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Detectable respiratory SARS-CoV-2 RNA is associated with low vitamin D levels and high social deprivation

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Abstract

Background: Accumulating evidence links COVID-19 incidence and outcomes with vitamin D status. We investigated if an interaction existed between vitamin D levels and social deprivation in those with and without COVID-19 infection.

Methods: Upper or lower respiratory tract samples from 104 patients were tested for SARS-CoV-2 RNA in accordance with Public Health England criteria (January-May 2020) using RT-PCR. The latest serum total 25-hydroxyvitamin D(25-OHD) levels, quantified by LC-MS/MS, was obtained for each patient (September 2019-April 2020). Index of Multiple Deprivation (IMD) was generated for each patient. Univariate and logistic regression analyses examined associations between age, gender, 25-OHD, IMD score and SARS-CoV-2 result in the total cohort and subgroups.

Results: In the total cohort, a positive SARS-CoV-2 test was significantly associated with lower 25-OHD levels and higher IMD. A positive test was associated with higher IMD in the male subgroup and with lower 25-OHD levels in those aged >72 years. Low 25-OHD and IMD quintile 5 were separately associated with positive COVID-19 outcome in the cohort. Patients in IMD quintile 5 with vitamin D levels ≤ 34.4 nmol/L were most likely to have a positive COVID-19 outcome, even more so if aged >72 years (OR: 19.07, 95%CI: 1.71-212.25; $P = .016$).

Conclusions: In this cohort, combined low vitamin D levels and higher social deprivation were most associated with COVID-19 infection. In older age, this combination was even more significant. Our data support the recommendations for normalising vitamin D levels in those with deficient / insufficient levels and in groups at high risk for deficiency.

What's known

Vitamin D deficiency and insufficiency are related to a range of adverse health outcomes. Low vitamin D levels appear related to pneumonia, cytokine burst and acute respiratory distress syndrome, all of which are associated with COVID-19. Accumulating evidence links COVID-19 incidence and outcomes with vitamin D status. We investigated to see if an interaction existed between vitamin D levels and social deprivation in those with and without COVID-19 infection.

What's new

Combined low vitamin D levels and higher social deprivation were most associated with COVID-19 infection. In older age, this combination was more significant. Our data support normalising vitamin D levels in those with deficient/insufficient levels and in high-risk groups.

1 | INTRODUCTION

Research over the past 30 years has shown that in addition to the well-established functions as a mediator of calcium and bone metabolism, the hormone 1,25-dihydroxyvitamin D has effects on a range of pathological processes.[1] These include associations with the pathogenesis of neoplastic, inflammatory, demyelinating and cardiovascular diseases, as well as diabetes; the aetiology possibly being because of the modulation of innate and adaptive immune functions via genes regulated by the transcription factor vitamin D receptor.[2,3] Hypovitaminosis D, identified by low serum levels of biologically inactive 25-hydroxyvitamin D (25-OHD), has a high worldwide prevalence.[4] Crowe et al[5] studied the prevalence of vitamin D deficiency (<30 nmol/L) between 2005 and 2015 in 210,502 individuals in the United Kingdom. A third (69 515 individuals) of the cohort had low hormone concentrations, this prevalence being higher in individuals who were of male gender, younger age, ethnic minorities and the economically deprived.[5]

It can be argued that currently active measures to counter COVID-19 have been mainly focussed on non-pharmaceutical methods, perhaps in view of the acute explosion of the disease worldwide. The association between hypovitaminosis D and COVID-19 appears to have some scientific merit and must be studied further.[6] Low vitamin D concentrations appear related to pneumonia, cytokine burst and acute respiratory distress syndrome, all of which are associated with COVID-19.[7] Furthermore, low vitamin D appears prevalent in critically ill patients in intensive care units (ICUs) and is associated with increased length of stay, readmission and mortality.[8] Han et al[8] carried out a pilot randomised controlled trial of 31 subjects admitted to ICU and ventilated and administered either placebo, 50 000 IU or 100 000 IU of vitamin D daily for 5 consecutive days. Length of stay in hospital was significantly correlated with the dose of vitamin D supplements (placebo: length of stay = 36 ± 19 days, day 7 vitamin D levels = 52.2 ± 28.0 nmol/L; 50 000 IU/day: length of stay = 25 ± 14 days, day 7 vitamin D levels = 114.3 ± 49.0 nmol/L; 100 000 IU/day: length of stay = 18 ± 11 days, day 7 vitamin D levels = 138.0 ± 36.0 nmol/L). The other clinical outcomes studied were not statistically different between the three groups. Laird et al[9] found a significant association between mean vitamin D levels and mortality attributed to COVID-19 in various European countries.[9] Interestingly, the Scandinavian countries Norway, Finland, Sweden, although receiving lower levels of sunlight, had higher mean vitamin D concentrations than their Southern European counterparts (owing to the widespread fortification of foods) and lower COVID-19 infection and mortality.[9] In view of the accumulating evidence, there have been recommendations that individuals at risk of COVID-19 should consider treatment with inactive vitamin D to reduce the risk of infection: 10 000 IU/day for a few days followed by 5000 IU/day to raise serum 25-OHD concentrations to 100-150 nmol/L.[6,10]

However, although a study by Hastie et al[11] using data from the UK Biobank did show an association between vitamin D levels and COVID-19 infection, this relationship was not sustained when confounders were included in the logistic regression model. Hence, the relationship between vitamin D levels and COVID-19 infection appears complex, and perhaps may only be seen in subgroups. This heterogeneity would make the association very dependent on the cohort studied.

A report from the UK Office for National Statistics suggested that COVID-19-related deaths (20 283 in England and Wales between March 1, 2020, and April 17, 2020) showed a relationship between mortality and deprivation; the age-standardised mortality rate in the most deprived areas of England was 55.1/100 000 population compared with 25.3/100 000 population in the least deprived areas.[12] Hayden et al[13] showed that vitamin D deficiency is related to ethnicity and social deprivation; an association ($P = .0001$) was observed between the Index of Multiple Deprivation (IMD) and percentage of patients with serum vitamin D levels < 50 nmol/L in Manchester and Trafford, UK. Similarly, Heald et al[14] showed a similar relationship between IMD and vitamin D levels in individuals aged >70 years.

The aim of this pilot study was to see whether any differences in serum vitamin D and social deprivation, using the IMD scores, existed between the patient groups with and without a SARS-CoV-2 detected PCR test. We also wished to see if an interaction existed between vitamin D concentration and deprivation with regard to COVID-19. Moreover, the analyses were repeated in subgroups associated with a poorer prognosis, in particular, male gender and older age.

2 | PATIENTS AND METHODS

Walsall Healthcare NHS Trust provides acute hospital and community health services for people living in Walsall, UK, and the surrounding areas, and serves a population of around 270 000 people. Acute hospital services are provided from Walsall Manor Hospital, a university-affiliated hospital, which has ~600-650 inpatient beds, and provides community health services from over 60 sites including primary care health centres and General Practitioner surgeries.

We obtained data from 104 consecutive individuals tested in the hospital according to UK Public Health England Guidelines for COVID-19, thus minimising selection bias.[15] All patients in this study were tested for COVID-19 between January 31, 2020, and May 7, 2020, in accordance with the UK Public Health England COVID-19 testing criteria, from samples received at the Department of Microbiology, Walsall Manor Hospital.

Clinical samples of the upper (nasopharyngeal swabs) or lower respiratory tract (sputum or bronchial washings) were tested for the presence of SARS-CoV-2 after inoculation into viral transport medium, using initially reference laboratory investigational RdRP-gene real-time reverse-transcriptase PCR assay until 6th April 2020. After this date, detection of SARS-CoV-2 was performed locally on a commercial assay detecting the ORF-1a/b and E-genes

with a reported limit of detection of <300 copies/mL (Roche Cobas; Roche Diagnostics GmbH, Manheim, Germany).[16] The relative clinical sensitivity and specificity of these targets are not yet known.

Vitamin D levels were the most recent for each patient, obtained from the Clinical Biochemistry laboratory database, from a period covering 6 months up to and including admission date (between September 1, 2019, and April 30, 2020). Liquid chromatography-tandem mass spectrometry (LC-MS/MS; Waters TQD LC-MS/MS; Waters Corporation, UK) was used to quantify serum 25-OHD_2 and 25-OHD_3 levels (combined to give the total 25-OHD level) (coefficient of variation (CV) was 6.5%, 5.5% and 5.2% for internal quality control (IQC) 25-OHD_3 levels of 19.4, 39.5 and 110.1 nmol/L, respectively; the CV was 10.9%, 5.6% and 5.4% for IQC 25-OHD_2 levels of 3.7, 37.7 and 108.8 nmol/L, respectively).

The English Indices of Deprivation combine factors of housing, social and economic issues to give a single deprivation score for small areas (known as Lower Layer Super Output Areas or LSOAs) in England. An overall weighted aggregation index of multiple deprivation (IMD) is generated based on 37 separate indicators, organised across seven distinct domains of deprivation and each area is ranked from the least to most deprived. The criteria and their associated weightings are: Income deprivation, 22.5%, Employment deprivation, 22.5%, Health deprivation and disability 13.5%, Education, skills and training deprivation 13.5%, Barriers to housing and services 9.3%, Crime 9.3% and Living environment deprivation 9.3%. The indices are a widely used standard measure for comparing areas across the country and help to identify areas with high levels of overall deprivation or areas with specific concerns (health for example) that may not be recognised from the overall index. The measures of deprivation are collected nationally and published every 3-4 years. In the IMD 2019, the most deprived LSOA in England is given a rank of 1 and the least deprived is ranked 32 844. Each vitamin D result was aligned with an associated postcode for each patient and linked to its LSOA using the geo-convert tool.[17] The LSOA is then linked to the 2019 IMD for the specified full postcode.[14] This was not possible using geo-convert for six patients included in this study.[18]

2.1 | Statistics

The association between a positive SARS-CoV-2 test compared with a negative SARS-CoV-2 test result and serum vitamin D levels, IMD, age and gender was initially studied using unpaired *t*-test (continuous variables), rank-sum non-parametric test (ordinal data: IMD) in the total cohort and subgroups; age, vitamin D by median values and IMD by the quintile threshold closest to the median.[19] Logistic regression analyses were then carried out with SARS-CoV-2 RNA real-time RT-PCR test result as the dichotomous outcome (detected or not detected) and vitamin D levels and factorised IMD as independent variables with age and gender included as confounders. The regression analyses were carried out in the total groups and the previously mentioned subgroups. All analyses were performed on Stata 14 (StataCorp LLC, Texas, USA).

3 | RESULTS

In the total cohort of 104 individuals tested for SARS-CoV-2, a positive result was significantly associated with low vitamin D concentrations and IMD, but not age and gender (Table 1). The total cohort was then stratified by gender, median age (72 years), vitamin D levels (34.4 nmol/L) and IMD (quintile 1-4 and 5; median IMD was 35.70, this figure within quintile 5, the threshold separating quintile 4 from 5 being 34.18). 57.1% of the total cohort had an IMD in quintile 5. In males and individuals aged >72 years, a positive SARS-CoV-2 test was associated with higher IMD (greater deprivation) and low vitamin D levels, respectively. Low vitamin D levels were associated with a positive COVID-19 test in individuals classified as IMD quintile 5, and whilst this was not seen in IMD quintiles 1-4, IMD was higher in COVID-19 positive individuals with vitamin D levels below the total cohort median value, this approaching statistical significance (Table 1).

We then performed a logistic regression analysis with COVID-19 positive diagnosis (reference: negative diagnosis) as the dichotomous outcome. Low vitamin D levels and IMD quintile 5 (compared with IMD quintiles 1-4) were significantly associated with the outcome whilst age and gender were not (Table 2: Model 1). Model 2 (Table 2) was a repeat of Model 1, but with vitamin D stratified by the median value; once again low vitamin D and IMD quintile 5 were significantly associated with a positive COVID-19 test. Models 3 and 4 (Table 2) comprised the cohort stratified by the median vitamin D levels, and IMD quintile 5 was only significantly associated with a positive COVID-19 test in the subgroup with low vitamin D levels (Table 2: Model 3). Vitamin D levels were associated with a positive SARS-CoV-2 test in the IMD quintile 5 subgroup (Table 2: Model 5) but not in the IMD quintiles 1-4 subgroup (Table 2: Model 6).

The above analyses (Table 2: Models 3 and 5) suggest the possibility of an interaction between IMD quintile 5 and low vitamin D levels, both associated with positive SARS-CoV-2 test (Table 2: Model 2). Hence, the total cohort was stratified into four groups by IMD quintiles (quintile 1-4 and 5) and vitamin D status (≤34.4, >34.4 nmol/L). A Chi-square analysis did not show an association between these four groups ($P = .41$). Model 7 (Table 2) shows that individuals belonging to IMD quintile 5 with vitamin D levels ≤ 34.4 nmol/L were more likely to have a positive SARS-CoV-2 test (reference: vitamin D > 34.4 nmol/L + IMD quintiles 1-4). Interestingly, the association with a diagnosis of COVID-19 was clearly not evident in individuals with only one risk factor (vitamin D ≤ 34.4 nmol/L or IMD quintile 5). The analysis with the combined IMD and vitamin D subgroups was repeated in patients aged ≤72 years (Model 8) and >72 years (Table 2: Model 9). The association between the 'at risk' group (IMD quintile 5 + vitamin D ≤ 34.4 nmol/L) appeared greater in patients aged >72 years (Table 2: Model 9). Although we did not have sufficient patient numbers to study the above associations in black and

TABLE 1 Univariate analyses studying associations between age, gender, serum total 25-hydroxyvitamin D levels and Index of Multiple Deprivation (IMD) scores and SARS-CoV-2 RT-PCR test results (for COVID-19) in the total cohort and selected subgroups

	SARS-CoV-2 PCR negative	SARS-CoV-2 PCR positive	*P*
Total cohort	n = 57	n = 47	
Age (years): mean ± SD, median (range)	68.5 ± 18.1, 73, (25-95)	68.6 ± 18.7, 72, (22-95)	.98 (*t*-test)
Males	19 (33.3%)	20 (42.6%)	.33 (Chi sq)
Females	38 (66.7%)	27 (57.5%)	
Serum vitamin D: mean ± SD, median (range)	**51.0 ± 31.4, 44.3, (10.3-129.8)**	**38.9 ± 28.2, (10.3-103)**	**.045** (*t*-test)
IMD: median (range)	**28.4 (4.5-67.8), n = 53**	**40.4 (7.0-67.8), n = 45**	**.018** (ranksum)
Subgroup analyses			
Males	n = 19	n = 20	
Age (years): mean ± SD, median (range)	68.7 ± 16.4, 73, (31-80)	69.9 ± 19.2, 73, (23-95)	.83 (*t*-test)
Serum vitamin D: mean ± SD, median (range)	42.6 ± 23.3, 39.8, (10.3-96.2)	34.4 ± 23.7, 30.2, (10.3-94.4)	.28 (*t*-test)
IMD: median (range)	**18.2 (4.5-58.6)**	**40.9 (8.3-54.1), n = 19**	**.0029** (ranksum)
Females	n = 38	n = 27	
Age (years): mean ± SD, median (range)	68.4 ± 16.4, 72, (25-95)	67.6 ± 18.6, 71, (22-91)	.87 (*t*-test)
Serum vitamin D: mean ± SD, median (range)	55.2 ± 34.3, 50.5, (11.3-129.8)	42.3 ± 31.2, 28.3, (10.3-103.0)	.13 (*t*-test)
IMD: median (range)	35.2 (8.7-67.8), n = 34	39.8 (7.0-67.8), n = 26	.38 (ranksum)
Age >72 years (Total cohort median)	n = 29	n = 22	
Males	11 (37.9%)	11 (50.0%)	.39 (Chi sq)
Females	18 (62.1%)	11 (50.0%)	
Serum vitamin D: mean ± SD, median (range)	**56.3 ± 31.6, 63.5, (10.3-114.0)**	**35.4 ± 24.2, 30.2, (10.3-84.8)**	**.013** (*t*-test)
IMD: median (range)	19.2 (5.9-67.8), n = 27	36.3 (7.0-54.2), n = 21	.15 (ranksum)
Age ≤72 years (Total cohort median)	n = 28	n = 25	
Males	8 (28.6%)	9 (36.0%)	.56 (Chi sq)
Females	20 (71.4%)	16 (64.0%)	
Serum vitamin D: mean ± SD, median (range)	45.5 ± 30.9, 39.7, (11.2-129.8)	42.0 ± 31.6, 28.3, (10.3-103.0)	.69 (*t*-test)
IMD: median (range)	36.0 (4.5-63.1), n = 26	43.0 (25.4-67.8), n = 24	.060 (ranksum)
Vitamin D > 34.4 nmol/L (Total cohort median)	n = 36	n = 16	
Age (years): mean ± SD, median (range)	69.1 ± 17.6, 72, (31-94)	72.3 ± 17.5, 72, (24-95)	.55 (*t*-test)
Males	11 (30.6%)	6 (37.5%)	.62 (Chi sq)
Females	25 (69.4%)	10 (62.5%)	
IMD: median (range)	34.5 (4.5-58.6), n = 34	36.3 (7.0-67.8), n = 15	.34 (ranksum)
Vitamin D ≤ 34.4 nmol/L (Total cohort median)	n = 21	n = 31	
Age (years): mean ± SD, median (range)	67.5 ± 19.4, 71, (25-95)	66.7 ± 19.2, 71, (22-91)	.88 (*t*-test)
Males	8 (38.1%)	14 (45.2%)	.61 (Chi sq)
Females	13 (61.9%)	17 (54.8%)	
IMD: median (range)	27.5 (5.9-67.8), n = 19	41.0 (8.3-58.6), n = 30	.059 (ranksum)
IMD > 34.18 (quintile 5)	n = 25	n = 31	
Age (years): mean ± SD, median (range)	62.3 ± 18.5, 70, (31-87)	64.4 ± 20.0, 70, (22-95)	.70 (*t*-test)
Males	**5 (20.0%)**	**14 (45.2%)**	**.048** (Chi sq)
Females	**20 (80.0%)**	**17 (54.8%)**	
Serum vitamin D: mean ± SD, median (range)	**54.3 ± 33.8, 45.5, (11.3-129.8)**	**32.6 ± 22.4, 26.3, (10.3-93.0)**	**.0057** (*t*-test)
IMD ≤ 34.18 (quintile 1-4)	n = 28	n = 14	
Age (years): mean ± SD, median (range)	75.4 ± 14.2, 78, (31-95)	78.2 ± 10.2, 81.5, (54-92)	.51 (*t*-test)
Males	14 (50.0%)	5 (35.7%)	.38 (Chi sq)
Females	14 (50.0%)	9 (64.3%)	
Serum vitamin D: mean ± SD, median (range)	50.2 ± 30.4, 42.1, (10.3-114.0)	50.4 ± 32.5, 37.2, (10.3-101.0)	.98 (*t*-test)

The bold values relate to results that are statistically significant.

TABLE 2 Logistic regression analyses studying associations between serum total 25-hydroxyvitamin D levels, Index of Multiple Deprivation (IMD) quintile 5, separately and in combination, and COVID-19 infection in the total cohort and selected subgroups, the analyses adjusted for age and gender

Logistic regression (Outcome: SARS-CoV-2 positive on RT-PCR)	OR (95% CI)	*P*
Total cohort, n = 98		
Age (years)	1.01 (0.99-1.04)	.34
Male gender (female gender: reference)	1.30 (0.54-3.12)	.56
Serum vitamin D (nmol/L)	**0.98 (0.97-1.00)**	**.044**
IMD: quintile 5 (quintile 1-4: reference)	**2.82 (1.10-7.21)**	**.030**
Total cohort, n = 98		
Age (years)	1.01 (0.99-1.04)	.360
Male gender (female gender: reference)	1.38 (0.57-3.37)	.480
Vitamin D > 34.4 nmol/L (≤34.4 nmol/L: reference)	**0.28 (0.12-0.66)**	**.004**
IMD: quintile 5 (quintile 1-4: reference)	**3.00 (1.15-7.85)**	**.025**
Vitamin D ≤34.4 nmol/L (Total cohort median), n = 49		
Age (years)	1.02 (0.98-1.06)	.38
Male gender (female gender: reference)	1.75 (0.42-7.30)	.44
Serum vitamin D (nmol/L)	1.08 (0.97-1.20)	.15
IMD: quintile 5 (quintile 1-4: reference)	**12.00 (2.14-67.21)**	**.005**
Vitamin D > 34.4 nmol/L (Total cohort median), n = 49		
Age (years)	1.02 (0.98-1.06)	.40
Male gender (female gender: reference)	1.53 (0.40-5.86)	.54
Serum vitamin D (nmol/L)	1.00 (0.97-1.03)	.94
IMD: quintile 5 (quintile 1-4: reference)	1.16 (0.33-4.13)	.810
IMD > 34.18 (quintile 5), n = 56		
Age (years)	1.01 (0.98-1.05)	.35
Male gender (female gender: reference)	3.21 (0.88-11.73)	.078
Serum vitamin D (nmol/L)	**0.97 (0.95-0.99)**	**.010**
IMD ≤ 34.18 (quintile 1-4), n = 42		
Age (years)	1.01 (0.96-1.07)	.65
Male gender (female gender: reference)	0.57 (0.13-2.43)	.45
Serum vitamin D (nmol/L)	1.00 (0.98-1.02)	.85
Total cohort, n = 98		
Age (years)	1.02 (0.99-1.05)	.21
Male gender (female gender: reference)	1.63 (0.64-4.15)	.3
IMD quintile 5 + serum vitamin D ≤ 34.4 nmol/L	**10.37 (2.68-40.12)**	**.001**
IMD quintile 5 + serum vitamin D > 34.4 nmol/L	1.16 (0.33-4.07)	.81
IMD quintile 1-4 + serum vitamin D ≤ 34.4 nmol/L	1.14 (0.30-4.26)	.85
IMD quintile 1-4 + serum vitamin D > 34.4 nmol/L: reference		

Abbreviations: CI, confidence intervals; OR, odds ratio.
The bold values relate to results that are statistically significant.

ethnic minorities, we were able to analyse the data in the known Caucasian subgroup (n = 59): individuals belonging to IMD quintile 5 with vitamin D levels ≤ 34.4 nmol/L being the only patients significantly associated (odds ratio: 19.00, 95% confidence interval: 2.73-132.27; *P* = .003) with a diagnosis of COVID-19 (reference: vitamin D > 34.4 nmol/L + IMD quintiles 1-4).

4 | DISCUSSION

There is accumulating evidence on the association between vitamin D levels and COVID-19 incidence and outcome following infection.[6-8,20] Ours is a relatively small study cohort fulfiling the PCR-based testing criteria for COVID-19. Univariate analyses showed that low vitamin D levels and IMD scores were associated with a positive test for SARS-CoV-2. It was clear that these associations appeared strengthened in some subgroups; males (IMD scores), age >72 years (vitamin D). Further, the association between low vitamin D and a positive SARS-CoV-2 result was seen in the IMD quintile 5 subgroup only. Logistic regression with age and gender added as confounding variables confirmed the results of the above-mentioned univariate association between low vitamin D, deprivation (IMD quintile 5) and a positive SARS-CoV-2 test. Interestingly, low vitamin D and IMD quintile 5 were associated with a positive test in patients belonging to IMD quintile 5 (Table 2: Model 5) and low vitamin D (Table 2: Model 3), respectively, and not the complementary subgroups.

These results are interesting as only a combination of low vitamin D levels and deprivation (IMD quintile 5) appear to be associated with COVID-19 (Table 2: Model 7), this association perhaps more evident in the older age group (Table 2: Model 9). Patients characterised by one of these factors were not at any higher risk of a diagnosis of COVID-19. Thus, associations between vitamin D levels, social deprivation and COVID-19 infection will be dependent on cohort characteristics. Consequently, we highlight the importance of acknowledging heterogeneity and studying subgroups. Our results were influenced by the fact that 57.1% with IMD scores belonged to IMD quintile 5, the most deprived group; each quintile should consist of ~20%, but accordingly, this shows the increased social deprivation present in this cohort. The 2019 Index of Multiple Deprivation ranks Walsall as the 25th most deprived English local authority (out of 317), placing Walsall within the most deprived 10% of districts in the UK. High deprivation is most likely a surrogate for either one or more risk factors. It is established that the rates of obesity and potentially insulin resistance are higher in more socially disadvantaged individuals.[21] Low vitamin D could be a causative or a surrogate factor in COVID-19 infection. Only normalising vitamin D levels with supplements would provide data on the role of the hormone in COVID-19 infection. Interestingly, whilst addressing social deprivation is a long-term programme, normalising serum vitamin D concentrations can be easily achieved in a relatively short period within existing clinical guidelines. In our clinical practice, we have for >10 years been using vitamin D supplements in patients with hormonal deficiency (<30 nmol/L) or insufficiency (30-50 nmol/L), these thresholds in

synchrony with laboratory distribution data and at slight odds with the UK National Institute for Health and Care Excellence (NICE) recommendations.[22] Depending on symptoms and concentrations of serum vitamin D, a clinical decision based on the NICE guidelines would be taken as to the dose of the hormone supplements.[22] This should be followed by a repeat test of vitamin D and a bone profile in 3-6 months to ensure adequate treatment efficacy. Adverse effects are uncommon[23]; hence, the importance of our findings.

In usual circumstances, ours would be considered an interesting observation meriting further investigation. Even when a significant association was observed, the relatively small numbers led to the odds ratio having wide confidence intervals. We acknowledge that false-negative SARS-CoV-2 RT-PCR test results could have a significant bearing on our study outcome. The relative clinical sensitivity and specificity of the targets in the Roche assay are not yet fully known, but the false-negative rate is estimated to be ~30%.[24] However, the current situation perhaps requires the usual scientific method processes to be accelerated, especially if any associated therapeutic intervention is perceived as safe. Our data add to results from other studies suggesting a possible role for vitamin D in COVID-19 infection.[20] As described previously there is mechanistic plausibility in view of vitamin D modulating immune function and viral replication.[2,3] A further positive aspect of our study is the inclusion of SARS-CoV-2 test negative patients who were suspected of a COVID-19 diagnosis for comparison (control group). A larger, more robust study with the analyses adjusted for ethnicity, body mass index, comorbidities are required to validate our findings, with the cohort size allowing for subgroup analyses of different populations (eg, different ethnic groups, patients on vitamin D supplements) at varying levels of risk,[25] which we could not consider as the data were not accessible. We realise the potential for low vitamin D levels to be attributed to a negative acute phase response, hence the inclusion of the control arm in our study (ie, SARS-CoV-2 negative patients) who presented with similar symptoms to the SARS-CoV-2 positive patients included and were tested accordingly for suspected COVID-19 (in accordance with the UK Public Health England COVID-19 testing criteria). We were unable to perform subgroup analysis on the non-Caucasian populations because of the limited subject numbers (Caucasian = 59; Southern Asian = 13; African/Caribbean = 2; not available = 30).

It would also be interesting to compare with similar global data to see if vitamin D levels could, at least partially account for differences in incidence / prevalence that is evident between nations.[26]

This should be followed by large well-designed outcome studies (either randomised controlled trials or longitudinal cohort studies) to see if vitamin D supplementation, especially in individuals subject to social deprivation, alters outcome trajectory at varying stages of the infection. However, at this time of necessary urgent action, our data add support to the recommendations for normalising vitamin D levels in those with deficient / insufficient levels and in groups at high risk for deficiency.

In conclusion, combined low vitamin D levels and higher social deprivation were most associated with COVID-19 infection. In older age, this combination was even more significant. The importance of studying subgroups and acknowledging heterogeneity is highlighted, with results being dependant on the cohort studied.

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A preprint of this publication in the Authorea repository: https://www.authorea.com/users/312296/articles/454940-detectable-respiratory-sars-cov-2-rna-is-associated-with-low-vitamin-d-levels-and-high-social-deprivation?commit=0a10ec6dd5905a5d717761c9ea66e9e366ca1f7d

CONFLICT OF INTEREST

None to declare.

DATA AVAILABILITY STATEMENT

We used patient level data which was fully anonymised prior to analysis. Any requests for access to this data should be made to the corresponding author, Prof Mark Livingston.

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