%)	1.19 (1.05–1.36)	0.009	1.06 (0.91–1.23)	0.461
1 to <2	559/3355 (16.7%)	1.14 (0.99–1.31)	0.061	0.99 (0.84–1.17)	0.929
≥2	35/237 (14.8%)	0.98 (0.67–1.43)	0.919	0.73 (0.48–1.12)	0.147
p for trend	..	..	0.092	..	0.560
Multigenerational household					
Living alone	265/1997 (13.3%)	1.00		1.00	
Single generation	925/6055 (15.3%)	1.16 (1.00–1.35)	0.044	1.11 (0.92–1.35)	0.263
Two-generation	488/2990 (16.3%)	1.18 (1.00–1.39)	0.053	1.13 (0.92–1.40)	0.249
Three-generation	18/88 (20.5%)	1.57 (0.92–2.69)	0.099	1.52 (0.84–2.73)	0.163
p for trend	..	..	0.043	..	0.233
Shares home with working-age adult (16–64 years)					

No	724/5353 (13.5%)	1.00		1.00	
Yes	968/5748 (16.8%)	1.20 (1.06–1.36)	0.004	1.08 (0.93–1.26)	0.335
Highest educational level attained					
Primary or secondary	198 (16.6%)	1.00		1.00	
Higher or further education (A levels or BTEC)	244 (15.3%)	0.90 (0.73–1.10)	0.308	0.93 (0.75–1.15)	0.521
College or university	777 (15.7%)	0.92 (0.78–1.10)	0.356	0.91 (0.76–1.09)	0.320
Postgraduate degree	476 (14.1%)	0.80 (0.67–0.96)	0.019	0.80 (0.66–0.97)	0.023
p for trend	..	..	0.021	..	0.015
Frontline worker					
No	1369/9422 (14.5%)	1.00		1.00	
Non-health	197/1201 (16.4%)	1.09 (0.92–1.29)	0.307	1.00 (0.84–1.20)	0.990
Health or care	130/499 (26.1%)	1.96 (1.59–2.43)	<0.001	1.86 (1.49–2.33)	<0.001
Travel to place of work or study in past week					
No	669/5031 (13.3%)	1.00		1.00	
Yes	1014/5981 (17.0%)	1.26 (1.12–1.40)	<0.001	1.20 (1.07–1.35)	0.002
Number of visits to shops per week					
0	251/1744 (14.4%)	1.00		1.00	
1	342/2234 (15.3%)	1.10 (0.92–1.31)	0.294	1.08 (0.90–1.30)	0.398
2–3	625/4040 (15.5%)	1.14 (0.97–1.34)	0.106	1.13 (0.96–1.34)	0.146
≥4	478/3105 (15.4%)	1.18 (0.99–1.39)	0.064	1.19 (0.99–1.42)	0.065
p for trend	..	..	0.065	..	0.057
Travel outside of the UK between November, 2019, and February, 2021‡					
No	926/6529 (14.2%)	1.00		1.00	
Yes	572/3507 (16.3%)	1.19 (1.06–1.33)	0.003	1.22 (1.08–1.37)	0.001
Tobacco smoking status					
Never-smoker	930/6281 (14.8%)	1.00		1.00	
Ex-smoker	690/4325 (16.0%)	1.10 (0.99–1.23)	0.078	1.05 (0.94–1.18)	0.393
Current smoker	76/524 (14.5%)	0.92 (0.71–1.18)	0.500	0.82 (0.62–1.09)	0.165
Regular environmental tobacco smoke exposure					
No	1672/10,925 (15.3%)	1.00		1.00	
Yes	23/203 (11.3%)	0.67 (0.43–1.03)	0.070	0.60 (0.37–0.97)	0.035
Alcohol (units per week)					
None	438/2986 (14.7%)	1.00		1.00	
1–7	610/3932 (15.5%)	1.09 (0.95–1.25)	0.206	1.09 (0.95–1.25)	0.238
8–14	318/2249 (14.1%)	0.99 (0.84–1.15)	0.860	1.01 (0.86–1.20)	0.874
≥15	330/1962 (16.8%)	1.20 (1.02–1.41)	0.024	1.26 (1.06–1.49)	0.009
p for trend	..	..	0.102	..	0.035
Vigorous physical exercise (hours per week)					
0	665/4101 (16.2%)	1.00		1.00	
1–3	619/4142 (14.9%)	0.93 (0.82–1.05)	0.227	0.96 (0.84–1.09)	0.502
≥4	409/2859 (14.3%)	0.88 (0.77–1.01)	0.066	0.97 (0.83–1.12)	0.652
p for trend	..	..	0.061	..	0.620

Light physical exercise (hours per week)					
0–4	614/3631 (16.9%)	1.00		1.00	
5–9	613/3714 (16.5%)	1.00 (0.89–1.14)	0.943	1.04 (0.91–1.19)	0.533
≥10	468/3764 (12.4%)	0.75 (0.66–0.86)	<0.001	0.80 (0.69–0.93)	0.003
p for trend	..	..	<0.001	..	0.004
Lower impact physical activity (hours per week)					
0	991/6272 (15.8%)	1.00		1.00	
1	322/2131 (15.1%)	0.95 (0.83–1.09)	0.450	0.99 (0.86–1.14)	0.894
≥2	378/2695 (14.0%)	0.89 (0.78–1.01)	0.071	0.97 (0.84–1.11)	0.659
Diet and supplemental micronutrient intake					
Zinc (only) supplement					
No	1602/10,608 (15.1%)	1.00		1.00	
Yes	94/522 (18.0%)	1.22 (0.97–1.54)	0.090	1.19 (0.93–1.51)	0.158
Portions of dairy products or calcium-fortified alternatives per day					
0–1	474/2928 (16.2%)	1.00		1.00	
2	460/3254 (14.1%)	0.87 (0.76–1.00)	0.049	0.89 (0.77–1.03)	0.123
3–5	389/2650 (14.7%)	0.91 (0.79–1.06)	0.220	0.93 (0.80–1.09)	0.379
≥6	368/2269 (16.2%)	1.04 (0.89–1.21)	0.609	1.06 (0.91–1.24)	0.436
p for trend	..	..	0.595	..	0.434
Medical conditions and prescribed medication use					
BMI, kg/m²					
<25	741/5424 (13.7%)	1.00		1.00	
25–30	604/3586 (16.8%)	1.28 (1.14–1.44)	<0.001	1.24 (1.10–1.41)	<0.001
>30	347/2096 (16.6%)	1.21 (1.05–1.39)	0.007	1.22 (1.05–1.42)	0.010
p for trend	..	..	0.001	..	0.002
COPD					
No	1656/10,917 (15.2%)	1.00		1.00	
Yes	40/213 (18.8%)	1.36 (0.96–1.93)	0.084	1.27 (0.87–1.86)	0.224
Beta-2 adrenergic agonists					
No	1528/10,176 (15.0%)	1.00		1.00	
Yes	168/954 (17.6%)	1.19 (1.00–1.42)	0.056	1.31 (0.49–3.53)	0.588
Bronchodilators					
No	1523 (15.0%)	1.00		1.00	
Yes	173 (17.5%)	1.18 (0.99–1.41)	0.058	0.94 (0.35–2.51)	0.904
Paracetamol					
No	1643/10,691 (15.4%)	1.00		1.00	
Yes	53/439 (12.1%)	0.77 (0.58–1.03)	0.083	0.70 (0.52–0.96)	0.026
Sex hormone therapy					
No	1551 (15.1%)	1.00		1.00	
Yes	145 (17.4%)	1.20 (0.99–1.45)	0.064	1.24 (1.01–1.50)	0.036
Vitamin D (over the counter or prescribed)					
No	1066/7300 (14.6%)	1.00		1.00	
Yes	630/3830 (16.4%)	1.18 (1.06–1.31)	0.003	1.20 (1.07–1.35)	0.002

Data are n/N (%) or OR (95% CI). BMI=body-mass index. BTEC=Business and Technology Education Council. COPD=chronic obstructive pulmonary disease. OR=odds ratio. *Adjusted for age, sex, and duration of follow-up. †Adjusted for all factors shown and duration of follow-up. The fully adjusted analysis includes 10,744 participants with data available for all factors. ‡The 1094 participants with unknown or missing travel status were included in the analysis as a separate category to ensure greater power.

Table 3: **Minimally adjusted and fully adjusted GMRs of antibody titres in seropositive participants, with exploratory analysis of disease severity**

	Seropositive participants (n=1774)	Minimally adjusted model*		Fully adjusted model†		Fully adjusted model plus adjustment for disease severity‡	
		GMR (95% CI)	p value	GMR (95% CI)	p value	GMR (95% CI)	p value
Sociodemographic, occupational, and lifestyle factors							
Age (years)							
<30	50 (2.8%)	1.00		1.00		1.00	
30 to <40	124 (7.0%)	0.96 (0.80–1.15)	0.664	0.97 (0.80–1.17)	0.718	0.94 (0.78–1.13)	0.489
40 to <50	257 (14.5%)	0.99 (0.83–1.17)	0.882	1.04 (0.86–1.25)	0.691	1.03 (0.86–1.23)	0.755
50 to <60	445 (25.1%)	0.95 (0.81–1.13)	0.579	1.03 (0.85–1.24)	0.769	1.03 (0.86–1.23)	0.747
60 to <70	575 (32.4%)	0.93 (0.79–1.10)	0.418	1.07 (0.88–1.30)	0.514	1.09 (0.90–1.32)	0.370
≥70	323 (18.2%)	0.93 (0.78–1.10)	0.402	1.07 (0.87–1.32)	0.505	1.12 (0.92–1.37)	0.270
p for trend	..	..	0.143	..	0.233	..	0.020
Sex							
Female	1234 (69.6%)	1.00		1.00		1.00	
Male	540 (30.4%)	0.99 (0.94–1.04)	0.686	0.95 (0.90–1.01)	0.079	0.95 (0.90–1.00)	0.045
Ethnicity							
White	1672 (94.3%)	1.00		1.00		1.00	
Black, African, Caribbean, or Black British	11 (0.6%)	1.34 (0.93–1.92)	0.112	1.11 (0.77–1.61)	0.567	1.17 (0.80–1.69)	0.419
Asian/Asian British	35 (2.0%)	1.21 (1.01–1.44)	0.036	1.23 (1.03–1.46)	0.023	1.23 (1.03–1.47)	0.023
Mixed, multiple, or other ethnic groups	56 (3.2%)	1.10 (0.95–1.27)	0.203	1.08 (0.92–1.27)	0.319	1.06 (0.91–1.24)	0.425
Housing							
Owns own home	1021 (57.6%)	1.00		1.00		1.00	
Mortgage	515 (29.0%)	1.12 (1.04–1.20)	0.002	1.09 (1.01–1.17)	0.021	1.07 (1.00–1.15)	0.048
Privately renting	112 (6.3%)	1.07 (0.96–1.20)	0.214	1.01 (0.90–1.13)	0.882	0.99 (0.89–1.10)	0.861
Renting from council	61 (3.4%)	1.04 (0.90–1.20)	0.592	1.01 (0.87–1.17)	0.916	1.00 (0.87–1.16)	0.953
Other	65 (3.7%)	1.17 (0.97–1.41)	0.103	1.12 (0.92–1.35)	0.263	1.11 (0.92–1.34)	0.260
Number of people per bedroom							
≤0.5	611/1761 (34.7%)	1.00		1.00		1.00	
>0.5 to <1	521/1761 (29.6%)	1.04 (0.98–1.11)	0.199	1.02 (0.96–1.08)	0.574	1.00 (0.95–1.06)	0.867
1 to <2	593/1761 (33.7%)	1.06 (0.99–1.14)	0.077	1.03 (0.97–1.11)	0.328	1.03 (0.97–1.10)	0.369
≥2	36/1761 (2.0%)	1.24 (0.98–1.57)	0.073	1.20 (0.93–1.55)	0.159	1.21 (0.96–1.54)	0.109
p for trend	..	..	0.028	..	0.136	..	0.157
IMD rank							

Quartile 1 (least wealthy)	432/1769 (24.4%)	1.01 (0.94–1.08)	0.854	0.97 (0.90–1.04)	0.440	0.98 (0.91–1.05)	0.550
Quartile 2	428/1769 (24.2%)	1.06 (0.98–1.14)	0.127	1.02 (0.95–1.10)	0.528	1.03 (0.96–1.11)	0.388
Quartile 3	444/1769 (25.1%)	0.94 (0.88–1.00)	0.049	0.93 (0.87–0.99)	0.021	0.93 (0.88–0.99)	0.032
Quartile 4 (most wealthy)	465/1769 (26.3%)	1.00		1.00		1.00	
p for trend	..	..	0.215	..	0.953	..	0.757
Frontline worker							
No	1402 (79.0%)	1.00		1.00		1.00	
Health or social care	166 (9.4%)	1.34 (1.20–1.49)	<0.001	1.26 (1.13–1.41)	<0.001	1.21 (1.08–1.35)	0.001
Other	206 (11.6%)	1.07 (0.98–1.16)	0.114	1.04 (0.95–1.13)	0.380	1.03 (0.95–1.11)	0.528
Highest educational level attained							
Primary or secondary	209/1773 (11.8%)	1.00		1.00		1.00	
Higher or further education (A levels or BTEC)	255/1773 (14.4%)	0.92 (0.83–1.02)	0.118	0.93 (0.84–1.02)	0.139	0.95 (0.87–1.05)	0.324
College or university	805/1773 (45.4%)	0.92 (0.84–1.00)	0.057	0.93 (0.85–1.02)	0.137	0.95 (0.87–1.03)	0.242
Postgraduate degree	504/1773 (28.4%)	0.92 (0.84–1.01)	0.096	0.93 (0.85–1.03)	0.160	0.95 (0.87–1.03)	0.223
p for trend	..	..	0.157	..	0.236	..	0.299
Tobacco smoking status							
Never-smoker	969 (54.6%)	1.00		1.00		1.00	
Ex-smoker	728 (41.0%)	1.06 (1.01–1.12)	0.029	1.06 (1.00–1.11)	0.035	1.04 (0.99–1.10)	0.091
Current smoker	77 (4.3%)	0.97 (0.86–1.08)	0.555	0.90 (0.80–1.02)	0.093	0.94 (0.84–1.06)	0.310
Regular environmental tobacco smoke exposure							
No	1750/1773 (98.7%)	1.00		1.00		1.00	
Yes	23/1773 (1.3%)	0.88 (0.75–1.02)	0.098	0.86 (0.72–1.03)	0.101	0.91 (0.77–1.07)	0.258
Actual sleep (hours per night)							
≤6	169/1773 (9.5%)	1.14 (1.03–1.27)	0.010	0.93 (0.83–1.03)	0.172	0.96 (0.87–1.07)	0.471
7	419/1773 (23.6%)	1.00 (0.94–1.06)	0.954	0.92 (0.83–1.03)	0.143	0.96 (0.87–1.06)	0.442
8	728/1773 (41.1%)	1.00		1.00		1.00	
≥9	457/1773 (25.8%)	1.03 (0.97–1.09)	0.369	0.94 (0.84–1.05)	0.287	0.97 (0.88–1.08)	0.595
p for trend	..	..	0.210	..	0.435	..	0.708
Vigorous physical exercise (hours per week)							
0	714/1771 (40.3%)	1.00		1.00		1.00	
1–3	635/1771 (35.9%)	0.92 (0.87–0.97)	0.004	0.95 (0.9–1.01)	0.109	0.96 (0.91–1.02)	0.171
≥4	422/1771 (23.8%)	0.96 (0.89–1.02)	0.195	1.00 (0.93–1.07)	0.926	1.01 (0.94–1.07)	0.875

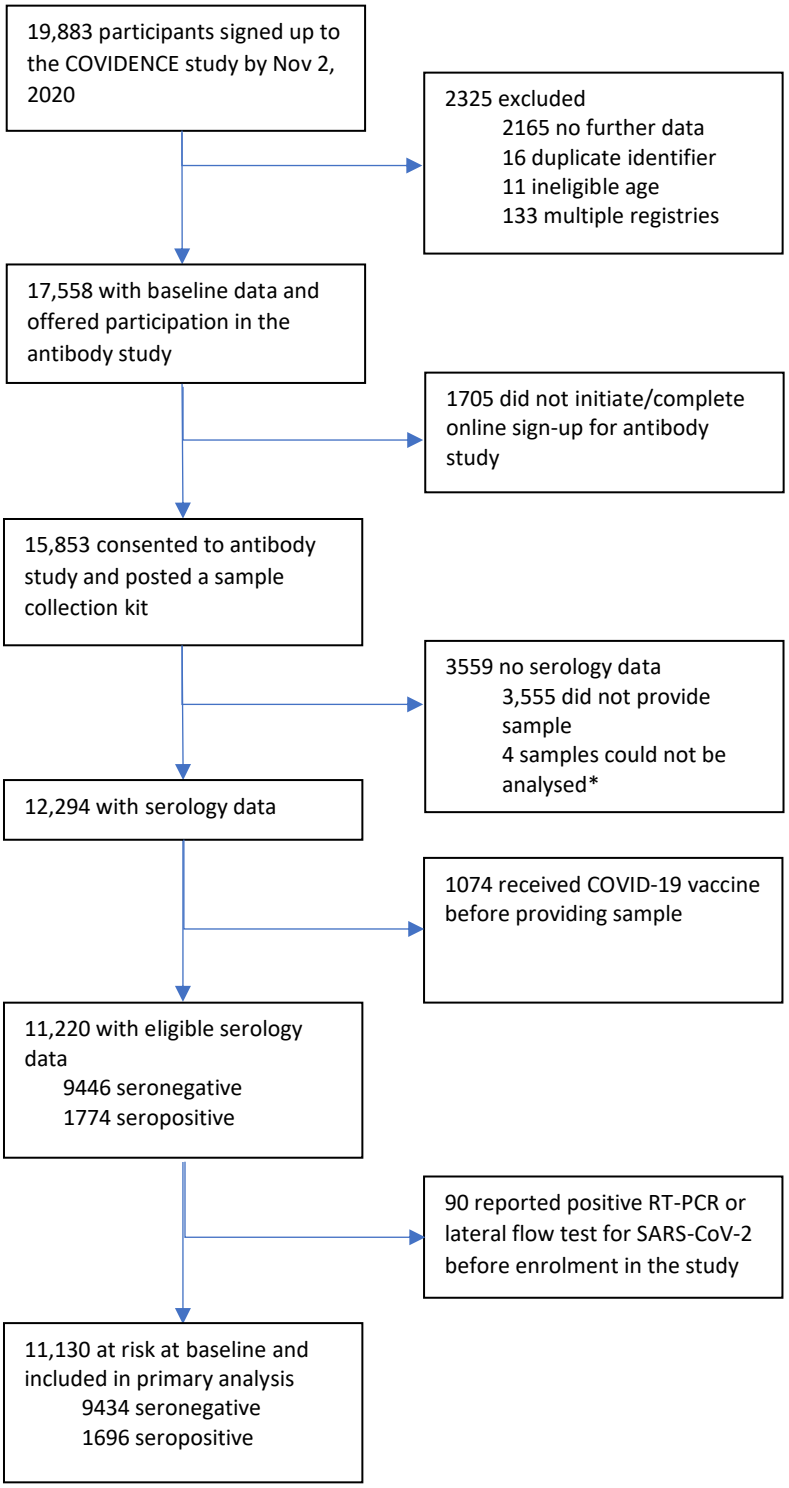
p for trend	..	..	0.104	..	0.874	..	0.988
Light physical exercise (hours per week)							
0–4	659/1773 (37.2%)	1.00		1.00		1.00	
5–9	631/1773 (35.6%)	0.92 (0.87–0.98)	0.008	0.98 (0.92–1.04)	0.491	1.00 (0.94–1.06)	0.957
≥10	483/1773 (27.2%)	0.98 (0.92–1.05)	0.538	1.03 (0.97–1.11)	0.331	1.04 (0.97–1.11)	0.271
p for trend	..	..	0.395	..	0.442	..	0.289
Travel to place of work or study in past week							
No	669/1683 (39.8%)	1.00		1.00		1.00	
Yes	1014/1683 (60.3%)	1.05 (1.00–1.10)	0.076	1.02 (0.97–1.07)	0.452	1.03 (0.98–1.08)	0.258
Travel outside of the UK between November, 2019, and February, 2021§							
No	955 (53.8%)	1.00		1.00		1.00	
Yes	602 (33.9%)	1.08 (1.02–1.13)	0.004	1.10 (1.04–1.16)	<0.001	1.09 (1.03–1.14)	0.002
Diet and supplemental micronutrient intake							
Multivitamin supplement							
No	1377 (77.6%)	1.00		1.00		1.00	
Yes	397 (22.4%)	1.10 (1.03–1.18)	0.003	1.09 (1.02–1.17)	0.007	1.09 (1.03–1.16)	0.005
Iron (only) supplement							
No	1713 (96.6%)	1.00		1.00		1.00	
Yes	61 (3.4%)	1.18 (0.99–1.39)	0.057	1.17 (0.99–1.37)	0.062	1.15 (0.98–1.36)	0.081
Zinc (only) supplement							
No	1673 (94.3%)	1.00		1.00		1.00	
Yes	101 (5.7%)	0.92 (0.84–1.01)	0.092	0.94 (0.85–1.03)	0.205	0.92 (0.84–1.02)	0.100
Fruit, vegetable, or salad intake per day							
0–2	266/1766 (15.1%)	1.00		1.00		1.00	
3–4	559/1766 (31.7%)	0.94 (0.87–1.02)	0.130	0.93 (0.86–1.01)	0.078	0.94 (0.87–1.01)	0.109
5	374/1766 (21.2%)	0.94 (0.87–1.03)	0.185	0.92 (0.84–1.00)	0.053	0.93 (0.85–1.01)	0.085
≥6	567/1766 (32.1%)	0.93 (0.86–1.01)	0.072	0.91 (0.84–0.99)	0.021	0.91 (0.84–0.98)	0.019
p for trend	..	..	0.146	..	0.112	..	0.029
Portions of dairy products or calcium-fortified alternatives per day							
0–1	491/1769 (27.8%)	1.00		1.00		1.00	
2	485/1769 (27.4%)	1.07 (1.01–1.14)	0.033	1.09 (1.03–1.17)	0.007	1.09 (1.03–1.17)	0.006
3–5	407/1769 (23.0%)	1.11 (1.03–1.19)	0.004	1.13 (1.05–1.21)	0.001	1.11 (1.04–1.19)	0.003

≥6	386/1769 (21.8%)	1.06 (0.99–1.14)	0.078	1.08 (1.01–1.16)	0.031	1.08 (1.00–1.15)	0.039
p for trend	..	..	0.035	..	0.011	..	0.020
Medical conditions and medication use							
Self-reported general health							
Excellent	341/1773 (19.2%)	1.00		1.00		1.00	
Very good	701/1773 (39.5%)	1.03 (0.96–1.10)	0.404	0.99 (0.92–1.06)	0.724	0.99 (0.93–1.06)	0.763
Good	474/1773 (26.7%)	1.02 (0.95–1.10)	0.530	0.98 (0.90–1.06)	0.570	0.97 (0.90–1.04)	0.405
Fair	198/1773 (11.2%)	1.08 (0.98–1.20)	0.109	0.98 (0.89–1.08)	0.699	0.97 (0.88–1.07)	0.507
Poor	59/1773 (3.3%)	1.19 (1.01–1.40)	0.037	1.09 (0.91–1.32)	0.346	1.02 (0.84–1.24)	0.844
p for trend	..	..	0.034	..	0.658	..	0.633
BMI, kg/m²							
<25	764/1769 (43.2%)	1.00		1.00		1.00	
25–30	626/1769 (35.4%)	1.06 (1.00–1.12)	0.044	1.03 (0.98–1.09)	0.258	1.03 (0.97–1.09)	0.299
>30	379/1769 (21.4%)	1.12 (1.05–1.21)	0.001	1.09 (1.01–1.17)	0.030	1.06 (0.99–1.14)	0.081
p for trend	..	..	0.034	..	0.009	..	0.071
Diabetes or pre-diabetes							
No diabetes	1636/1772 (92.3%)	1.00		1.00		1.00	
Pre-diabetes	52/1772 (2.9%)	1.02 (0.88–1.19)	0.755	0.98 (0.85–1.12)	0.748	0.99 (0.87–1.13)	0.897
Type 1	12/1772 (0.7%)	1.03 (0.78–1.36)	0.809	0.97 (0.74–1.28)	0.842	1.02 (0.77–1.35)	0.902
Type 2	72/1772 (4.1%)	1.15 (0.99–1.34)	0.066	0.98 (0.82–1.18)	0.862	0.98 (0.83–1.16)	0.828
COPD							
No	1728 (97.4%)	1.00		1.00		1.00	
Yes	46 (2.6%)	1.23 (1.01–1.50)	0.044	1.12 (0.93–1.36)	0.235	1.08 (0.90–1.30)	0.402
Heart disease¶							
No	1708 (96.3%)	1.00		1.00		1.00	
Yes	66 (3.7%)	1.15 (0.98–1.34)	0.088	0.97 (0.83–1.13)	0.700	0.99 (0.86–1.14)	0.912
Reported feeling anxious or depressed at baseline							
No	1294/1773 (73.0%)	1.00		1.00		1.00	
Yes	479/1773 (27.0%)	0.95 (0.90–1.01)	0.092	0.91 (0.86–0.97)	0.002	0.91 (0.86–0.96)	0.001
Anticholinergics							
No	1685 (95.0%)	1.00		1.00		1.00	
Yes	89 (5.0%)	1.17 (1.01–1.35)	0.034	1.13 (0.99–1.30)	0.077	1.13 (0.99–1.29)	0.077
Beta blockers							
No	1659 (93.5%)	1.00		1.00		1.00	
Yes	115 (6.5%)	1.14 (1.02–1.27)	0.019	1.12 (1.01–1.25)	0.035	1.13 (1.01–1.25)	0.025

H2-receptor antagonists							
No	1763 (99.4%)	1.00		1.00		1.00	
Yes	11 (0.6%)	1.24 (0.96–1.59)	0.101	1.21 (0.93–1.57)	0.149	1.29 (1.00–1.66)	0.052
Metformin							
No	1720 (97.0%)	1.00		1.00		1.00	
Yes	54 (3.0%)	1.26 (1.05–1.50)	0.011	1.13 (0.90–1.41)	0.310	1.16 (0.94–1.43)	0.179
Statins							
No	1487 (83.8%)	1.00		1.00		1.00	
Yes	287 (16.2%)	1.08 (1.00–1.16)	0.044	1.04 (0.96–1.13)	0.293	1.04 (0.96–1.12)	0.331
COVID-19 severity ||							
Asymptomatic	1242/1759 (70.6%)	1.00				1.00	
Symptomatic, not hospitalised	473/1759 (26.9%)	1.31 (1.23–1.38)	<0.001	..	..	1.26 (1.19–1.34)	<0.001
Hospitalised	44/1759 (2.5%)	2.17 (1.73–2.72)	<0.001	..	..	1.95 (1.55–2.45)	<0.001
p for trend	..	..	<0.001	..	..	..	<0.001

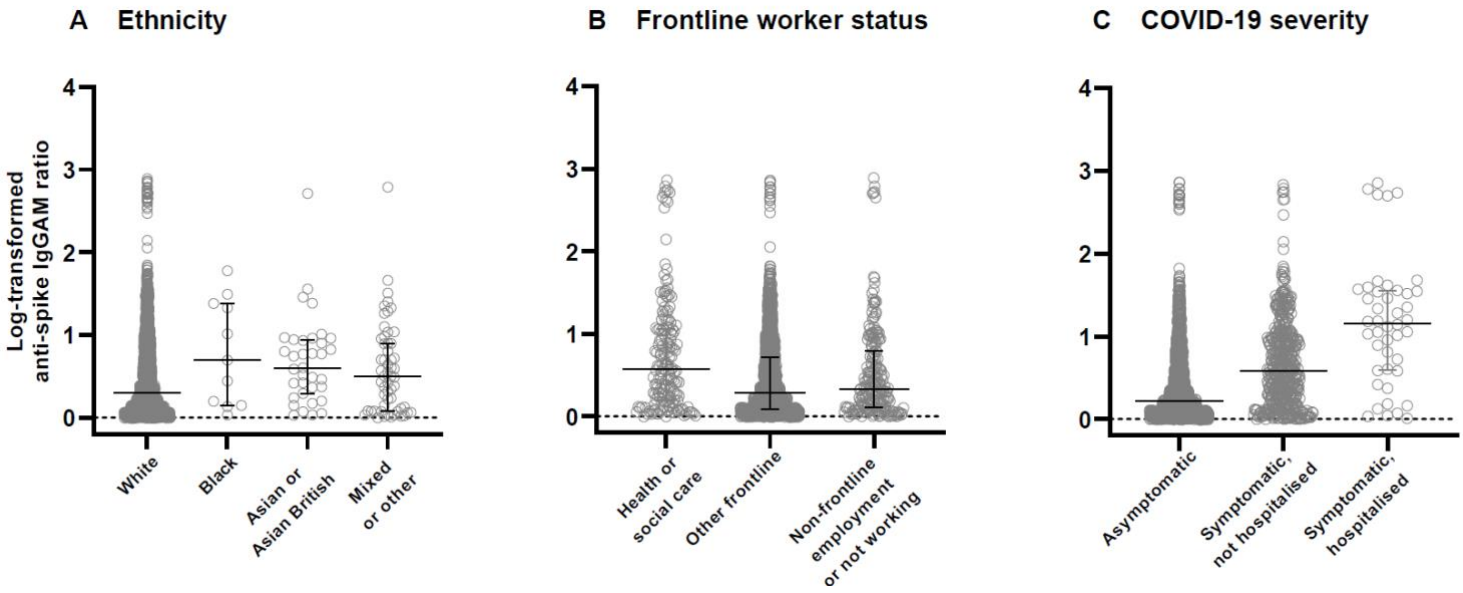
Data are n (%), n/N (%), or GMR (95% CI). Both fully adjusted analyses included 1697 participants with data available for all factors. BMI=body-mass index. BTEC=Business and Technology Education Council. COPD=chronic obstructive pulmonary disease. GMR=geometric mean ratio. IMD=index of multiple deprivation. *Adjusted for age, sex, and duration of follow-up. †Adjusted for duration of follow-up and all factors shown except symptom severity. ‡Adjusted for duration of follow-up and all factors shown. §The 217 participants with unknown or missing travel status were included in the analysis as a separate category to ensure greater power. ¶Coronary artery disease or heart failure. || COVID-19 severity was classified as 'asymptomatic' (non-hospitalised participants who either did not report any symptoms of acute respiratory infection, or whose symptoms were classified as having <50% probability of being due to COVID-19); 'symptomatic, not hospitalised' (non-hospitalised participants reporting symptoms of acute respiratory infection that were classified as having ≥50% probability of being due to COVID-19); and 'hospitalised' (participants hospitalised for treatment of COVID-19)

Figure 1: **Study profile**



*103 participants provided insufficient samples, but 99 were successfully analysed upon repeat test.

Figure 2: **Combined IgG, IgA and IgM anti-S titres in seropositive participants by ethnicity, frontline worker status and COVID-19 severity**



Log-transformed anti-spike IgGAM ratios are shown for all seropositive participants (n=1774) by ethnic group (A), frontline worker status (B), and COVID-19 severity (C), with horizontal lines showing median and IQR. (A) 'Black' indicates people of Black, African, Caribbean, and Black British origin. 'Mixed or other' indicates people of mixed, multiple, or other ethnic origin. (C) COVID-19 severity was classified as 'asymptomatic' (non-hospitalised participants who either did not report any symptoms of acute respiratory infection, or whose symptoms were classified as having <50% probability of being due to COVID-19); 'symptomatic, not hospitalised' (non-hospitalised participants reporting symptoms of acute respiratory infection that were classified as having ≥50% probability of being due to COVID-19); and 'hospitalised' (participants hospitalised for treatment of COVID-19). IgGAM=IgG, IgA, and IgM.