Vitamin D Supplements for Prevention of Covid-19 or other Acute Respiratory Infections: a Phase 3 Randomized Controlled Trial (CORONAVIT)

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ABSTRACT

BACKGROUND: Vitamin D metabolites support innate immune responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and other respiratory pathogens. Randomized controlled trials of vitamin D to prevent coronavirus disease 2019 (Covid-19) have not yet reported.

METHODS: We randomly assigned 6200 U.K. adults to receive an offer of a postal finger-prick 25-hydroxyvitamin D (25[OH]D) test with provision of a 6-month supply of higher-dose vitamin D (3200 IU/d, n=1550) or lower-dose vitamin D (800 IU/d, n=1550) to those with blood 25(OH)D concentration <75 nmol/L, vs. no offer of testing or supplementation (n=3100). The primary outcome was the proportion of participants experiencing at least one swab test- or doctor-confirmed acute respiratory infection (ARI) of any cause at six months. Secondary outcomes included incidence of swab test-confirmed Covid-19.

RESULTS: Of 3100 participants offered testing, 2958 (95.4%) accepted, and 2690 (86.8%) had 25(OH)D <75 nmol/L and were sent vitamin D supplements (1356 higher-dose, 1334 lower-dose). 76 (5.0%) vs. 87 (5.7%) vs. 136 (4.6%) participants in higher-dose vs. lower-dose vs. no-offer groups experienced at least one ARI of any cause (odds ratio [OR] for higher-dose vs. no-offer 1.09, 95% CI 0.82-1.46; lower-dose vs. no-offer 1.26, 0.96-1.66). 45 (3.0%) vs. 55 (3.6%) vs. 78 (2.6%) participants in higher-dose vs. lower-dose vs. no-offer groups developed Covid-19 (OR for higher-dose vs. no-offer 1.13, 0.78-1.63; lower-dose vs. no-offer 1.39, 0.98-1.97).

CONCLUSIONS: Among adults with a high baseline prevalence of vitamin D insufficiency, implementation of a test-and-treat approach to vitamin D replacement did not reduce risk of all-cause ARI or Covid-19.

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INTRODUCTION

The coronavirus disease 2019 (Covid-19) pandemic has refocused attention on strategies to prevent acute respiratory infection (ARI). Although vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) represents the mainstay for disease control, its effectiveness at a global level is compromised by factors including 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 causing ARI are needed.

Vitamin D metabolites have long been recognized to support diverse innate immune responses to respiratory viruses and bacteria, while simultaneously regulating immunopathological inflammation.[4-6] The vitamin D-inducible antimicrobial peptides cathelicidin LL-37 and human beta defensin 2 have both been shown to bind SARS-CoV-2 spike protein and inhibit binding to Angiotensin Converting Enzyme 2, its cellular receptor.[7,8] Longitudinal studies investigating potential associations between higher vitamin D status or vitamin D supplement use and reduced risk of Covid-19 or SARS-CoV-2 infection have yielded mixed results, with some reporting protective associations and others reporting null or negative associations;[9-14] meta-analyses including these and other observational studies report protective associations overall.[15,16] Findings of randomized controlled trials (RCTs) of vitamin D supplementation to prevent ARIs caused by pathogens other than SARS-CoV-2 have also been heterogeneous.[17-21] Meta-analysis of these and other RCTs shows a small, but statistically significant, protective effect that is strongest where modest daily doses of vitamin D (400-1000 IU) are given for periods of up to one year.[22] Phase 3 clinical trials of prophylactic vitamin D to reduce incidence and severity of Covid-19 are lacking, as are studies comparing effectiveness of different doses of vitamin D supplementation for the prevention of ARIs of any cause among adults. There is also a lack 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 RCT (CORONAVIT) to evaluate the effectiveness of a ‘test-and-treat’ approach to identification and treatment of vitamin D insufficiency for prevention of

Covid-19 and other ARIs in U.K. adults from December 2020 to June 2021 - a period when Covid-19 incidence was high and Covid-19 vaccine coverage was initially low.

METHODS

TRIAL DESIGN, SETTING AND PARTICIPANTS

We conducted a three-arm parallel open-label individually-randomized controlled trial nested within the population-based COVIDENCE UK cohort study,[12,13] using 'trial-within-cohort' methodology.[23] Eligibility was assessed using self-reported data from on-line questionnaires. Principal inclusion criteria were age 16 years or more at screening and participation in the COVIDENCE UK cohort; principal exclusion criteria were current use of vitamin D supplements, known diagnosis of sarcoidosis, primary hyperparathyroidism, nephrolithiasis, or renal failure requiring dialysis; known allergy to any ingredient in the study capsules; and known pregnancy.

RANDOMIZATION AND INTERVENTION

A randomly-selected subset of 6200 cohort participants who were assessed as eligible on the basis of data from their enrolment questionnaire, and who reported no supplemental vitamin D intake at baseline, were individually randomized by the trial statistician using a computer program (Stata v14.2) to receive an offer of a postal vitamin D test with supply of 3200 IU vitamin D/day if their blood 25(OH)D concentration was found to be less than 75 nmol/L ('higher-dose offer group') vs. the same testing offer with supply of 800 IU vitamin D/day if 25(OH)D was less than 75 nmol/L ('lower-dose offer group') vs. no offer of vitamin D testing or supplementation ('no offer group'), with a 1:1:2 allocation ratio. Treatment allocation was not concealed.

FOLLOW-UP ASSESSMENTS

Study participants were invited to complete follow-up on-line questionnaires at monthly intervals, which captured details of incident ARIs, exacerbations of asthma

and chronic obstructive pulmonary disease (COPD), chronic Covid-19 symptoms, adherence, and adverse events. The final invitation to complete a follow-up questionnaire was sent in June 2021, at 6-month follow-up. End-trial postal vitamin D testing was offered to a randomly selected subset of 1600 participants who received study supplements (800 in each offer group) and 400 cohort participants who were randomized to the no offer group.

OUTCOMES

The primary outcome was the proportion of participants developing at least one swab test- or doctor-confirmed ARI of any cause. Secondary efficacy outcomes were the proportion of all participants developing Covid-19 confirmed by reverse transcription polymerase chain reaction (RT-PCR) or antigen testing; the proportion of all participants hospitalized for treatment of Covid-19; the proportion of participants hospitalized for treatment of Covid-19 who required ventilatory support; the proportion of all participants dying of 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 on-going symptoms at the end of the study; mean values for the MRC dyspnea score[24], the FACIT Fatigue Scale score[25] and the Post-Covid Physical Health Symptom Score[26] among participants developing test-confirmed Covid-19 who reported on-going symptoms at the end of the study; the proportion of all participants prescribed one or more courses of antibiotics for treatment of ARI of any cause; the proportion of all participants hospitalized for treatment of ARI of any cause; the proportion of all participants dying of ARI of any cause; the proportion of participants with asthma or COPD developing at least one severe acute exacerbation; and mean end-study 25(OH)D concentrations in the sub-set of participants for whom this was measured.

Safety outcomes were incidence of death, serious adverse events, adverse events leading to discontinuation of study medication, and other monitored safety conditions: hypercalcemia (serum corrected calcium concentration >2.65 mmol/L), hypervitaminosis D (25[OH]D concentration >220 nmol/L) and nephrolithiasis.

SAMPLE SIZE AND STATISTICAL METHODS

We used https://mjgrayling.shinyapps.io/multiarm/[27] to calculate that a total of 6200 participants would need to be randomized to detect a 20% reduction in the proportion of participants meeting the primary outcome with 84% marginal power[28] and 5% type 1 error rate, assuming a 20% risk of experiencing at least one swab test- or doctor-confirmed ARI in the no offer group at six months, 25% loss to follow-up, and a 1:1:2 ratio of participants randomized to higher-dose, lower-dose or no offer, respectively. Statistical analyses were performed according to intention-to-treat; adjustment for multiple testing for the primary outcome used Dunnett's test[29] with a critical P-value threshold of 0.027. Treatment effects for dichotomous outcomes were estimated using logistic regression and presented as odds ratios (ORs) with 95% confidence intervals (CIs). We pre-specified sub-group analyses comparing the effect of the intervention on major outcomes in individuals who received at least one dose of Covid-19 vaccine during follow-up vs. those who did not, and in those with lower vs. higher actual or predicted baseline 25(OH)D concentrations. A sensitivity analysis was also pre-specified, which excluded data from participants in the intervention arms who reported that they took vitamin D capsules '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. Further details of statistical methods are presented in the Supplementary Appendix.

RESULTS

PARTICIPANTS

A total of 17700 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 randomly assigned to higher-dose vs. lower-dose vs. no offer groups (Fig. 1). Table 1 shows baseline characteristics of the trial participants by study arm. Median age was 60.2 years, 4156/6200 (67.0%) were female and 154/6200 (2.5%) had received one or more

doses of Covid-19 vaccine. Among participants whose baseline vitamin D status was tested, mean 25(OH)D concentration was 39.7 nmol/L (s.d. 14.5), and 2674/2745 (97.4%) had 25(OH)D concentrations <75 nmol/L. Characteristics were balanced between the three groups. Of 3100 participants randomized to the higher- or lower-dose offer groups, 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 with provision of study supplements (1346 vs. 1328 supplied with 3200 IU vs. 800 IU capsules, respectively). Follow-up was for 6.0 months, from December 2020 to June 2021; by the end of this period, 5523/6200 (89.1%) of participants had received one or more doses of a Covid-19 vaccine (Table S1, Supplementary Appendix). Self-reported adherence to study supplements among participants randomized to either intervention arm was good, with 90.9% of participants reporting that they took study supplements at least 6 times per week (Table S2, Supplementary Appendix). In the subset of participants included in the intention-to-treat analysis for whom measures of end-study vitamin D status was available, mean 25(OH)D concentrations were significantly elevated in the higher-dose vs. no offer group (102.9 vs. 66.6 nmol/L respectively; mean difference 36.3 nmol/L, 95% CI 32.9 to 39.6 nmol/L), and in the lower-dose vs. no offer group (79.4 vs. 66.6 nmol/L respectively; mean difference 12.7 nmol/L, 95% CI 9.8 to 15.6 nmol/L; Table 2, Fig. 2). Among those included in the sensitivity analysis (i.e. excluding non-adherent participants randomized to intervention, and participants in the no-offer arm who took vitamin D supplements), mean differences in end-study 25(OH)D concentrations between intervention vs. no-offer arms were greater (for higher-dose vs. no offer group, 49.7 nmol/L, 95% CI 45.1 to 54.2 nmol/L; for lower-dose vs. no-offer group, 25.8 nmol/L (95% CI 22.0 to 29.5 nmol/L; Table 3, Fig. 2).

PRIMARY AND SECONDARY OUTCOMES

The primary end point of at least one episode of swab test- or doctor-confirmed ARI occurred in 290 participants, with no statistically significant difference in proportions experiencing such an event in either offer group vs. the no offer group (for higher-dose vs. no offer: 76/1515 (5.0%) vs. 136/2949 (4.6%), respectively; OR 1.09; 95% CI 0.82 to 1.46, P=0.55; for lower-dose vs. no offer: 87/1515 (5.7%) vs. 136/2949 (4.6%), respectively; OR 1.26; 95% CI 0.96 to 1.66, P=0.10; Table 2).

No statistically significant differences in outcomes relating to incidence or severity of acute Covid-19, prolonged symptoms of Covid-19 were seen between those randomized to either offer vs. no offer (Table 2). We also found no evidence to suggest that allocation to either offer vs. no offer influenced prescription of antibiotics for ARI treatment, hospitalization or death from all-cause ARI, or incidence of acute exacerbations of asthma or COPD (Table 2).

SUB-GROUP ANALYSES

Sub-group analysis revealed no evidence to suggest that Covid-19 vaccination modified the effect of allocation on incidence of Covid-19 or prolonged Covid-19 symptoms (Table S2, Supplementary Appendix). Planned sub-group 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 25(OH)D concentrations in participants randomized to either intervention arm (Figure S1, Supplementary Appendix), calling the validity of the imputation into question.

SENSITIVITY ANALYSIS

Of 3100 people randomized to the no offer group, 1547 (49.9%) reported that they took supplemental vitamin D on at least one occasion during the study, while 2523/2674 (94.4%) participants supplied with study supplements reported that they took them 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).

ADVERSE EVENTS

7 participants (2 vs. 1 vs. 4 allocated to higher-dose vs. lower-dose vs. no offer groups, respectively) died during the study, and 313 (85 vs. 85 vs. 143 allocated to higher-dose vs. lower-dose vs. no offer groups) experienced one or more non-fatal serious adverse events (Table S4, Supplementary Appendix). Causes of these

events are presented in Table S5, Supplementary Appendix: none was adjudged to be related to administration of study supplements. Four participants in the higher dose offer group developed hypercalcemia (serum corrected calcium >2.65 mmol/L): study supplements were discontinued, and the hypercalcemia and symptoms resolved. One participant in the no offer group was found to have asymptomatic hypervitaminosis D (25[OH]D 250 nmol/L) at 6-month follow-up, after taking a non-study vitamin D supplement at a dose of 4000 IU/day. One participant in the higher dose offer group was hospitalized on two occasions with renal colic due to nephrolithiasis. A total of 47 non-severe adverse events led to discontinuation of study supplements (24 vs. 23 in higher- vs. lower-dose offer groups, respectively: Table S6, Supplementary Appendix).

DISCUSSION

We present results of the first RCT to evaluate the effectiveness of a test-and-treat approach to correction of sub-optimal vitamin D status for prevention of ARIs. It is also the first clinical trial to investigate whether vitamin D supplementation reduces risk of Covid-19. Among participants randomized to receive an offer of vitamin D testing, uptake of this intervention was good, prevalence of 25(OH)D concentrations <75 nmol/L was high, and end-study 25(OH)D concentrations were elevated when compared to those who were randomized to no such offer, providing objective evidence of a high level of adherence. However, no statistically significant effect of either dose was seen on the primary outcome of incident doctor- or swab test-confirmed ARI, or on the major secondary outcome of incident 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.

The design of our study was informed by findings from a recent meta-analysis, suggesting that protective effects of vitamin D against ARI 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 ARI, and 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 ARIs.[20,21,30] 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 supplemental vitamin D and risk of Covid-19 in a prospective observational study undertaken in this cohort prior to initiation of this trial,[12] as well as null results from a Mendelian randomization study that tested for associations between genetically predicted 25(OH)D concentrations and susceptibility to Covid-19.[31] Positive findings from other observational studies[9,14] may therefore be attributable to confounding or collider bias.[32]

Our study has several strengths. In contrast to recent large clinical trials of vitamin D supplementation for the prevention of ARIs,[21,30] our study population had a very high prevalence of vitamin D insufficiency at baseline, with 97.4% of those tested having 25(OH)D concentrations <75 nmol/L. We investigated two dosing regimens utilizing daily dosing (thereby avoiding large and unphysiologic fluctuations in 25[OH]D that are seen with administration of intermittent bolus dosing),[33] and there was good adherence (evidenced by self-report and by 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 a pressing global public health question. Linkage with routinely collected data from medical records allowed comprehensive capture of outcomes in those who did not complete study questionnaires, allowing us to minimize loss to follow-up and to capture important events that precluded questionnaire completion such as severe illness and death. The trial was initiated prior to 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 Covid-19 cases that arose, which allowed for potential effects of vitamin D on prevention of this specific cause of ARI to be investigated. Other strengths include a high retention rate (just 0.6% of participants withdrew without any follow-up), a rigorous case definition for the primary outcome that required objective confirmation of ARI (as opposed to self-report of symptoms), and use of an externally accredited laboratory to measure vitamin D status 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 randomized to intervention was contingent on demonstrating inadequate vitamin D status: thus, a subset (13.7%) of participants randomized to intervention did not receive study supplements. On the other hand, another subset (49.9%) of participants randomized to no offer took a vitamin D supplement on one or more occasions during follow-up. This may 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 vs. December) will also have contributed. Together, these factors could have diluted any effect of vitamin D in the primary intention-to-treat analysis. We sought to overcome this by conducting a sensitivity analysis, which included only those randomized to offer vs. no offer who did vs. did not take supplemental vitamin D, respectively. The fact that this analysis showed no effect of vitamin D supplementation on all outcomes investigated, despite the larger differences in end-study 25(OH)D concentrations between intervention vs. no-offer arms seen for this analysis vs. the intention-to-treat analysis (Fig. 2), 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 biologic efficacy of vitamin D to prevent ARIs, and our findings should be interpreted accordingly. Ascertainment bias could have arisen because of the open-label design since knowledge of allocation could have influenced retention and the likelihood of an outcome being reported. We attempted to off-set effects of differential rates of loss to follow-up between arms by use of medical record linkage, which allowed us to capture outcomes in those who were lost to follow-up but who did not actively withdraw from the study. The proportion of those randomized to 'no offer' 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 ARIs.[34] This could have compromised power; however, the lower bounds for the 95% CIs of ORs relating to the effect of higher- or lower-dose offers on our primary outcome (0.82 and 0.96, respectively) effectively rule out relative reductions

in odds of ARI of more than 18% and 4%, respectively. Arguably, effects of this size or less are unlikely to be considered of sufficient magnitude to implement the study intervention for the purpose of ARI prevention. Incidence of hospitalization for ARI was low, and we therefore lacked power to detect an effect of the intervention on severity of Covid-19 and other ARIs. Finally, prevalence of profound vitamin D deficiency (25[OH]D <25 nmol/L) at baseline was also low, and we therefore lacked power to detect an effect of the intervention in this group, who may be more likely to derive clinical benefit from vitamin D replacement than those with higher baseline 25(OH)D concentrations.[35]

In conclusion, we report that implementation of a test-and-treat approach to correcting sub-optimal vitamin D status in the U.K. population was safe and effective in boosting 25(OH)D concentrations of adults with baseline concentrations <75 nmol/L. However, this was not associated with protection against all-cause ARI or Covid-19.

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STUDY DESIGN AND AUTHOR CONTRIBUTIONS

ARM, DAJ and CR designed the study, with input from PP, JS, DF, RAL, GAD, FK, CJG, JN, AS, SEF, AGR and SOS. The trial was managed by DAJ, HH, NP, SM, MT and ARM. Laboratory assays were performed by AN, NLB and RG. Data were managed and analyzed by DAJ, MG, MT and CO. 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.

COMPETING INTERESTS

JS declares receipt of payments from Reach plc for news stories written about recruitment to, and findings of, the COVIDENCE UK study. RAL declares membership of the Welsh Government COVID19 Technical Advisory Group. AS and JN declare research infrastructure report to the University of Edinburgh from ISCF/HDR UK. 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 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. All other authors declare that they have no competing interests.

REFERENCES

1. Wouters OJ, Shadlen KC, Salcher-Konrad M, et al. Challenges in ensuring global access to COVID-19 vaccines: production, affordability, allocation, and deployment. Lancet 2021;397:1023-34.
2. Dror AA, Eisenbach N, Taiber S, et al. Vaccine hesitancy: the next challenge in the fight against COVID-19. Eur J Epidemiol 2020;35:775-9.
3. Williams TC, Burgers WA. SARS-CoV-2 evolution and vaccines: cause for concern? The Lancet Respiratory Medicine 2021;9:333-5.
4. Greiller CL, Martineau AR. Modulation of the Immune Response to Respiratory Viruses by Vitamin D. Nutrients 2015;7:4240-70.
5. Bishop E, Ismailova A, Dimeloe SK, Hewison M, White JH. Vitamin D and immune regulation: antibacterial, antiviral, anti-inflammatory. JBMR Plus 2020.
6. Chauss D, Freiwald T, McGregor R, et al. Autocrine vitamin D signaling switches off pro-inflammatory programs of TH1 cells. Nature Immunology 2022;23:62-74.
7. Roth A, Lütke S, Meinberger D, et al. LL-37 fights SARS-CoV-2: The Vitamin D-Inducible Peptide LL-37 Inhibits Binding of SARS-CoV-2 Spike Protein to its Cellular Receptor Angiotensin Converting Enzyme 2 In Vitro. bioRxiv 2020.
8. Zhang L, Ghosh SK, Basavarajappa SC, et al. Molecular dynamics simulations and functional studies reveal that hBD-2 binds SARS-CoV-2 spike RBD and blocks viral entry into ACE2 expressing cells. bioRxiv 2021.
9. Merzon E, Tworowski D, Gorohovski A, et al. Low plasma 25(OH) vitamin D level is associated with increased risk of COVID-19 infection: an Israeli population-based study. FEBS J 2020;287:3693-702.
10. Raisi-Estabragh Z, McCracken C, Bethell MS, et al. Greater risk of severe COVID-19 in Black, Asian and Minority Ethnic populations is not explained by cardiometabolic, socioeconomic or behavioural factors, or by 25(OH)-vitamin D status: study of 1326 cases from the UK Biobank. Journal of Public Health (Oxford, England) 2020;42:451-60.
11. Ma H, Zhou T, Heianza Y, Qi L. Habitual use of vitamin D supplements and risk of coronavirus disease 2019 (COVID-19) infection: a prospective study in UK Biobank. Am J Clin Nutr 2021;113:1275-81.
12. Holt H, Talaei M, Greenig M, et al. Risk factors for developing COVID-19: a population-based longitudinal study (COVIDENCE UK). Thorax 2021.
13. Talaei M, Faustini S, Holt H, et al. Determinants of pre-vaccination antibody responses to SARS-CoV-2: a population-based longitudinal study (COVIDENCE UK). BMC Medicine 2022;20:87.
14. Louca P, Murray B, Klaser K, et al. Modest effects of dietary supplements during the COVID-19 pandemic: insights from 445 850 users of the COVID-19 Symptom Study app. BMJ Nutrition, Prevention & Health 2021;4:149-57.
15. Chiodini I, Gatti D, Soranna D, et al. Vitamin D Status and SARS-CoV-2 Infection and COVID-19 Clinical Outcomes. Front Public Health 2021;9:736665.
16. Dissanayake HA, de Silva NL, Sumanatilleke M, et al. Prognostic and therapeutic role of vitamin D in COVID-19: systematic review and meta-analysis. J Clin Endocrinol Metab 2021.
17. Camargo CA, Jr., Ganmaa D, Frazier AL, et al. Randomized trial of vitamin D supplementation and risk of acute respiratory infection in Mongolia. Pediatrics 2012;130:e561-7.

18. Bergman P, Norlin AC, Hansen S, et al. Vitamin D3 supplementation in patients with frequent respiratory tract infections: a randomised and double-blind intervention study. BMJ Open 2012;2:e001663.
19. Martineau AR, Hanifa Y, Witt KD, et al. Double-blind randomised controlled trial of vitamin D3 supplementation for the prevention of acute respiratory infection in older adults and their carers (ViDiFlu). Thorax 2015;70:953-60.
20. Ganmaa D, Uyanga B, Zhou X, et al. Vitamin D Supplements for Prevention of Tuberculosis Infection and Disease. N Engl J Med 2020;383:359-68.
21. Pham H, Waterhouse M, Baxter C, et al. The effect of vitamin D supplementation on acute respiratory tract infection in older Australian adults: an analysis of data from the D-Health Trial. The Lancet Diabetes & Endocrinology 2021;9:69-81.
22. Jolliffe DA, Camargo CA, Jr., Sluyter JD, et al. Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials. The Lancet Diabetes & Endocrinology 2021;9:276-92.
23. Relton C, Torgerson D, O'Cathain A, Nicholl J. Rethinking pragmatic randomised controlled trials: introducing the "cohort multiple randomised controlled trial" design. BMJ 2010;340:c1066.
24. Fletcher CM. Standardised questionnaire on respiratory symptoms: a statement prepared and approved by the MRC Committee on the Aetiology of Chronic Bronchitis (MRC breathlessness score). BMJ 1960;2:1665.
25. Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. J Pain Symptom Manage 1997;13:63-74.
26. Taylor RR, Trivedi B, Patel N, et al. Post-COVID symptoms reported at asynchronous virtual review and stratified follow-up after COVID-19 pneumonia. Clin Med (Lond) 2021.
27. Grayling MJ, Wason JM. A web application for the design of multi-arm clinical trials. BMC Cancer 2020;20:80.
28. Vickerstaff V, Omar RZ, Ambler G. Methods to adjust for multiple comparisons in the analysis and sample size calculation of randomised controlled trials with multiple primary outcomes. BMC Med Res Methodol 2019;19:129.
29. Dunnett CW. A multiple comparison procedure for comparing several treatments with a control. Journal of the American Statistical Association 1955;50:1096-121.
30. Camargo CA, Sluyter J, Stewart AW, et al. Effect of monthly high-dose vitamin D supplementation on acute respiratory infections in older adults: A randomized controlled trial. Clin Infect Dis 2020;71:311-7.
31. Butler-Laporte G, Nakanishi T, Mooser V, et al. Vitamin D and COVID-19 susceptibility and severity in the COVID-19 Host Genetics Initiative: A Mendelian randomization study. PLoS Med 2021;18:e1003605.
32. Griffith GJ, Morris TT, Tudball MJ, et al. Collider bias undermines our understanding of COVID-19 disease risk and severity. Nature Communications 2020;11:5749.
33. Ilahi M, Armas LA, Heaney RP. Pharmacokinetics of a single, large dose of cholecalciferol. Am J Clin Nutr 2008;87:688-91.
34. Redlberger-Fritz M, Kundi M, Aberle SW, Puchhammer-Stockl E. Significant impact of nationwide SARS-CoV-2 lockdown measures on the circulation of other

respiratory virus infections in Austria. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology 2021;137:104795.
35. Emerging Risk Factors Collaboration E-CVDVDSC. Estimating dose-response relationships for vitamin D with coronary heart disease, stroke, and all-cause mortality: observational and Mendelian randomisation analyses. The Lancet Diabetes & Endocrinology 2021;9:837-46.

Table 1: Baseline Characteristics of the Participants

		Overall (n=6200)	3200 IU/day offer (n=1550)	800 IU/day offer (n=1550)	No offer (n=3100)
Age	Median age, years (IQR)	60.2 (49.8 – 67.8)	60.7 (50.2 – 68.5)	59.8 (50.3 – 67.4)	60.8 (49.9 – 68.2)
	Age range, years	16.1 – 89.8	16.4 – 88.6	16.5 – 88.2	16.1 – 89.8
Sex, N (%)	Male	2044 (33.0)	506 (32.6)	498 (32.1)	1040 (32.5)
	Female	4156 (67.0)	1044 (67.4)	1052 (67.9)	2060 (64.4)
Ethnicity, N (%)	White	5867 (94.6)	1469 (94.8)	1473 (95.0)	2925 (94.4)
	Asian/Asian British	142 (2.3)	31 (2.0)	32 (2.1)	79 (2.5)
	Black/African/Caribbean/Black British	33 (0.5)	11 (0.7)	10 (0.6)	12 (0.4)
	Mixed/Multiple/Other	154 (2.5)	37 (2.4)	34 (2.2)	83 (2.6)
Country of residence, N (%)	England	5515 (89.0)	1374 (88.6)	1384 (89.3)	2757 (86.2)
	Northern Ireland	123 (2.0)	29 (1.9)	33 (2.1)	61 (1.9)
	Scotland	340 (5.5)	97 (6.3)	74 (4.8)	169 (5.3)
	Wales	222 (3.6)	50 (3.2)	59 (3.8)	113 (3.5)
Highest educational level attained, N (%)	Primary/Secondary	52 (0.8)	17 (1.1)	12 (0.8)	23 (0.7)
	Higher/Further (A levels)	924 (14.9)	215 (13.9)	233 (15.0)	476 (14.9)
	College	2740 (44.2)	674 (43.5)	700 (45.2)	1366 (42.7)
	Post-graduate	1817 (29.3)	473 (30.5)	459 (29.6)	885 (27.7)
Occupational status, N (%)	Employed, health or social care worker	566 (9.1)	149 (9.6)	147 (9.5)	270 (8.7)
	Employed, other frontline worker	755 (12.2)	182 (11.8)	192 (12.4)	381 (12.3)
	Employed, non-frontline worker	1,406 (22.7)	336 (21.7)	348 (22.5)	722 (23.3)
	Self-employed	564 (9.1)	154 (9.9)	144 (9.3)	266 (8.3)
	Retired	2504 (40.4)	635 (41.0)	606 (39.1)	1263 (39.5)
	Furloughed	141 (2.3)	32 (2.1)	43 (2.8)	66 (2.1)
	Unemployed	126 (2.0)	34 (2.2)	42 (2.7)	50 (1.6)
	Student	150 (2.4)	33 (2.1)	34 (2.2)	83 (2.6)
	Other	147 (2.4)	35 (2.3)	36 (2.3)	76 (2.4)
Body mass index, kg/m^2, N (%)	<25	2903 (46.8)	739 (47.7)	724 (46.7)	1440 (45.0)
	25-30	2036 (32.8)	514 (33.2)	496 (32.0)	1026 (32.1)
	>30	1249 (20.1)	297 (19.2)	322 (20.8)	630 (19.7)
Medically diagnosed disease, N (%)	Hypertension	227 (3.7)	53 (3.4)	54 (3.5)	120 (3.8)
	Diabetes	259 (4.2)	81 (5.2)	56 (3.6)	122 (3.8)
	Heart disease	1207 (19.5)	319 (20.6)	298 (19.2)	590 (18.4)
	Asthma	946 (15.3)	215 (13.9)	265 (17.1)	466 (14.6)
	COPD	114 (1.8)	26 (1.7)	27 (1.7)	61 (1.9)
Tobacco smoking history, N (%)	Never-smoker	3460 (55.8)	864 (55.7)	887 (57.2)	1709 (53.4)
	Ex-smoker	2346 (37.8)	583 (37.6)	553 (35.7)	1210 (37.8)
	Current smoker	393 (6.3)	103 (6.6)	109 (7.0)	181 (5.7)
Alcohol consumption/week, units, N (%)	None	1651 (26.6)	383 (24.7)	411 (26.5)	857 (26.8)
	1-14	3403 (54.9)	873 (56.3)	865 (55.8)	1665 (52.0)
	≥15	1145 (18.5)	294 (19.0)	274 (17.7)	577 (18.0)
Covid-19 vaccination status	Unvaccinated	5774 (93.1)	1483 (95.7)	1465 (94.5)	2826 (91.2)
	Partially vaccinated	55 (0.9)	9 (0.6)	19 (1.2)	27 (0.9)
	Fully vaccinated	22 (0.4)	6 (0.4)	5 (0.3)	11 (0.4)
	Not known / missing data	349 (5.6)	52 (3.4)	61 (3.9)	236 (7.6)
Mean 25(OH)D, nmol/L (s.d.) [range][1]		--[2]	40.9 (16.4) [10.3-122.0]	41.5 (18.0) [10.3-179.6]	--[2]
25(OH)D category, nmol/L, N (%)[1]	<25.0	--[2]	216 (13.9)	232 (15.0)	--[2]
	25.0-49.9	--[2]	797 (51.4)	759 (49.0)	--[2]
	50-74.9	--[2]	333 (21.5)	337 (21.7)	--[2]
	≥75.0	--[2]	28 (1.8)	43 (2.7)	--[2]
	Not determined	--[2]	176 (11.4)	179 (11.6)	3100 (100.0)

Abbreviations: IQR, inter-quartile range; s.d., standard deviation; 25(OH)D, 25-hydroxyvitamin D.
(1) Missing values: 25(OH)D concentration missing for 189 participants in 3200 IU/day arm and 198 participants in 800 IU/day arm. (2) Baseline 25(OH)D not determined for participants randomized to the 'no offer' arm

Table 2. Primary and Secondary Outcomes, by Allocation: Intention-to-Treat Analysis

		3200 IU/day offer	800 IU/day offer	No offer	Odds ratio for 3200 IU/day vs. no offer (95% CI)	P	Mean difference for 3200 IU/day vs. no offer (95% CI)	P	Odds ratio / mean difference for 800 IU/day vs. no offer (95% CI)	P	Mean difference for 800 IU/day vs. no offer (95% CI)	P
Primary outcome	Proportion of all participants developing at least one swab test- or doctor-confirmed ARI of any cause[1] (%)	5.02% (76/1515)	5.74% (87/1515)	4.61% (136/2949)	1.09 (0.82, 1.46)	0.55	--	--	1.26 (0.96, 1.66)	0.10	--	--
Acute Covid-19 outcomes	Proportion of all participants developing swab test-confirmed Covid-19[2] (%)	2.97% (45/1515)	3.63% (55/1515)	2.64% (78/2949)	1.13 (0.78, 1.63)	0.53	--	--	1.39 (0.98, 1.97)	0.07	--	--
	Proportion of all participants hospitalized for treatment of Covid-19 (%)	1.91% (29/1515)	1.58% (24/1515)	1.36% (40/2949)	1.42 (0.88, 2.30)	0.16	--	--	1.17 (0.70, 1.95)	0.55	--	--
	Proportion of participants hospitalized for treatment of Covid-19 who required ventilatory support[3] (%)	3.45% (1/29)	4.17% (1/24)	2.50% (1/40)	1.39 (0.08, 23.23)	0.82	--	--	1.70 (0.10, 28.43)	0.71	--	--
	Proportion of all participants dying of Covid-19 (%)	0.00% (0/1515)	0.00% (0/1515)	0.00% (0/2949)	--[4]	--	--	--	--[4]	--	--[4]	--
'Long Covid' outcomes	Proportion of participants developing swab test-confirmed Covid-19 who reported symptoms lasting more than four weeks[2] (%)	24.44% (11/45)	38.18% (21/55)	24.36% (19/78)	1.00 (0.43, 2.36)	0.99	--	--	1.92 (0.91, 4.06)	0.09	--	--
	Proportion of participants developing swab test-confirmed Covid-19 who reported on-going symptoms at the end of the study (%)	17.78% (8/45)	20.00% (11/55)	8.97% (7/78)	2.19 (0.74, 6.52)	0.16	--	--	2.54 (0.91, 7.03)	0.07	--	--
	Mean MRC dyspnea score among participants developing swab test-confirmed Covid-19 who reported on-going symptoms at the end of the study (s.d.) [n]	2.13 (0.64) [8]	1.55 (0.93) [11]	2.14 (1.46) [7]	--	--	-0.02 (-1.40, 1.36)	0.98	--	--	-0.60 (-2.00, 0.90)	0.36
	Mean FACIT Fatigue Scale score among participants developing swab test-confirmed Covid-19 who reported on-going symptoms at the end of the study (s.d.) [n]	28.00 (8.75) [8]	25.22 (5.74) [9]	28.43 (7.25) [7]	--	--	-0.43 (-9.36, 8.50)	0.92	--	--	-3.21 (-10.54, 4.13)	0.36
	Mean Post-COVID Physical Health Symptom Score among participants developing swab test-confirmed COVID-19 who reported on-going symptoms at the end of the study (s.d.) [n]	33.25 (12.33) [8]	31.90 (10.70) [10]	30.71 (10.16) [7]	--	--	2.54 (-10.02, 15.09)	0.67	--	--	1.19 (-9.83, 12.20)	0.82
All-cause ARI outcomes[1]	Proportion of all participants prescribed one or more courses of antibiotics for treatment of ARI of any cause[1,8] (%)	0.93% (14/1498)	0.34% (5/1489)	0.77% (22/2864)	1.22 (0.62, 2.39)	0.57	--	--	0.44 (0.16, 1.15)	0.09	--	--
	Proportion of all participants hospitalized for treatment of ARI of any cause[1] (%)	0.73% (11/1515)	0.46% (7/1515)	0.41% (12/2949)	1.79 (0.79, 4.07)	0.16	--	--	1.14 (0.45, 2.89)	0.79	--	--
	Proportion of all participants dying of ARI of any cause[1] (%)	0.00% (0/1515)	0.00% (0/1515)	0.00% (0/2949)	--[4]	--	--	--	--[4]	--	--[4]	--
Airways disease outcomes	Proportion of participants with asthma developing at least one severe acute asthma exacerbation[5]	6.70% (14/209)	3.14% (8/255)	4.87% (21/431)	1.40 (0.70, 2.82)	0.34	--	--	0.63 (0.28, 1.45)	0.28	--	--
	Proportion of participants with COPD	7.41%	21.43%	15.87%	0.42 (0.09, 2.08)	0.29	--	--	1.45 (0.47, 4.46)	0.52	--	--

		3200 IU/day offer	800 IU/day offer	No offer	Odds ratio for 3200 IU/day vs. no offer (95% CI)	P	Mean difference for 3200 IU/day vs. no offer (95% CI)	P	Odds ratio / mean difference for 800 IU/day vs. no offer (95% CI)	P	Mean difference for 800 IU/day vs. no offer (95% CI)	P
	developing at least one severe acute COPD exacerbation[6]	(2/27)	(6/28)	(10/63)								
Biochemical outcome	Mean end-study 25(OH)D concentration, nmol/L[7] (s.d.) [n]	102.9 (23.6) [741]	79.4 (18.3) [742]	66.6 (28.6) [306]	--	--	36.3 (32.9, 39.6)	<0.001	--	--	12.7 (9.8, 15.6)	<0.001

Abbreviations: MRC, United Kingdom Medical Research Council. FACIT, Functional Assessment of Chronic Illness Therapy. Covid-19, coronavirus disease 2019.

Footnotes: 1, including both Covid-19 and other acute respiratory infections. 2, confirmed by RT-PCR and/or antigen testing for SARS-CoV-2. 3, includes invasive and non-invasive respiratory support. 4, OR incalculable due to zero events. 5, defined as an acute worsening of asthma symptoms requiring treatment with oral corticosteroids and/or requiring hospital treatment. 6, defined as an acute worsening of COPD symptoms requiring treatment with oral corticosteroids and/or antibiotics and/or requiring hospital treatment. 7, end-study 25(OH)D concentrations available for a total of 1,789 participants (741 randomized to 3200 IU/day offer, 742 randomized to 800 IU/day offer, 306 randomized to no offer). 8, data on antibiotics prescribed for treatment of ARI available from self-report only.

Table 3. Primary and Secondary Outcomes, by Allocation: Sensitivity Analysis[1]

		3200 IU/day offer	800 IU/day offer	No offer	Odds ratio for 3200 IU/day vs. no offer (95% CI)	P	Mean difference for 3200 IU/day vs. no offer (95% CI)	P	Odds ratio / mean difference for 800 IU/day vs. no offer (95% CI)	P	Mean difference for 800 IU/day vs. no offer (95% CI)	P
Primary outcome	Proportion of all participants developing at least one swab test- or doctor-confirmed ARI of any cause[2] (%)	4.33% (55/1269)	5.31% (66/1243)	4.43% (59/1331)	0.98 (0.67, 1.42)	0.90	--	--	1.21 (0.84, 1.73)	0.30	--	--
Acute Covid-19 outcomes	Proportion of all participants developing swab test-confirmed Covid-19[3] (%)	2.52% (32/1269)	3.14% (39/1243)	2.55% (34/1331)	0.99 (0.61, 1.61)	0.96	--	--	1.24 (0.77, 1.97)	0.37	--	--
	Proportion of all participants hospitalized for treatment of Covid-19 (%)	1.65% (21/1269)	1.37% (17/1243)	1.50% (20/1331)	1.10 (0.59, 2.04)	0.31	--	--	0.91 (0.47, 1.74)	0.77	--	--
	Proportion of participants hospitalized for treatment of Covid-19 who required ventilatory support[4] (%)	4.76% (1/21)	0.00% (0/17)	5.00% (1/20)	0.95 (0.55, 16.29)	0.97	--	--	--[4]	--	--	--
	Proportion of all participants dying of Covid-19 (%)	0.00% (0/1269)	0.00% (0/1243)	0.00% (0/1331)	--[4]	--	--	--	--[4]	--	--	--
'Long Covid' outcomes	Proportion of participants developing swab test-confirmed Covid-19 who reported symptoms lasting more than four weeks[3] (%)	31.25% (10/32)	35.90% (14/39)	26.47% (9/34)	1.26 (0.43, 3.67)	0.67	--	--	1.56 (0.57, 4.25)	0.39	--	--
	Proportion of participants developing swab test-confirmed Covid-19 who reported on-going symptoms at the end of the study (%)	18.75% (6/32)	20.51% (8/39)	5.88% (2/34)	3.69 (0.69, 19.85)	0.13	--	--	4.13 (0.81, 21.00)	0.09	--	--
	Mean MRC dyspnea score among participants developing swab test-confirmed Covid-19 who reported on-going symptoms at the end of the study (s.d.) [n]	2.29 (0.49) [7]	1.29 (0.76) [7]	1.00[6] [1]	--	--	1.29[7]	--	--	--	0.29[7]	--
	Mean FACIT Fatigue Scale score among participants developing swab test-confirmed Covid-19 who reported on-going symptoms at the end of the study (s.d.) [n]	25.29 (4.53) [7]	23.00 (4.69) [6]	34.00[6] [1]	--	--	-8.71[7]	--	--	--	-11.00[7]	--
	Mean Post-COVID Physical Health Symptom Score among participants developing swab test-confirmed COVID-19 who reported on-going symptoms at the end of the study (s.d.) [n]	30.57 (10.50) [7]	30.50 (11.33) [6]	29.00[6] [1]	--	--	1.57[7]	--	--	--	1.50[7]	--
All-cause ARI outcomes[1]	Proportion of all participants prescribed one or more courses of antibiotics for treatment of ARI of any cause[2, 11] (%)	0.55% (7/1269)	0.32% (4/1243)	0.98% (13/1331)	0.56 (0.22, 1.41)	0.22	--	--	0.33 (0.11, 1.00)	0.05	--	--
	Proportion of all participants hospitalized for treatment of ARI of any cause[1] (%)	0.79% (10/1269)	0.24% (3/1243)	0.45% (6/1331)	1.75 (0.64, 4.84)	0.28	--	--	0.53 (0.13, 2.14)	0.38	--	--
	Proportion of all participants dying of ARI of any cause[2] (%)	0.00% (0/1269)	0.00% (0/1243)	0.00% (0/1331)	--[5]	--	--	--	--[5]	--	--	--
Airways disease outcomes	Proportion of participants with asthma developing at least one severe acute asthma exacerbation[8]	4.73% (8/169)	3.33% (7/210)	6.11% (11/180)	0.76 (0.30, 1.95)	0.57	--	--	0.53 (0.20, 1.40)	0.20	--	--
	Proportion of participants with COPD developing at least one severe acute COPD	4.55% (1/22)	25.00% (6/24)	17.86% (5/28)	0.22 (0.02, 2.03)	0.18	--	--	1.53 (0.40, 5.84)	0.53	--	--

		3200 IU/day offer	800 IU/day offer	No offer	Odds ratio for 3200 IU/day vs. no offer (95% CI)	P	Mean difference for 3200 IU/day vs. no offer (95% CI)	P	Odds ratio / mean difference for 800 IU/day vs. no offer (95% CI)	P	Mean difference for 800 IU/day vs. no offer (95% CI)	P
	exacerbation[9]											
Biochemical outcome	Mean end-study 25(OH)D concentration, nmol/L[10] (s.d.) [n]	103.4 (23.3) [729]	79.5 (18.3) [736]	53.7 (23.1) [116]	--	--	49.7 (45.1, 54.2)	<0.001	--	--	25.8 (22.0, 29.5)	<0.001

Abbreviations: MRC, United Kingdom Medical Research Council. FACIT, Functional Assessment of Chronic Illness Therapy. Covid-19, coronavirus disease 2019.

Footnotes: 1, this analysis excludes data from participants randomized to either intervention arm who reported that they took vitamin D capsules 'less than half the time' as well as those randomized to the no-offer arm who reported any intake of supplemental vitamin D during follow-up. 2, including both Covid-19 and other acute respiratory infections. 3, confirmed by RT-PCR and/or antigen testing for SARS-CoV-2. 4, includes invasive and non-invasive respiratory support. 5, OR incalculable due to zero events. 6, s.d. incalculable as single participant with outcome in no offer arm. 7, 95% CI incalculable as single participant with outcome in no offer arm. 8, defined as an acute worsening of asthma symptoms requiring treatment with oral corticosteroids and/or requiring hospital treatment. 9, defined as an acute worsening of COPD symptoms requiring treatment with oral corticosteroids and/or antibiotics and/or requiring hospital treatment. 10, end-study 25(OH)D concentrations available for a total of 1,789 participants (741 randomized to 3200 IU/day offer, 742 randomized to 800 IU/day offer, 306 randomized to no offer), 11, data on antibiotics prescribed for treatment of ARI available from self-report only.

Figure 1: Screening, Randomization, and Follow-up of the Participants

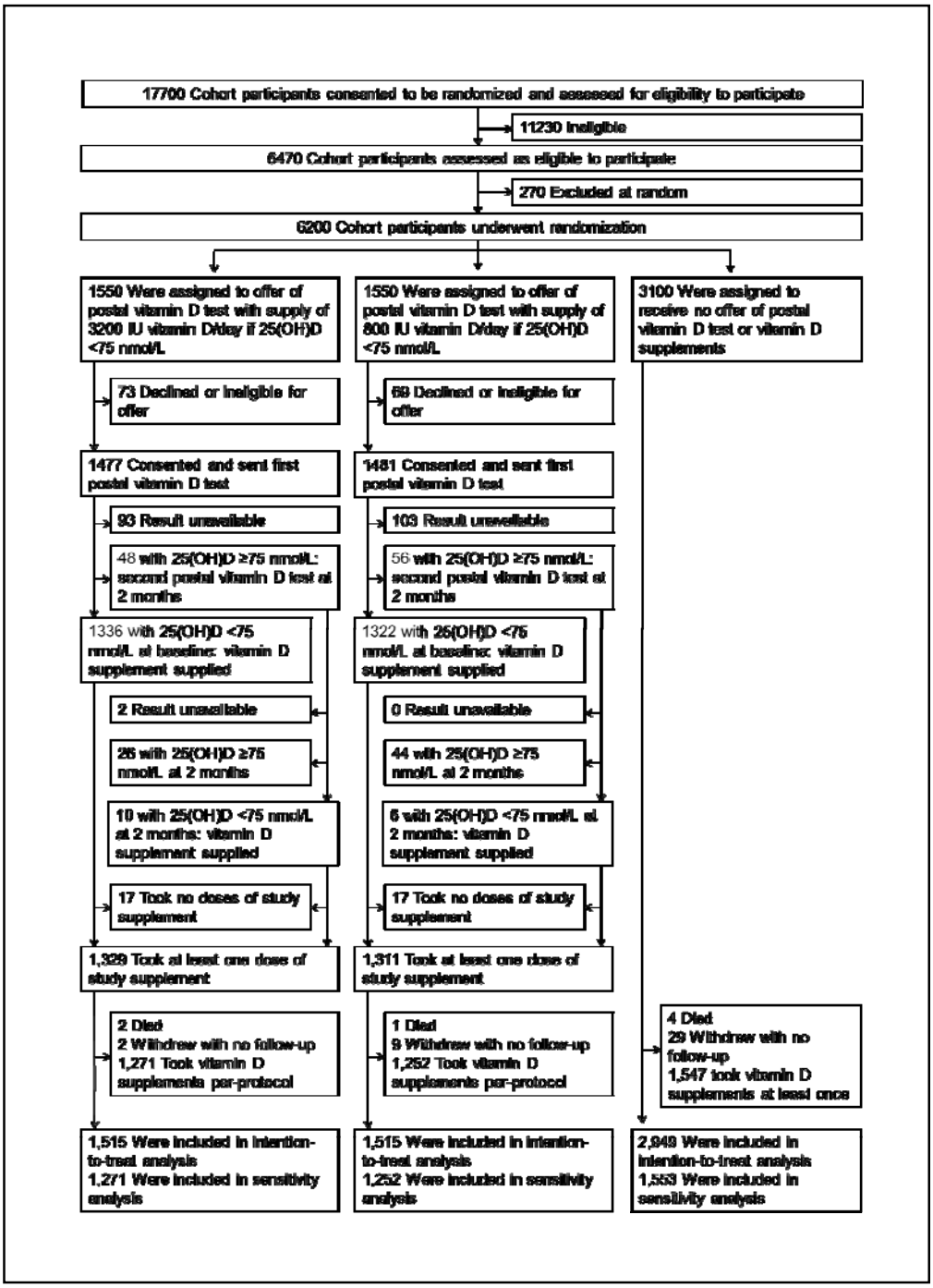

Figure 2: 25-hydroxyvitamin D (25[OH]D) concentrations by time-point and allocation, A for participants included in the intention-to-treat analysis, and B, for participants included in the sensitivity analysis excluding data from participants randomized to either intervention arm who reported that they took vitamin D capsules 'less than half the time' and those randomized 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.