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Effect of a test-and-treat approach to vitamin D supplementation on risk of all cause acute respiratory tract infection and covid-19: phase 3 randomised controlled trial (CORONAVIT)

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ABSTRACT

OBJECTIVE

To determine the effect of population level implementation of a test-and-treat approach to correction of suboptimal vitamin D status (25-hydroxyvitamin D (25(OH)D) <75 nmol/L) on risk of all cause acute respiratory tract infection and covid 19.

DESIGN

Phase 3 open label randomised controlled trial.

SETTING

United Kingdom.

PARTICIPANTS

6200 people aged ≥16 years who were not taking vitamin D supplements at baseline.

INTERVENTIONS

Offer of a postal finger prick test of blood 25(OH)D concentration with provision of a six month supply of lower dose vitamin D (800 IU/day, n=1550) or higher dose vitamin D (3200 IU/day, n=1550) to those with blood 25(OH)D concentration <75 nmol/L, compared with no offer of testing or supplementation (n=3100). Follow-up was for six months.

MAIN OUTCOME MEASURES

The primary outcome was the proportion of participants with at least one swab test or doctor confirmed acute respiratory tract infection of any cause. A secondary outcome was the proportion

of participants with swab test confirmed covid-19. Logistic regression was used to calculate odds ratios and associated 95% confidence intervals. The primary analysis was conducted by intention to treat.

RESULTS

Of 3100 participants offered a vitamin D test, 2958 (95.4%) accepted and 2674 (86.3%) had 25(OH)D concentrations <75 nmol/L and received vitamin D supplements (n=1328 lower dose, n=1346 higher dose). Compared with 136/2949 (4.6%) participants in the no offer group, at least one acute respiratory tract infection of any cause occurred in 87/1515 (5.7%) in the lower dose group (odds ratio 1.26, 95% confidence interval 0.96 to 1.66) and 76/1515 (5.0%) in the higher dose group (1.09, 0.82 to 1.46). Compared with 78/2949 (2.6%) participants in the no offer group, 55/1515 (3.6%) developed covid-19 in the lower dose group (1.39, 0.98 to 1.97) and 45/1515 (3.0%) in the higher dose group (1.13, 0.78 to 1.63).

CONCLUSIONS

Among people aged 16 years and older with a high baseline prevalence of suboptimal vitamin D status, implementation of a population level test-and-treat approach to vitamin D supplementation was not associated with a reduction in risk of all cause acute respiratory tract infection or covid-19.

TRIAL REGISTRATION

ClinicalTrials.gov NCT04579640.

Introduction

The covid-19 pandemic has refocused attention on strategies to prevent acute respiratory tract infection. Although vaccination against SARS-CoV-2 represents the mainstay for disease control, its effectiveness at a global level is compromised by factors such as cost, availability, vaccine hesitancy, vaccine failure, and vaccine escape.¹⁻³ Complementary, low cost approaches to enhance immunity to SARS-CoV-2 and other pathogens responsible for acute respiratory tract infections are needed.

Vitamin D metabolites have long been recognised to support innate immune responses to respiratory viruses and bacteria, and regulate immunopathological inflammation.⁴⁻⁶ The vitamin D inducible antimicrobial peptides cathelicidin LL-37 and human β defensin 2 bind to the SARS-CoV-2 spike protein and inhibit viral binding to angiotensin converting enzyme 2, its

WHAT IS ALREADY KNOWN ON THIS TOPIC

Vitamin D metabolites support innate immune responses to SARS-CoV-2 and other respiratory pathogens

Suboptimal vitamin D status (25-hydroxyvitamin D <75 nmol/L) is associated with increased susceptibility to all cause acute respiratory tract infections and covid-19

Phase 3 randomised controlled trials of vitamin D to prevent covid-19 have not yet reported

WHAT THIS STUDY ADDS

This phase 3 randomised controlled trial (6200 participants) shows that implementation of a population level test-and-treat approach to oral vitamin D replacement at daily doses of 800 IU or 3200 IU was not associated with a reduction in risk of all cause acute respiratory tract infection or covid-19 among people aged 16 years and older with a high baseline prevalence of suboptimal vitamin D status

cellular receptor.^{7 8} Longitudinal studies investigating potential associations between higher vitamin D status or vitamin D supplement use and reduced risk of SARS-CoV-2 infection have shown mixed results, with some reporting protective associations and others reporting null or negative associations⁹⁻¹⁴; meta-analyses including these and other observational studies report protective associations overall.^{15 16} Findings of randomised controlled trials of vitamin D supplementation to prevent acute respiratory tract infections caused by pathogens other than SARS-CoV-2 have also been heterogeneous.¹⁷⁻²¹ Meta-analysis of these and other randomised controlled trials shows a small but statistically significant protective effect that is strongest when modest daily doses of vitamin D (400-1000 IU) are given for periods of up to one year.²² A phase 2 randomised controlled trial in 321 healthcare workers in Mexico reported a large protective effect of daily oral vitamin D supplementation against covid-19 (relative risk 0.23, 95% confidence interval 0.09 to 0.55).²³ However, phase 3 clinical trials of prophylactic vitamin D to reduce the incidence and severity of covid-19 are lacking, as are studies comparing the effectiveness of different doses of vitamin D supplements for the prevention of acute respiratory tract infections of any cause among adults. There is also a dearth of studies designed to evaluate the effectiveness of practical approaches to identification and treatment of vitamin D deficiency at scale in the general population to improve health outcomes. We therefore established a phase 3 pragmatic randomised controlled trial (CORONAVIT) to evaluate the effectiveness of a test-and-treat approach to identification and treatment of suboptimal vitamin D status to prevent acute respiratory tract infection and covid-19 in UK adults from December 2020 to June 2021—a period when the incidence of covid-19 was high and SARS-CoV-2 vaccine coverage was initially low.

Methods

Study design

We conducted a three arm, parallel, open label individually randomised controlled trial nested within the population based COVIDENCE UK cohort study (NCT04330599), using trial-within-cohort methodology.²⁴ COVIDENCE UK was established to determine risk factors for incident covid-19,^{12 13} characterise the clinical course of the disease, evaluate impacts of covid-19 on physical and mental health and economic vulnerability,²⁵ and provide a platform from which to conduct clinical trials of interventions to reduce the incidence and severity of acute respiratory tract infections. The study was launched on 1 May 2020 and closed to recruitment on 6 October 2021; a total of 19 981 participants enrolled.²⁶

Participants

Trial participants were drawn from those taking part in COVIDENCE UK who provided information for the following variables using an online questionnaire

completed at enrolment: age, sex, ethnic origin, postal address, highest educational level attained, occupational status, weight, height, history of SARS-CoV-2 infection, covid-19 vaccination status, chronic health conditions, tobacco smoking history, alcohol consumption, intake of micronutrient supplements, hours spent outdoors, and dietary consumption of oily fish and red meat. Inclusion criteria for the trial were current residence in the UK, age 16 years or older at screening, enrolment in COVIDENCE UK, and online provision of informed consent. Exclusion criteria were taking vitamin D supplements, digoxin, alfacalcidol, calcitriol, dihydrotachysterol or paricalcitol; diagnosis of sarcoidosis, primary hyperparathyroidism, nephrolithiasis, or renal failure requiring dialysis; allergy to any ingredient in the study capsules; and pregnancy.

Randomisation

A randomly selected subset of 6200 cohort participants were assessed as eligible on the basis of their enrolment questionnaire data and report of no supplemental vitamin D intake at baseline. Using a computer program (Stata v14.2), the trial statistician individually randomised participants to receive no offer of vitamin D testing or supplementation (no offer group) or an offer of a postal vitamin D test with supply of 800 IU/day vitamin D supplements if blood 25-hydroxyvitamin D (25(OH)D) concentrations were <75 nmol/L (lower dose group) or 3200 IU/day if blood concentrations were >75 nmol/L (higher dose group). To implement the randomisation, the study statistician downloaded unique identifiers of all participants in the COVIDENCE UK longitudinal study with questionnaire responses indicating eligibility to participate in the CORONAVIT trial. The trial statistician then used Stata software to randomly select 6200 of those reporting no supplemental vitamin D intake and to randomly assign them to no offer, lower dose offer, or higher dose offer groups in a 2:1:1 ratio in blocks of 10. Overall, 3100 participants were randomised to the no offer group and 1550 participants each were randomised to each of the lower or higher dose offer groups. Treatment allocation was not concealed, and randomisation was not stratified.

Intervention

Consenting participants randomised to either intervention arm of the trial were sent a blood spot testing kit through the post for determination of 25(OH)D concentrations in capillary blood, as described previously.²⁷ Those found to have concentrations <75 nmol/L received a six month supply of capsules containing either 800 IU/day or 3200 IU/day vitamin D₃ according to their treatment allocation. The 75 nmol/L threshold for 25(OH)D is widely considered to discriminate between those with optimal vitamin D status and those with suboptimal status.²⁸⁻³⁰ We adopted a test-and-treat approach to avoid the potential risk of inducing hypervitaminosis D by providing higher dose supplementation to individuals with baseline

25(OH)D concentrations >75 nmol/L, and in response to feedback from our patient and public involvement group who advised that participants might be better motivated to adhere to supplementation if they knew that their baseline vitamin D status was suboptimal.

Participants in both intervention groups were supplied with D-Pearls capsules (Pharma Nord, Vejle, Denmark), unless they expressed a preference for a vegetarian or vegan supplement, in which case they received Pro D₃ vegan capsules (Synergy Biologics, Walsall, UK). Participants with 25(OH)D concentrations ≥ 75 nmol/L at initial testing were offered a second postal vitamin D test two months after the first test: those whose second 25(OH)D result was <75 nmol/L were offered a postal supply of vitamin D supplements. Participants receiving study supplements were instructed to take one capsule daily until the capsules were finished. Administration of supplements was not supervised.

Follow-up assessments

Follow-up was for six months, from 17 December 2020 to 16 June 2021. At monthly intervals we emailed the participants links to follow-up online questionnaires, which captured information on: incident swab test positive or doctor diagnosed acute respiratory tract infections, including covid-19; hospital admission for treatment of acute respiratory tract infections, including covid-19; requirement for ventilatory support; prescription of antibiotics for acute respiratory tract infection; incidence of acute exacerbations of asthma or chronic obstructive pulmonary disease, and other adverse events; uptake of covid-19 vaccination; presence or absence of ongoing covid-19 symptoms at four weeks post-diagnosis and at six month follow-up (participants with swab test positive covid-19); and MRC (Medical Research Council) dyspnoea score,³¹ FACIT (Functional Assessment of Chronic Illness Therapy) Fatigue Score,³² and Post-Covid Physical Health Symptom Score³³ at six month follow-up (participants with swab test positive covid-19). The Post-Covid Physical Health Symptom Score was based on the participants' responses to questions on 16 symptoms commonly experienced after covid-19: excessive shortness of breath, cough, unusual tiredness or fatigue, problems with sleeping, memory problems, difficulty concentrating, joint or muscle pain, problems with taste or smell, diarrhoea, stomach (abdominal) pains, changes to voice, hair loss, unusual racing of the heart, light-headedness or dizziness, unusual sweating, and episodes of ringing or buzzing in the head or in one or both ears for more than five minutes. Participants were given four response options to each question: "No" (1 point), "Yes, but improving" (2 points), "Yes, but not improving or worsening" (3 points), and "Yes, and worsening" (4 points). We summed the responses to provide the symptom score (lower scores signifying fewer post-covid-19 symptoms).

Details of incident swab test confirmed or doctor confirmed acute respiratory tract infections, admissions

to hospital, and deaths were also captured through electronic linkage to routinely collected medical record data. End trial postal vitamin D testing was offered to a randomly selected subset of 1600 participants who received study supplements (800 each in the lower and higher dose arms) and 400 participants who were randomised to no offer. Participants randomised to no offer who were found to have 25(OH)D concentrations <50 nmol/L at the end of the trial received a 60 day supply of capsules, each containing 2500 IU vitamin D₃ (Cytoplan, Hanley Swan, UK).

Each monthly questionnaire contained the following advice encouraging participants with symptoms of covid-19 to be tested for SARS-CoV-2 infection: "If you currently have symptoms of coronavirus (a high temperature, a new, continuous cough or loss of or altered sense of smell or taste), call NHS111 or visit <https://www.nhs.uk/conditions/coronavirus-covid-19/> for more information." This wording was identical for questionnaires sent to all participants. In addition to the monthly questionnaires, we sent participants in the intervention arms a link to an online adherence questionnaire on 31 March 2021. This captured information on frequency of study supplement use.

Laboratory testing

Black Country Pathology Services (Sandwell General Hospital, West Bromwich, UK) performed the 25(OH)D assays; this laboratory participates in the UK National External Quality Assessment Service (NEQAS) for Vitamin D and the Vitamin D External Quality Assessment Scheme (DEQAS) for serum 25(OH)D. Concentrations of 25(OH)D₃ and 25(OH)D₂ were determined in dried blood spot eluates using liquid chromatography tandem mass spectrometry (Acquity UPLC-TQS or TQS-Micro Mass Spectrometers; Waters, Milford, MA) after derivatisation and liquid-liquid extraction as described elsewhere.²⁷ The results were summed to give total 25(OH)D concentrations. Good overall agreement has been observed between using the blood spot method and plasma 25(OH)D concentrations in paired capillary and venous samples,²⁷ showing a minimal overall bias of -0.2% (bias range -16.9 - 26.7%). For the current study, we used the following reference ranges for total 25(OH)D concentrations: deficient or suboptimal <75.0 nmol/L, adequate 75.0 - 220.0 nmol/L, and high >220.0 nmol/L. The between day coefficients of variation for 25(OH)D₃ were 11.1% at 16.9 nmol/L, 8.2% at 45.5 nmol/L, 6.9% at 131.7 nmol/L, and for 25(OH)D₂ were 7.0% at 222.2 nmol/L, 13.7% at 18.1 nmol/L, 7.5% at 42.7 nmol/L, and 6.4% at 127.3 nmol/L. The mean bias of dried blood spot compared with serum 25(OH)D₃ concentrations during 2018-21 was 4.0% . Limits of quantitation were 7.5 nmol/L for 25(OH)D₃ and 2.8 nmol/L for 25(OH)D₂.

Main outcome measures

The primary outcome was the proportion of participants who had at least one swab test confirmed

or doctor confirmed acute respiratory tract infection of any cause. These events were captured either through self-report using structured monthly online questionnaires and/or through linkage to one or more of the following databases containing routinely collected virology test results and medical record data from primary, secondary, and tertiary healthcare facilities: the UK Office for National Statistics mortality database, the UK National Health Service Hospital Episode Statistics, the COVID-19 Hospitalisation in England Surveillance System, the General Practice Extraction Service, and the Second Generation Surveillance Service. The last of these is a national laboratory reporting system used to capture routine laboratory data on infectious diseases. Supplementary table S1 shows the wording of questions in monthly follow-up questionnaires that was used to capture self-reported swab test confirmed or doctor confirmed acute respiratory tract infections, along with the algorithms used to define these events. Supplementary table S2 lists ICD-10 (international classification of diseases, 10th revision) codes for acute respiratory tract infections that were used in computerised searches to capture events documented in medical records.

Secondary efficacy outcomes were the proportion of all participants developing covid-19 confirmed by reverse transcription polymerase chain reaction or antigen testing; the proportion of all participants admitted to hospital for treatment of covid-19; the proportion of participants admitted to hospital for treatment of covid-19 who required ventilatory support; the proportion of all participants dying with covid-19; the proportion of participants developing test confirmed covid-19 who reported symptoms lasting more than four weeks; the proportion of participants developing test confirmed covid-19 who reported ongoing symptoms at the end of the study; the proportion of all participants prescribed one or more courses of antibiotics for treatment of an acute respiratory tract infection of any cause; the proportion of all participants admitted to hospital for treatment of an acute respiratory tract infection of any cause; the proportion of all participants dying of an acute respiratory tract infection of any cause; the proportion of participants with asthma or chronic obstructive pulmonary disease developing at least one severe acute exacerbation; mean values for the MRC dyspnoea score,³¹ the FACIT Fatigue Scale score,³² and the Post-Covid Physical Health Symptom Score³³ among participants developing test confirmed covid-19 who reported ongoing symptoms at the end of the study; and mean end study 25(OH)D concentrations in the subset of participants for whom this was measured. Safety outcomes were incidence of death, serious adverse events, adverse events leading to discontinuation of study drugs, and other monitored safety conditions: hypercalcaemia (serum corrected calcium concentration >2.65 mmol/L), hypervitaminosis D (25(OH)D concentration >220 nmol/L), and nephrolithiasis.

Sample size calculation

Using a graphical user interface,³⁴ we determined that a total of 6200 participants would need to be randomised to detect a 20% reduction in the proportion of participants meeting the primary outcome with 84% marginal power³⁵ and 5% type 1 error rate. The calculation was based on the following assumptions: 20% risk of participants in the no offer group experiencing at least one swab test or doctor confirmed acute respiratory tract infection at six months, 25% loss to follow-up, and a 2:1:1 ratio of participants randomised to no offer, lower dose offer, or higher dose offer, respectively.

Statistical analysis

Statistical analyses were performed using Stata 14.2 (College Station, TX). Primary analyses were done according to intention to treat, with pairwise comparisons between each intervention arm and the no offer arm. The intention-to-treat analysis included participants with data for at least one follow-up time point. We used logistic regression to compare the proportions of participants experiencing dichotomous study endpoints between intervention and no offer arms, with treatment effects presented as odds ratios and corresponding 95% confidence intervals. Dunnett's test was used to adjust for multiple testing for the primary outcome (ie, owing to two comparisons),³⁶ with a critical P value threshold of 0.027. We compared continuous outcomes between the intervention and no offer arms using unpaired Student's *t* tests, with treatment effects presented as mean differences with corresponding 95% confidence intervals.

We prespecified subgroup analyses comparing the effect of the intervention on major outcomes in participants who received at least one dose of a covid-19 vaccine during follow-up with those who did not, and in those with lower versus higher actual or predicted baseline 25(OH)D concentrations. For each of these subgroup analyses, we prespecified testing for interactions between allocation and the potential effect modifier of interest. Additionally, we conducted a post hoc exploratory Cox regression analysis to determine effects of allocation before and after a first dose of covid-19 vaccine. Predicted baseline 25(OH)D concentrations for participants in the no offer arm were calculated according to published methodology³⁷ using baseline 25(OH)D values of participants randomised to either intervention arm and employing a random forest regression model³⁸ with 11 features (age, sex, body mass index, ethnicity, portions of red meat intake per week, portions of oily fish intake per week, use of multivitamin supplements (yes or no), use of vitamin D supplements (yes or no), use of cod liver oil supplements (yes or no), sunshine hours per week, and latitude). We obtained sunshine hours per week from HadUK's 2019 5 km gridded climate measurements using the mean value of sunshine hours per week from October to December 2019 in the postcode grid square for each participant. Participants with missing data on age, body mass index, sunshine hours per week, and

latitude were imputed with the median value of that covariate among participants with non-missing data. For all other covariates, participants with missing data were imputed with the mode of that covariate among participants with non-missing data. Using a training set comprising 75% of all participants with measured 25(OH)D values, we conducted a grid search over hyperparameter values using a cross validation procedure with five folds. We searched several hyperparameter values: split criterion (mean squared error and mean absolute error), maximum tree depth (3, 4, 5, or 6 layers), bootstrap sample size (50%, 65%, or 80% of participants in the training set), and number of trees (250, 500, 1000). The mean gamma deviance was used to evaluate hyperparameter combinations over all five folds of the cross validation split. The optimal hyperparameter combination produced a mean gamma deviance of 0.151 across all validation folds. To verify the generalisation accuracy of the model trained with these hyperparameters, we used a test set comprising 25% of all participants with measured 25(OH)D values, which yielded a gamma deviance of 0.141, showing that the out-of-sample performance observed in the cross validation was indicative of test set performance. The final model was trained on all instances with available data and used to impute baseline 25(OH)D concentrations for participants randomised to the no offer arm. These imputed baseline values were then compared with measured baseline 25(OH)D values for participants randomised to the supplement arms (see supplementary figure S1): the distribution of imputed 25(OH)D concentrations in the no offer arm at baseline (range 25.0-86.2 nmol/L, SD 8.2 nmol/L) was constrained compared with that of measured 25(OH)D concentrations in the lower dose arm (range 10.3-179.6 nmol/L, SD 17.8 nmol/L) and higher dose arm (range 10.3-122.0 nmol/L, SD 16.2 nmol/L). This finding questioned the validity of the imputation, which precluded conduct of subgroup analyses by baseline 25(OH)D concentration.

A sensitivity analysis was also prespecified, which excluded data from participants in either intervention arm who reported taking vitamin D capsules for less than half the time, as well as those in the no offer arm who reported any intake of supplemental vitamin D during follow-up. Two post hoc exploratory analyses were also performed in response to reviewer comments. The first compared mean end study 25(OH)D concentrations of participants in the no offer arm who contributed data to the intention-to-treat analysis but not to the sensitivity analysis (ie, participants randomised to no offer who reported use of off-trial vitamin D supplements) with those who contributed data to both intention-to-treat and sensitivity analyses (ie, participants randomised to no offer who reported no use of off-trial vitamin D supplements). The second evaluated the effect of allocation in the subset of participants who completed all six follow-up questionnaires.

No interim analysis was planned or performed owing to the short duration of the trial and because linkage

to routinely collected health data was not done until the end of the trial. The independent data monitoring committee did, however, review accumulating data on serious adverse events by study arm on one occasion (three months into study follow-up), at which point it recommended continuation of the trial.

Patient and public involvement

Three patient and public involvement representatives were active in development of the research questions and the choice of outcome measures specified in the study protocol. One of them also led on development and implementation of strategies to maximise participant recruitment.

Results

Participants

A total of 17 700 participants in the COVIDENCE UK cohort study were assessed for eligibility to take part in the CORONAVIT trial in October 2020: 6200 of 6470 participants classified as eligible based on their responses to study questionnaires were randomly selected for invitation to the trial, and then randomly assigned to no offer versus lower dose offer versus higher dose offer groups (fig 1). Table 1 shows the baseline characteristics of participants by study arm. Median age was 60.2 years, 4156/6200 (67.0%) participants were female, and 77/6200 (1.2%) had received one dose or more of a covid-19 vaccine. Characteristics were balanced between the three groups. Of 3100 participants randomised to either lower dose or higher dose vitamin D, 2958 (95.4%) consented to receive a postal 25(OH)D test, and 2674 (86.3%) had blood 25(OH)D concentrations <75 nmol/L at baseline or two months and received vitamin D supplements (800 IU capsules to 1328 participants and 3200 IU capsules to 1346 participants). Follow-up was for six months, from December 2020 to June 2021; by the end of this period, 5523/6200 (89.1%) participants had received one dose or more of a covid-19 vaccine (see supplementary table S3). Self-reported adherence to study supplements among participants randomised to either intervention arm was good, with 90.9% of participants reporting that they took study supplements at least six times per week (see supplementary table S4). Availability of questionnaire and linkage data was also good, with 5979/6200 (96.4%) randomised participants contributing data to the intention-to-treat analysis. Compared with the no offer group, in the subset of participants included in the intention-to-treat analysis for whom measures of end study vitamin D status were available, mean 25(OH)D concentrations were significantly increased in the lower dose (79.4 v 66.6 nmol/L; mean difference 12.7 nmol/L, 9.8 to 15.6 nmol/L) and higher dose arms (102.9 v 66.6 nmol/L; mean difference 36.3 nmol/L, 95% confidence interval 32.9 to 39.6 nmol/L); table 2 and fig 2.

Among those included in the sensitivity analysis (ie, excluding non-adherent participants randomised to either intervention, and participants in the no offer arm who took vitamin D supplements), mean

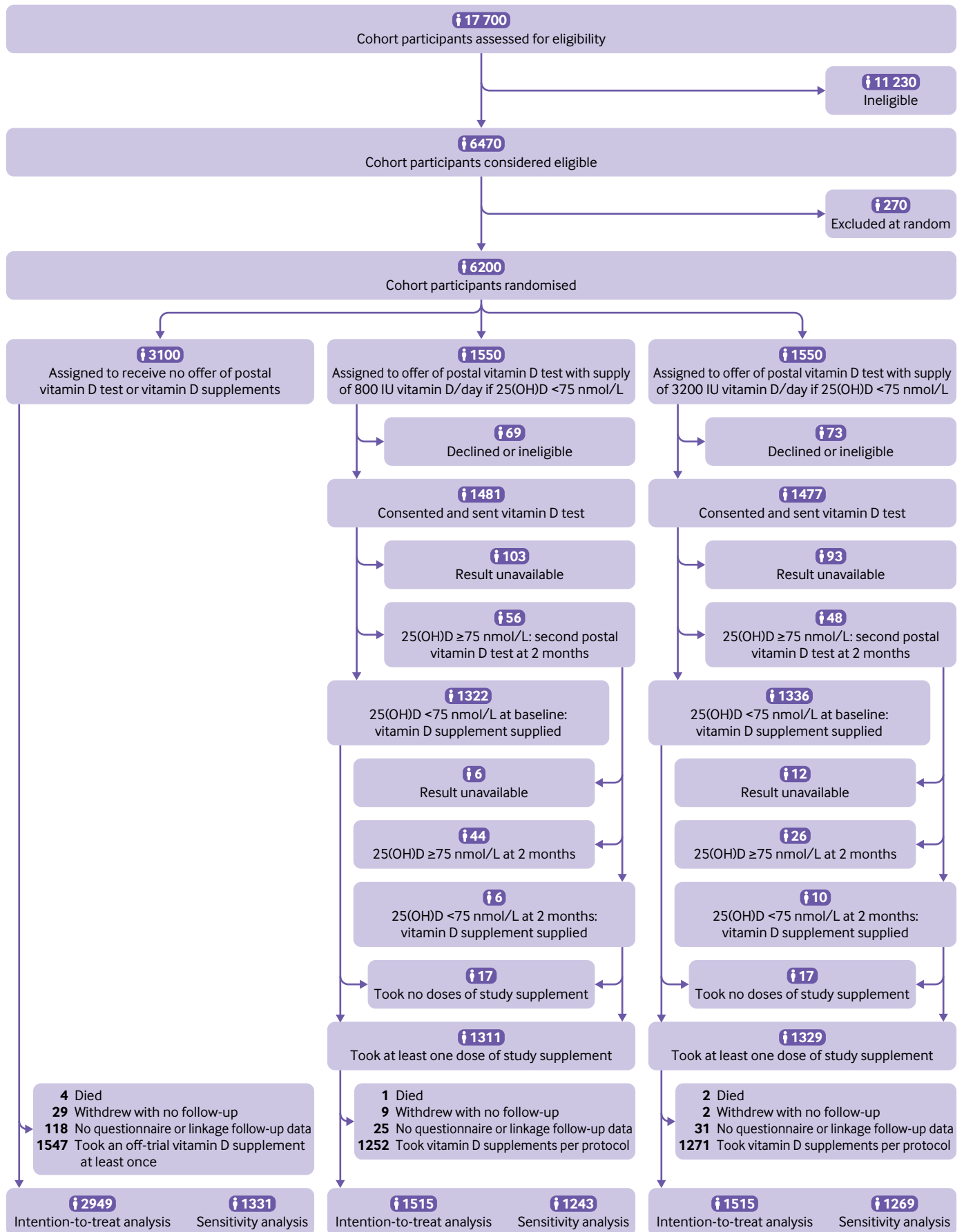


Fig 1 | Flow of participants through study

Table 1 | Baseline characteristics of participants by allocation. Values are numbers (percentages) unless stated otherwise

Characteristics	Overall (n=6200)	No offer (n=3100)	800 IU/day offer (n=1550)	3200 IU/day offer (n=1550)
Age				
Median (IQR) age (years)	60.2 (49.8-67.8)	60.8 (49.9-68.2)	59.8 (50.3-67.4)	60.7 (50.2-68.5)
Age range (years)	16.1-89.8	16.1-89.8	16.5-88.2	16.4-88.6
Sex				
Male	2044 (33.0)	1040 (32.5)	498 (32.1)	506 (32.6)
Female	4156 (67.0)	2060 (64.4)	1052 (67.9)	1044 (67.4)
Ethnicity				
White	5867 (94.6)	2925 (94.4)	1473 (95.0)	1469 (94.8)
Asian, Asian British	142 (2.3)	79 (2.5)	32 (2.1)	31 (2.0)
Black, African, Caribbean, black British	33 (0.5)	12 (0.4)	10 (0.6)	11 (0.7)
Mixed, multiple, other	154 (2.5)	83 (2.6)	34 (2.2)	37 (2.4)
Country of residence				
England	5515 (89.0)	2757 (86.2)	1384 (89.3)	1374 (88.6)
Northern Ireland	123 (2.0)	61 (1.9)	33 (2.1)	29 (1.9)
Scotland	340 (5.5)	169 (5.3)	74 (4.8)	97 (6.3)
Wales	222 (3.6)	113 (3.5)	59 (3.8)	50 (3.2)
Highest educational attainment				
Primary or secondary school	52 (0.8)	23 (0.7)	12 (0.8)	17 (1.1)
Higher or further education (A levels)	924 (14.9)	476 (14.9)	233 (15.0)	215 (13.9)
College	2740 (44.2)	1366 (42.7)	700 (45.2)	674 (43.5)
Postgraduate	1817 (29.3)	885 (27.7)	459 (29.6)	473 (30.5)
Occupational status				
Employed, health or social care worker	566 (9.1)	270 (8.7)	147 (9.5)	149 (9.6)
Employed, other frontline worker	755 (12.2)	381 (12.3)	192 (12.4)	182 (11.8)
Employed, non-frontline worker	1406 (22.7)	722 (23.3)	348 (22.5)	336 (21.7)
Self-employed	564 (9.1)	266 (8.3)	144 (9.3)	154 (9.9)
Retired	2504 (40.4)	1263 (39.5)	606 (39.1)	635 (41.0)
Furloughed	141 (2.3)	66 (2.1)	43 (2.8)	32 (2.1)
Unemployed	126 (2.0)	50 (1.6)	42 (2.7)	34 (2.2)
Student	150 (2.4)	83 (2.6)	34 (2.2)	33 (2.1)
Other	147 (2.4)	76 (2.4)	36 (2.3)	35 (2.3)
Body mass index				
<25	2903 (46.8)	1440 (45.0)	724 (46.7)	739 (47.7)
25-30	2036 (32.8)	1026 (32.1)	496 (32.0)	514 (33.2)
>30	1249 (20.1)	630 (19.7)	322 (20.8)	297 (19.2)
Medical conditions				
Hypertension	227 (3.7)	120 (3.8)	54 (3.5)	53 (3.4)
Diabetes mellitus	259 (4.2)	122 (3.8)	56 (3.6)	81 (5.2)
Heart disease	1207 (19.5)	590 (18.4)	298 (19.2)	319 (20.6)
Asthma	946 (15.3)	466 (14.6)	265 (17.1)	215 (13.9)
COPD	114 (1.8)	61 (1.9)	27 (1.7)	26 (1.7)
Smoking status				
Never smoker	3460 (55.8)	1709 (53.4)	887 (57.2)	864 (55.7)
Former smoker	2346 (37.8)	1210 (37.8)	553 (35.7)	583 (37.6)
Current smoker	393 (6.3)	181 (5.7)	109 (7.0)	103 (6.6)
Alcohol intake (units/wk)				
None	1651 (26.6)	857 (26.8)	411 (26.5)	383 (24.7)
1-14	3403 (54.9)	1665 (52.0)	865 (55.8)	873 (56.3)
≥15	1145 (18.5)	577 (18.0)	274 (17.7)	294 (19.0)
Covid-19 vaccine status				
Unvaccinated	5774 (93.1)	2826 (91.2)	1465 (94.5)	1483 (95.7)
Partially vaccinated	55 (0.9)	27 (0.9)	19 (1.2)	9 (0.6)
Fully vaccinated	22 (0.4)	11 (0.4)	5 (0.3)	6 (0.4)
Not known or missing data	349 (5.6)	236 (7.6)	61 (3.9)	52 (3.4)
25(OH)D				
Mean (SD) concentration (nmol/L); range*	–†	–†	41.5 (18.0); 10.3-179.6	40.9 (16.4); 10.3-122.0
25(OH)D category (nmol/L)				
<25.0	–†	–†	232 (15.0)	216 (13.9)
25.0-49.9	–†	–†	759 (49.0)	797 (51.4)
50-74.9	–†	–†	337 (21.7)	333 (21.5)
≥75.0	–†	–†	43 (2.7)	28 (1.8)
Not determined	–†	3100 (100.0)	179 (11.6)	176 (11.4)

COPD=chronic obstructive pulmonary disease; IQR=interquartile range; SD=standard deviation; 25(OH)D=25-hydroxyvitamin D.

*Data missing for 189 participants in 3200 IU/day arm and 198 participants in 800 IU/day arm.

†Not determined for participants randomised to no offer arm.

differences in end study 25(OH)D concentrations between intervention versus no offer arms were greater (for lower dose versus no offer group, 25.8 nmol/L

22.0 to 29.5 nmol/L; for higher dose versus no offer group, 49.7 nmol/L, 95% confidence interval 45.1 to 54.2 nmol/L; table 3 and fig 2).

Table 2 | Primary and secondary outcomes, by allocation: intention-to-treat analysis. Values are percentages (number with event/number in group) unless specified otherwise

	800 IU/day v no offer			3200 IU/day v no offer			Mean difference (95% CI)	P value	Mean difference (95% CI)	P value
	No offer	800 IU/day offer	Odds ratio (95% CI)	800 IU/day offer	3200 IU/day offer	Odds ratio (95% CI)				
Primary outcome										
≥1 swab test or doctor confirmed ARI of any cause*	4.6 (136/2949)	5.7 (87/1515)	1.26 (0.96 to 1.66)	0.10	–	5.0 (76/1515)	1.09 (0.82 to 1.46)	0.55	–	–
Secondary outcomes										
Acute covid-19 outcomes:										
Swab test confirmed covid-19†	2.6 (78/2949)	3.6 (55/1515)	1.39 (0.98 to 1.97)	0.07	–	3.0 (45/1515)	1.13 (0.78 to 1.63)	0.53	–	–
Admitted to hospital for covid-19	1.4 (40/2949)	1.6 (24/1515)	1.17 (0.70 to 1.95)	0.55	–	1.9 (29/1515)	1.42 (0.88 to 2.30)	0.16	–	–
In-hospital ventilatory support for covid-19‡	2.5 (1/40)	4.2 (1/24)	1.70 (0.10 to 28.43)	0.71	–	3.4 (1/29)	1.39 (0.08 to 23.23)	0.82	–	–
Deaths with covid-19	0.0 (0/2949)	0.0 (0/1515)	–\$	–	–\$	0.0 (0/1515)	–\$	–	–	–
Long covid outcomes:										
Swab test confirmed covid-19: symptoms for >4 weeks†	24.4 (19/78)	38.2 (21/55)	1.92 (0.91 to 4.06)	0.09	–	24.4 (11/45)	1.00 (0.43 to 2.36)	0.99	–	–
Swab test confirmed covid-19: symptoms at study end	9.0 (7/78)	20.0 (11/55)	2.54 (0.91 to 7.03)	0.07	–	17.8 (8/45)	2.19 (0.74 to 6.52)	0.16	–	–
Mean (SD) MRC dyspnoea score (No)	2.14 (1.46) (7)	1.55 (0.93) (11)	–	–	–0.60 (–2.00 to 0.90)	2.13 (0.64) (8)	–	–	–0.02 (–1.40 to 1.36)	0.98
Mean (SD) FACIT Fatigue Scale score (No)	28.43 (7.25) (7)	25.22 (5.74) (9)	–	–	–3.21 (–10.54 to 4.13)	28.00 (8.75) (8)	–	–	–0.43 (–9.36 to 8.50)	0.92
Mean Post-COVID Physical Health Symptom Score (No)	30.71 (10.16) (7)	31.90 (10.70) (10)	–	–	1.19 (–9.83 to 12.20)	33.25 (12.33) (8)	–	–	2.54 (–10.02 to 15.09)	0.67
All cause ARI outcomes*:										
≥1 courses of antibiotics for ARI of any cause**††	0.8 (22/2864)	0.3 (5/1489)	0.44 (0.16 to 1.15)	0.09	–	0.9 (14/1498)	1.22 (0.62 to 2.39)	0.57	–	–
Admitted to hospital for ARI of any cause*	0.4 (12/2949)	0.5 (7/1515)	1.14 (0.45 to 2.89)	0.79	–	0.7 (11/1515)	1.79 (0.79 to 4.07)	0.16	–	–
Death due to ARTI of any cause*	0.0 (0/2949)	0.0 (0/1515)	–\$	–	–\$	0.0 (0/1515)	–\$	–	–	–
Airways disease outcomes:										
≥1 severe acute asthma exacerbation in patients with asthma**	4.9 (21/431)	3.1 (8/255)	0.63 (0.28 to 1.45)	0.28	–	6.7 (14/209)	1.40 (0.70 to 2.82)	0.34	–	–
≥1 severe acute COPD exacerbation in patients with COPD††	15.9 (10/63)	21.4 (6/28)	1.45 (0.47 to 4.46)	0.52	–	7.4 (2/27)	0.42 (0.09 to 2.08)	0.29	–	–
Biochemical outcome:										
Mean 25 (OH)D concentration (nmol/L)‡‡ (No)	96.6 (28.6) (306)	94.4 (18.3) (742)	–	–	12.7 (9.8 to 15.6)	102.9 (23.6) (741)	–	–	36.3 (32.9 to 39.6)	<0.001

ARI=acute respiratory tract infection; CI=confidence interval; COPD=chronic obstructive pulmonary disease; FACIT=Functional Assessment of Chronic Illness Therapy; MRC=Medical Research Council; 25(OH)D=25-hydroxyvitamin D.
 †Confirmed using reverse transcriptase polymerase chain reaction and/or antigen testing for SARS-CoV-2.
 ‡Invasive and non-invasive respiratory support.
 \$Not calculable because of zero events.
 ††Data on antibiotics from self-report only.
 **Acute worsening of asthma symptoms requiring treatment with oral corticosteroids and/or requiring hospital treatment.
 ††Acute worsening of COPD symptoms requiring treatment with oral corticosteroids and/or requiring hospital treatment.
 ‡‡End study 25(OH)D concentrations available for 1789 participants (741 randomised to 3200 IU/day, 742 randomised to 800 IU/day, 306 randomised to no offer).

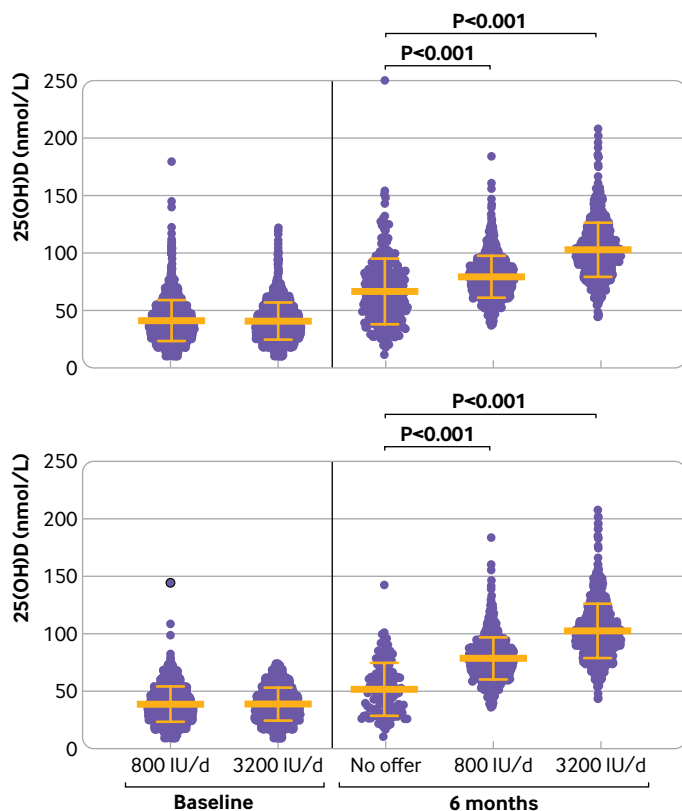


Fig 2 | 25-hydroxyvitamin D (25(OH)D) concentrations by time point and allocation for participants included in the intention-to-treat analysis (top panel) and for participants included in the sensitivity analysis (bottom panel), which excludes data from those randomised to either intervention arm who reported taking vitamin D capsules less than half the time, and those randomised to the no offer arm who reported any intake of supplemental vitamin D during follow-up. Bars show mean and standard deviation for each group. P values are from unpaired Student's *t* tests

Primary and secondary outcomes

Overall, 299 participants experienced the primary end point of at least one episode of swab test confirmed or doctor confirmed acute respiratory tract infection. Compared with the no offer group, no statistically significant difference was found in proportions of participants with these events in the lower dose offer arm (87/1515 (5.7%) *v* 136/2949 (4.6%); 1.26, 0.96 to 1.66, $P=0.10$) or higher dose offer arm (76/1515 (5.0%) *v* 136/2949 (4.6%); odds ratio 1.09, 95% confidence interval 0.82 to 1.46, $P=0.55$; table 2).

No statistically significant differences in outcomes relating to incidence or severity of acute covid-19 or prolonged symptoms of covid-19 were seen between those randomised to either the lower or the higher dose offer group compared with the no offer group (table 2). We also found no evidence to suggest that allocation to either offer compared with no offer influenced prescription of antibiotics for acute respiratory tract infection, admission to hospital, or death from all cause acute respiratory tract infection, or incidence of acute exacerbations of asthma or chronic obstructive pulmonary disease (table 2).

Subgroup analyses

In subgroup analysis we found no evidence to suggest that covid-19 vaccination modified the effect of allocation on incidence of covid-19 or prolonged covid-19 symptoms (see supplementary table S5). Planned subgroup analysis by baseline vitamin D status was not conducted, as the range and distribution of imputed 25(OH)D concentrations in the no offer arm at baseline did not match those of measured concentrations in participants randomised to the lower dose or higher dose arm (see supplementary figure S1), questioning the validity of the imputation. Exploratory survival analysis to determine effects of allocation before versus after administration of a first dose of covid-19 vaccine did not show protective effects of the intervention during either phase of follow-up (for lower dose versus no offer, pre-vaccination phase, hazard ratio 1.37, 95% confidence interval 0.90 to 2.07, $P=0.14$; post-vaccination phase, 1.68, 0.87 to 3.22, $P=0.12$; for higher dose versus no offer, pre-vaccination phase, 0.93, 0.58 to 1.49, $P=0.73$; post-vaccination phase, 1.57, 0.81 to 3.05, $P=0.18$; see supplementary figure S2).

Sensitivity analyses

Of 3100 people randomised to the no offer group, 1547 (49.9%) reported taking supplemental vitamin D on at least one occasion during the study, whereas 2523/2674 (94.4%) participants supplied with study supplements reported taking the supplements more than half the time. Results of sensitivity analyses excluding the former group and including the latter (table 3) were not materially different to those yielded by intention-to-treat analyses (table 2). A post hoc exploratory analysis comparing mean end study 25(OH)D concentrations in participants in the no offer arm who contributed data to the intention-to-treat analysis but not to the sensitivity analysis (ie, participants randomised to no offer who reported use of off-trial vitamin D supplements) compared with those who contributed data to both the intention-to-treat and the sensitivity analyses (ie, participants randomised to no offer who reported no use of off-trial vitamin D supplements) showed mean end trial 25(OH)D concentrations to be higher in the former group compared with the latter group (74.5 *v* 53.7 nmol/L, 95% confidence interval for difference, 14.6 to 27.0 nmol/L, $P<0.001$). A post hoc exploratory sensitivity analysis evaluating the effect of allocation among participants who completed all six follow-up questionnaires showed null results (higher dose *v* no offer, odds ratio 1.01, 95% confidence interval 0.73 to 1.39, $P=0.96$; lower dose *v* no offer 1.16, 0.85 to 1.56, $P=0.35$).

Adverse events

Seven participants (four in the no offer group, one in the lower dose group, and two in the higher dose group) died during the study, and 313 (143 in the no offer group and 85 in each of the intervention groups) experienced one or more serious adverse events (see supplementary

Table 3 | Primary and secondary outcomes, by allocation: sensitivity analyses. * Values are percentages (number with event/number in group) unless specified otherwise

	800 IU/day v no offer				3200 IU/day v no offer						
	No offer	800 IU/day offer	Odds ratio (95% CI)	P value	Mean difference (95% CI)	P value	3200 IU/day offer	Odds ratio (95% CI)	P value	Mean difference (95% CI)	P value
Primary outcome											
≥1 swab test or doctor confirmed ARI of any causet	4.4 (59/1331)	5.3 (66/1243)	1.21 (0.84 to 1.73)	0.30	-	-	4.3 (55/1269)	0.98 (0.67 to 1.42)	0.90	-	-
Secondary outcomes											
Acute covid-19 outcomes:											
Swab test confirmed covid-19†	2.5 (34/1331)	3.1 (39/1243)	1.24 (0.77 to 1.97)	0.37	-	-	2.5 (32/1269)	0.99 (0.61 to 1.61)	0.96	-	-
Admitted to hospital for covid-19	1.5 (20/1331)	1.4 (17/1243)	0.91 (0.47 to 1.74)	0.77	-	-	1.6 (21/1269)	1.10 (0.59 to 2.04)	0.31	-	-
In-hospital ventilatory support for covid-19§	5.0 (1/20)	0.0 (0/17)	—¶	-	-	-	4.8 (1/21)	0.95 (0.55 to 16.29)	0.97	-	-
Deaths with covid-19	0.0 (0/1331)	0.0 (0/1243)	—¶	-	-	-	0.0 (0/1269)	—¶	-	-	-
Long covid outcomes:											
Swab test confirmed covid-19; symptoms for >4 weeks†	26.5 (9/34)	35.9 (14/39)	1.56 (0.57 to 4.25)	0.39	-	-	31.2 (10/32)	1.26 (0.43 to 3.67)	0.67	-	-
Swab test confirmed covid-19; symptoms at study end	5.9 (2/34)	20.5 (8/39)	4.13 (0.81 to 21.00)	0.09	-	-	18.7 (6/32)	3.69 (0.69 to 19.85)	0.13	-	-
Mean (SD) MRC dyspnoea score (No)	1.00** (1)	1.29 (0.76) (7)	-	0.29††	-	-	2.29 (0.49) (7)	-	-	1.29††	-
Mean (SD) FACIT Fatigue Scale score (No)	34.00** (1)	23.00 (4.69) (6)	-	-11.00††	-	-	25.29 (4.53) (7)	-	-	-8.71††	-
Mean (SD) Post-COVID Physical Health Symptom Score (No)	29.00** (1)	30.50 (11.33) (6)	-	1.50††	-	-	30.57 (10.50) (7)	-	-	1.57††	-
All cause ARI outcomes*:											
≥1 courses of antibiotics for ARI of any causet§§	1.0 (13/1331)	0.3 (4/1243)	0.33 (0.11 to 1.00)	0.05	-	-	0.6 (7/1269)	0.56 (0.22 to 1.41)	0.22	-	-
Admitted to hospital for any cause* any causet*	0.4 (6/1331)	0.2 (3/1243)	0.53 (0.13 to 2.14)	0.38	-	-	0.8 (10/1269)	1.75 (0.64 to 4.84)	0.28	-	-
Death due to ART† of any causet	0.0 (0/1331)	0.0 (0/1243)	—¶	-	-	-	0.0 (0/1269)	—¶	-	-	-
Airways disease outcomes:											
≥1 severe acute asthma exacerbation in patients with asthma ††	6.1 (11/180)	3.3 (7/210)	0.53 (0.20 to 1.40)	0.20	-	-	4.7 (8/169)	0.76 (0.30 to 1.95)	0.57	-	-
≥1 severe acute COPD exacerbation in patients with COPD†††	17.9 (5/28)	25.0 (6/24)	1.53 (0.40 to 5.84)	0.53	-	-	4.5 (1/22)	0.22 (0.02 to 2.03)	0.18	-	-
Biochemical outcome:											
Mean (SD) end study 25(OH)D concentration (nmol/L)***	53.7 (23.1) (116)	79.5 (18.3) (736)	-	25.8 (22.0 to 29.5)	>0.001	-	103.4 (23.3) (729)	-	-	49.7 (45.1 to 54.2)	<0.001

ARI=acute respiratory tract infection; CI=confidence interval; COPD=chronic obstructive pulmonary disease; FACIT=Functional Assessment of Chronic Illness Therapy; MRC=Medical Research Council; 25(OH)D=25-hydroxyvitamin D.
 *Excludes data from participants randomised to either supplement arm who reported taking vitamin D capsules less than half the time as well as those randomised to no offer arm who reported any intake of supplemental vitamin D during follow-up.
 †Includes covid-19 and other ARI.
 ††Confirmed using reverse transcriptase polymerase chain reaction and/or antigen testing for SARS-CoV-2.
 †††Standard deviation not calculable as only one participant had the outcome in the no offer arm.
 ††††95% confidence interval not calculable as the no offer arm had one participant with outcome.
 †††††Acute worsening of asthma symptoms requiring treatment with oral corticosteroids and/or requiring hospital treatment.
 ††††††Data on antibiotics for acute respiratory tract infection from self-report only.
 †††††††Acute worsening of COPD symptoms requiring treatment with oral corticosteroids and/or antibiotics and/or hospital treatment.
 ††††††††End study 25(OH)D concentrations available for 1789 participants (741 randomised to 3200 IU/day, 742 randomised to 800 IU/day, 306 randomised to no offer).

table S6). Supplementary table S7 lists these events: none were considered to be related to vitamin D supplementation. Four participants in the higher dose group developed hypercalcaemia (serum corrected calcium >2.65 mmol/L): the study supplements were discontinued, and the hypercalcaemia and symptoms resolved. One participant in the no offer group had asymptomatic hypervitaminosis D (25(OH)D concentration 250 nmol/L) at six month follow-up, after taking a non-study vitamin D supplement at a dose of 4000 IU/day. One participant in the higher dose group was twice admitted to hospital with renal colic due to nephrolithiasis. A total of 47 non-severe adverse events led to discontinuation of study supplements (23 v 24 in lower and higher dose offer groups, respectively; see supplementary table S8).

Discussion

We present results of the first phase 3 randomised controlled trial to evaluate the effectiveness of a test-and-treat approach for correction of suboptimal vitamin D status to prevent acute respiratory tract infections. The trial also investigated whether vitamin D supplementation is associated with a reduction in risk of covid-19. Among participants randomised to receive an offer of postal vitamin D testing, uptake of testing and supplementation was good, prevalence of 25(OH)D concentrations <75 nmol/L was high, and end study 25(OH)D concentrations were increased compared with the group not offered testing or supplementation, providing objective evidence of a high level of adherence. However, no statistically significant effect of either dose was seen on the primary outcome of swab test or doctor confirmed acute respiratory tract infection, or on the major secondary outcome of swab test confirmed covid-19. Oral vitamin D supplementation was safe and well tolerated at both doses investigated: incidence of adverse events was balanced between arms, and no serious adverse event was attributed to study supplements.

Comparison with other studies

The design of our study was informed by findings from a recent meta-analysis, suggesting that protective effects of vitamin D against acute respiratory tract infection might be strongest when daily doses of 400-1000 IU were given for up to one year.²² The results from the current study do not support the hypothesis that such regimens offer protection against acute respiratory tract infection, and our null findings are consistent with those of several other recent phase 3 trials of vitamin D supplementation that have reported no effect of vitamin D supplementation on risk of acute respiratory tract infections.^{20 21 39} The null result for the major secondary outcome of incident covid-19 in this trial is consistent with our finding of no independent association between intake of supplementary vitamin D and risk of covid-19 in a prospective observational study undertaken in this cohort before initiation of this trial,¹² as well as null results from a mendelian

randomisation study that tested for associations between genetically predicted 25-hydroxyvitamin D concentrations and susceptibility to covid-19.⁴⁰ However, the result contrasts with recent findings from a phase 2 randomised controlled trial in healthcare workers in Mexico, which reported a strong protective effect of a daily dose of 4000 IU vitamin D.²³ The difference in findings might be because participants in the Mexican trial had not been vaccinated against SARS-CoV-2, or it may reflect the relatively short duration of follow-up (one month). The former hypothesis is not supported by results from subgroup analysis in the current study, showing no effect of vitamin D on risk of covid-19 either before or after covid-19 vaccination.

Strengths and limitations of this study

Our study has several strengths. In contrast with some recent large clinical trials of vitamin D supplementation for the prevention of acute respiratory tract infections,^{21 39} the prevalence of suboptimal vitamin D status at baseline in our study population was high, with 25(OH)D concentrations <75 nmol/L in 97.4% of those tested. We investigated daily dosing regimens (thereby avoiding large and non-physiological fluctuations in 25(OH)D that are seen with intermittent bolus dosing),⁴¹ and adherence was good (evidenced by self-report and by statistically significant differences in end study 25(OH)D concentrations between arms). The trial-within-cohort design allowed a rapid and efficient evaluation of a pragmatic approach to boosting vitamin D status in the general population to provide a timely answer to the pressing question of whether or not vitamin D supplements reduce risk of covid-19. Linkage with routinely collected data from medical records allowed comprehensive capture of outcomes in those who did not complete study questionnaires, allowing us to minimise loss to follow-up and to capture important events that precluded completion of questionnaires, such as severe illness and death. The trial was initiated before the widespread roll-out of covid-19 vaccination, and follow-up coincided with the second wave of covid-19 in the UK: both factors contributed to the appreciable number of participants who experienced covid-19 during follow-up, which allowed for potential effects of vitamin D on prevention of this specific cause of acute respiratory tract infection to be investigated. Other strengths include a rigorous case definition for the primary outcome that required objective confirmation of acute respiratory tract infection (as opposed to self-report of symptoms) and use of an externally accredited laboratory to measure 25(OH)D concentrations using liquid chromatography-tandem mass spectrometry, which is the gold standard assay for this determination.

Our study also has limitations. Provision of supplements to participants randomised to intervention was contingent on their having inadequate vitamin D status: thus, a subset (13.7%) of participants randomised to intervention did not receive study supplements. Conversely, another subset (49.9%) of participants randomised to the no offer

of supplementation group reported taking a vitamin D supplement on one or more occasions during follow-up. This could have led to increases in 25(OH)D concentrations in the no offer arm over the course of the study, although seasonal effects (sampling in June versus in December) will also have contributed. Together, these factors could have diluted any effect of vitamin D supplementation in the primary intention-to-treat analysis. We sought to overcome this by conducting a sensitivity analysis, which included only those randomised to offer versus no offer who did versus did not take supplemental vitamin D, respectively. That this analysis showed no effect of vitamin D supplementation on all outcomes investigated provides some reassurance that the null result yielded by the intention-to-treat analysis is valid. Ultimately, however, this trial was designed to investigate the effectiveness of a pragmatic test-and-treat approach to boosting population vitamin D status, rather than biological efficacy of vitamin D to prevent acute respiratory tract infections, and our findings should be interpreted accordingly: specifically, we highlight that our results are not inconsistent with findings from meta-analyses of placebo controlled trials of vitamin D to prevent acute respiratory tract infection,^{22 42} which better address questions of efficacy. The open label design might have introduced ascertainment bias by influencing the likelihood of participants completing follow-up questionnaires. This potential problem was offset by the use of medical record linkage, which allowed us to capture outcomes in participants who did not complete all follow-up questionnaires. Moreover, a post hoc sensitivity analysis restricted to participants who completed all follow-up questionnaires yielded null results, consistent with those of the primary analysis. The proportion of those randomised to the no offer arm who experienced the primary outcome (4.6%) was lower than the 20% anticipated in the sample size calculation, possibly reflecting the impact of public health measures to control transmission of SARS-CoV-2 (such as lockdowns, social distancing, and mask wearing) on incidence of other acute respiratory tract infections.⁴³ Alternatively, it might reflect a reduction in consultations for acute respiratory tract infection because of participants' reluctance to attend a doctor's surgery with respiratory symptoms, as face-to-face consultations were actively discouraged during the pandemic, and the general public being reluctant to over-burden an already over-stretched health service.^{44 45} This could have compromised power; however, the lower bounds for the 95% confidence intervals of odds ratios relating to the effect of lower and higher dose vitamin D supplements on our primary outcome (0.96 and 0.82, respectively) effectively rule out relative reductions in odds of acute respiratory tract infection of more than 4% and 18%, respectively. Some may not consider effects of this size or less to be of sufficient magnitude to implement the study intervention for the purpose of preventing acute respiratory tract infections. Incidence of some secondary outcomes, including admission to hospital

for acute respiratory tract infection, was low: our study therefore lacked power to detect an effect of the intervention on severity of covid-19 and other acute respiratory tract infections. Prevalence of profound vitamin D deficiency (25(OH)D <25 nmol/L) at baseline was also low, and therefore our study lacked power to detect an effect of the intervention in participants in this group, who may be more likely to derive clinical benefit from vitamin D supplementation than those with higher baseline 25(OH)D concentrations.⁴⁶ Men, people from ethnic minorities, and those with lower educational attainment were relatively under-represented among study participants compared with the general population, which may have compromised the generalisability of our findings. We also highlight that other groups at increased risk of severe covid-19 were over-represented among trial participants, of whom 35.6% were aged ≥65 years (compared with 18.3% of the UK population)⁴⁷ and 19.5% had heart disease (compared with 3-4% of the UK population).⁴⁸ This over-representation, along with the presence of many participants who were unvaccinated or partially vaccinated during follow-up, might explain why a relatively high proportion of participants with covid-19 required admission to hospital.

Conclusions

This study found that implementation of a test-and-treat approach to correct suboptimal vitamin D status in the UK population was safe and effective in increasing 25(OH)D concentrations in people aged 16 years and older with baseline concentrations <75 nmol/L. This was not, however, associated with protection against all cause acute respiratory tract infection or covid-19.

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Contributors: ARM, DAJ, and CR designed the study, with input from PP, JS, DF, RAL, GAD, FK, CJG, JN, AS, SEF, AGR, and SOS. DAJ, HH, NP, SM, MT, and ARM managed the trial. AN, NLB, and RG performed the laboratory assays. DAJ, MG, MT, GV, and CO managed and analysed the data. DAJ and ARM contributed equally and are the guarantors. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. ARM wrote the first draft of the paper. All authors contributed to the interpretation of the results, review and approval of the manuscript, and the decision to submit it for publication. There were no agreements concerning confidentiality of the data between the sponsor and the authors or the institutions named in the credit lines. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: The study was approved by the Queens Square Research Ethics Committee, London, UK (ref 20/HRA/5095). Participants gave informed consent before taking part.

Data sharing: Anonymised participant level data will be made available on reasonable request to a.martineau@qmul.ac.uk, subject to the terms of research ethics committee and sponsor approval.

The guarantors (DAJ and ARM) affirm that the manuscript is an honest, accurate, and transparent account of the study results; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained. All outcomes prespecified in the protocol and the trial registry are reported here, except for those relating to potential effects of vitamin D on SARS-CoV-2 vaccine immunogenicity, which have been reported in a separate manuscript (<https://doi.org/10.1101/2022.07.15.22277678>).

Dissemination to participants and related patient and public communities: Trial participants were emailed the following link to a webinar in which results are presented in plain language: <https://www.youtube.com/watch?v=QpVl0xRPOA>. The trial report was published on a preprint server (<https://www.medrxiv.org/content/10.1101/2022.03.22.22271707v2>), and results attracted the interest of national and international media (eg, <https://inews.co.uk/news/vitamin-d-supplements-do-not-stop-you-catching-covid-or-reduce-symptoms-major-trial-reveals-1536673>, <https://www.news-medical.net/news/20220325/Effectiveness-of-a-test-and-treat-approach-for-identification-and-treatment-of-vitamin-D-insufficiency-for-prevention-of-COVID-19.aspx>).

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Supplementary information: study staff, additional tables 1-8, and additional figures 1 and 2