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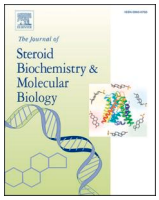

Prevalence and determinants of profound vitamin D deficiency (25-hydroxyvitamin D <10 nmol/L) in the UK Biobank and potential implications for disease association studies

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ABSTRACT

Background: 25-hydroxyvitamin D (25OHD) is the principal biomarker of vitamin D status. Values below the assay detection limit (<10 nmol/L) are often reported as missing. Thus the most severely deficient participants are excluded from research which can lead to inaccurate findings such as underestimated prevalence of deficiency, overlooked risk factors, and biased evaluation of disease associations.
Methods: In total 369,626 individuals from the UK Biobank cohort were included in this study. Data on 25OHD concentration and relevant demographic and lifestyle factors such as age, supplement intake, diet, and time spent outdoors were used in the analyses. Ambient UVB radiation was approximated for each participant. 25OHD was evaluated as a categorical outcome and we reintroduced participants with 25OHD values < 10 nmol/L (conventionally reported as missing values) back to the dataset. Adjusted regression models were used to investigate the determinants of profound (25OHD <10 nmol/L) and severe (10–25 nmol/L) vitamin D deficiency and to assess disease associations (with 25–50 nmol/L as the reference category).
Results: 1,784 (0.48 %) individuals were profoundly deficient and a further 47,226 (12.78 %) individuals were severely vitamin D deficient. The proportions of profoundly and severely deficient were highest among Asians, 9 % and 47 %, respectively. Ambient UVB radiation was the second strongest predictor: comparing the lowest vs. highest quartile, the risk of profound deficiency was 17-fold increased and that of severe deficiency 7.5-fold increased. Use of vitamin D supplements substantially reduced risk of profound (4.4-fold) and severe (2.5-fold) deficiency, as did fish intake (5- and 1.9-fold, respectively). Profound deficiency was more strongly associated with chronic illness, diabetes, and emphysema compared to severe deficiency.
Conclusion: The prevalence of profound and severe vitamin D deficiency among Asian and Black ethnicities in the UK is high and requires targeted action. Solar radiation is potent in protecting against profound and severe vitamin D deficiency. Studies evaluating the relationship between vitamin D status and other health outcomes may be biased if profoundly deficient participants are excluded.

1. Introduction

Vitamin D is essential for calcium absorption and skeletal health. Despite these benefits, a significant proportion of the population suffers from vitamin D deficiency, with some individuals requiring clinical intervention. Severe vitamin D deficiency is typically defined as having serum 25-hydroxyvitamin D (25OHD) levels below 25 nmol/L [1]. This condition is associated with significant health risks, including rickets in children and osteomalacia in adults. Profound deficiency (25OHD below 10 nmol/L) can lead to serious complications such as hypocalcaemia and secondary hyperparathyroidism. Furthermore, vitamin D deficiency has been linked with many illnesses, including diabetes, colorectal cancer, and cardiovascular disease among others [2]. Treatment for vitamin D deficiency generally involves high-dose vitamin D supplementation of

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40,000–50,000 IU per week over 6–8 weeks [3]. The initial treatment is typically followed by a maintenance dose to ensure sufficient levels are sustained.

Prevalence of severe vitamin D deficiency (25OHD <25 nmol/L) varied between European cohorts from none to 27 % [4]. Overall, 13 % had 25OHD below 30 nmol/L. In darker skinned individuals, the prevalence was 3- to 71-fold higher compared to White individuals living in Europe. In the UK Biobank cohort, 13 % of participants had 25OHD < 25 nmol/L, which also differed dramatically by ethnicity: 12 % of White, 35 % of Black, and 49 % of Asian participants were severely deficient [5]. Strikingly, a third of Asian participants in the UK Biobank cohort had 25OHD < 15 nmol/L [6].

Dermal synthesis is the most important source of vitamin D for the majority of people [7–10]. Solar ultraviolet B (UVB) radiation triggers the conversion of 7-dehydrocholesterol to pre-vitamin D3, which is then converted to vitamin D in the skin. Therefore, it is unsurprising that the key risk factors linked with vitamin D deficiency relate to the dermal potential to synthesise vitamin D, which is affected by the intensity of solar radiation, skin pigmentation, and individual behaviours such as time spent outdoors, clothing, and sunscreen use [5]. Other well-known risk factors include older age, obesity, malabsorption disorders, and kidney or liver diseases that interfere with the conversion of vitamin D into its active form. Natural food is scarce in vitamin D— the main sources of dietary vitamin D are oily fish and fortified foods [12]—but vitamin D supplements can be very effective at preventing deficiency [5,11,12].

The UK Biobank cohort enables unprecedented large-scale studies of environmental and lifestyle factors that influence health and disease. Numerous studies to date have used this resource to investigate the determinants of vitamin D status and the role of vitamin D deficiency in disease aetiology. However, 25OHD values below the assay detection limit of < 10 nmol/L were reported as missing in the main dataset. This means that participants with the poorest vitamin D status are regularly being excluded from vitamin D research (with some exceptions such as in Darling et al. [6] and Vearing et al. [13]). This can result in an underestimated prevalence of deficiency and lack of understanding of the risk factors linked to severe deficiency. Furthermore, it can lead to biased evaluation of the association between 25OHD and disease, since individuals at the highest risk are excluded, leading to a weakened association between vitamin D status and the disease of interest.

In this study, we reintroduced 25OHD values originally reported as missing due to being below the assay detection limit. This allowed us to investigate the prevalence and determinants of profound and severe vitamin D deficiency in the UK Biobank cohort, and to uncover the underlying factors that contribute to this clinically significant, preventable health problem. Finally, we explored the impact that the exclusion of profoundly deficient people may have on disease association estimates.

2. Methods

2.1. UK Biobank

Approximately half a million participants (N= 502,415) living in England, Scotland or Wales were recruited to the UK Biobank (UKBB) cohort between 2006 and 2010. UKBB ethical approval was granted by the North West Multi-centre Research Ethics Committee [14]. During baseline assessments participants completed a questionnaire and interview, underwent physical measurements and provided biological samples [15,16]. Furthermore, data linkage to a wide range of electronic health-related records, including death, cancer, hospital admissions, and primary care records was established.

This is a cross-sectional study based on data from 369,626 UKBB participants. Participants with missing data in any of the covariates included in the multinomial model were excluded (baseline characteristics of the entire cohort are shown in Supplementary Table 1). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed.

2.2. Vitamin D status

25-hydroxyvitamin D (25OHD) concentration was measured from blood samples using chemiluminescent immunoassay (DiaSorin, Stillwater, USA; detectable range: 10–375 nmol/L) [17]. The UKBB variable 'Vitamin D reportability' (data-field 30896) indicates the underlying reason for each participant whose vitamin D assay was not reportable and was thus used to identify UKBB participants with 25OHD below the detectable range of the assay (i.e. <10 nmol/L, "*Not reportable at assay (too low)*"). To enable the analysis of 25OHD, including values below the detectable range, vitamin D status was categorised as profound deficiency for 25OHD < 10 nmol/L and as severe deficiency for 10–24.99 nmol/L. Additionally, as per the Institute of Medicine 2011 report, 25–50 nmol/L suggests insufficiency and > 50 nmol/L sufficiency [1].

2.3. Covariates

Ambient daily UVB doses at wavelengths that can induce vitamin D synthesis (D-UVB) adjusted for cloud attenuation, surface elevation, and UV reflectivity were extracted from the Tropospheric Emission Monitoring Internet Service (TEMIS) database [18]. To account for 25OHD accumulation and utilisation, a cumulative and weighted estimate of D-UVB (CW-D-UVB) was calculated based on each participant's residential address and date of blood sample, as previously described [5,7,8]. In addition to age and sex, we used the following covariates: self-reported ethnicity, time spent outdoors, use of UV protection, use of vitamin D or fish oil supplements, time spent watching TV, time spent using the computer, consumption of oily fish, body mass index (BMI), smoking status, cholesterol, calcium, C-reactive protein (CRP), and Townsend deprivation index (referred to as 'deprivation'). Ethnicity was self-reported and grouped as follows: Asian (Indian, Pakistani, Bangladeshi, and 'any other Asian background'), Chinese, Black (Carribean, African, 'any other Black background'), Mixed ('White and Black Carribean', 'White and Black African', 'White and Asian', and 'any other Mixed background'), White (British, Irish, 'any other White background'), and Other ('other ethnic group'). Adjusted OR (AOR) are reported unless indicated otherwise. We reported details on covariate selection and processing previously [5]. Additionally, the variable 'night shift work' was created using responses to UKBB variables reporting on employment status and shift work. For all of the questionnaire covariates, responses of "I don't know" or "Prefer not to answer" were recoded as missing. Additional covariates were included in the disease association analysis (see below). These included deep vein thrombosis (DVT, yes/no), allergies (yes/no), and skin colour (fair, very fair, light olive, dark olive, and brown). From the dietary questionnaire, processed meat, beef, pork, and lamb consumption were combined into a 'red meat' variable (never, <1/week, 1–2/week, and ≥3/week).

2.4. Statistical methods

All analyses were conducted in R (4.3.2). Counts and proportions are reported for categorical variables. Median and interquartile range (IQR) were calculated for numerical variables. Risk factors for profound (25OHD <10 nmol/L) and severe (25OHD 10–25 nmol/L) vitamin D deficiency were investigated in a multinomial logistic regression model with 25OHD level of 25–50 nmol/L as the reference. The model also included 25OHD level > 50 nmol/L for completeness. Variance inflation factors (VIF) were used to assess multicollinearity (≥5 considered indicative of collinearity). Age as a continuous variable and calcium concentration showed high VIF levels so calcium was excluded from the model and age was categorised as 38–57 and 58–73. Odds ratio (OR) estimates were considered significant at Bonferroni-corrected p-value of 0.0025. We selected several diseases that have been linked with vitamin

D deficiency, to investigate the difference in the effect size (OR) between the profoundly and severely deficient groups using binomial logistic regression models, adjusted for age, sex, known modifiers, using 25OHD 25–50 nmol/L group as the reference.

3. Results

3.1. Descriptive statistics

The median age was 58 years, 53 % were female, 42 % were taking vitamin D or fish oil supplements and 95 % were White (Table 1). Median 25OHD concentration was 47 nmol/L (IQR: 33–63 nmol/L). Vitamin D deficiency was profound in 1,784 (0.48 %) individuals (25OHD <10 nmol/L) and severe in further 47,226 (12.78 %) individuals (25OHD 10–25 nmol/L, Fig. 1). Profound and severe deficiency were particularly high among Asian participants wherein 9.1 % (556 of 6,086) were profoundly and a further 47.2 % (2,875 of 6,086) were severely deficient, which is much higher compared to the White (0.3 % and 11.6 %, respectively), or Black participants (1.5 % and 34.3 %, respectively). A large majority of profoundly and severely deficient participants did not take vitamin D supplements (85 % and 79 %, respectively), and the majority ate oily fish less than once per week (76 % and 55 %, respectively).

3.2. Multivariable analysis

Asian individuals were 41.8 times more likely to be profoundly deficient (AOR=41.81 [95 %CI: 36.04–48.49]) and 6.2 times more likely to be severely deficient (6.23 [5.83–6.65]) (Fig. 2 and Supplementary Table 2), relative to White participants. The risk also increased for other ethnicities, although this was less pronounced: for example, Black participants were 4 times more likely to be profoundly deficient and 2.7 times more likely to be severely deficient. Low ambient UVB radiation was the second most strongly associated factor, with 17-fold higher risk of profound (17.4 [14.07–21.52]) and 7-fold higher risk of severe (6.72 [6.43–7.03]) deficiency in the adjusted model for the lowest vs. the highest CW-D-UVB quartile. Risk for profound deficiency almost doubled in those who spend < 1 hr per day outdoors (1.78 [1.54–2.04]) and increased 1.39-fold for severe deficiency [1.34–1.43], with similar findings in those who avoid sun exposure (1.71 [1.23–2.38] and 1.84 [1.64–2.06], respectively). Not taking vitamin D supplements or fish oil supplements increased the risk of profound deficiency 4-fold (4.42 [3.85–5.07]), and eating fish less than once per week 5-fold (5.01 [4.04–6.21]). Current smokers were at increased risk of both profound and severe deficiency (2.12 [1.86–2.42] and 1.53 [1.48–1.58], respectively). In contrast with participants who do not consume alcohol, moderate alcohol use was linked with reduced risk of deficiency (1–2 times per week, 0.4 [0.34–0.47]). Risk factors for profound deficiency compared to severe deficiency largely mirror what was shown in the multinomial model (Supplementary Table 3).

As expected, the likelihood of being vitamin D sufficient (>50 nmol/L *vs.* 25–50 nmol/L) by and large showed the inverse: vitamin D sufficiency was linked with being White, high ambient UVB, taking vitamin D supplements, spending more time outside, and being in the normal weight BMI range.

3.3. Health & disease

The overall health rating was strongly linked with vitamin D status in a dose-response manner, with participants who were more deficient being more likely to report poorer health. When we investigated the associations between vitamin D status and selected health outcomes, we noted a non-negligible change in disease risk when comparing profoundly and severely vitamin D deficient (Fig. 3; see Fig. S1 for models adjusted only for age and sex). In chronic illness, adjusted for age, sex, and deprivation, the OR for profoundly deficient 25OHD was 1.65 [1.49–1.82] compared to 1.3 [1.27–1.32] for severely deficient. Similarly, in a diabetes model adjusted for age, sex, and BMI, the risk in profoundly deficient increased 2.64-fold [2.27–3.06] compared to 1.48-fold [1.42–15.4] in severely deficient as well as in an emphysema model adjusted for age, sex, smoking, and deprivation, 1.83 [1.38–2.38] compared to 1.37 [1.27–1.47], respectively. A similar trend was observed in colorectal cancer, although the effect estimate for profoundly deficient participants was only nominally significant ($p = 0.009$, OR=1.62 [1.1–2.29] and 1.15 [1.05–1.25], respectively). The inverse was observed for skin cancers, with OR = 0.54 [0.38–0.73] in profoundly deficient 25OHD and 0.83 [0.79–0.87] in severely deficient.

4. Discussion

Approximately 0.48 % of the UK Biobank were profoundly deficient in vitamin D (25OHD <10 nmol/L) and a further 12.66 % severely deficient (10–25 nmol/L), in line with previous reports [4,5]. Extrapolating to 23 million older adults (50 years or older) living in England and Wales based on UK Census 2021, this would suggest there are about 3 million severely and about 100,000 profoundly vitamin D deficient individuals over 50 years old [19]. To avoid osteomalacia, hypocalcaemia and secondary hyperparathyroidism, the clinical need for vitamin D supplementation for those individuals is unequivocal [20]. A striking 9.1 % of the Asian participants were found to be profoundly deficient (<10 nmol/L) which is in line with the high prevalence of severe deficiency that was previously found in this group, with further 47 % being severely deficient (25OHD 10–25 nmol/L) [6,21,22]. Our findings reiterate an epidemic of profound and severe vitamin D deficiency, particularly among Asians at Northern latitudes. This underscores the need for targeted public health action, as the observed deficiencies may be associated with the disproportionately higher disease prevalence reported in minority populations in the UK and elsewhere [23,24]. Furthermore, given that vitamin D deficiency has been linked with a range of outcomes such as cancer, autoimmune disease, and infections among others, there may be further detrimental health effects of vitamin D deficiency [2].

Determinants of profound and severe deficiency. Factors most strongly associated with profound deficiency included Asian ethnicity, followed by low ambient UVB, eating fish less than once per week, and not taking vitamin D supplements. Similar factors affected the risk of severe deficiency, albeit the effect sizes were more modest. The risk of profound and severe deficiency was higher in Asian than Black ethnicities (41-fold vs 4-fold for profound, and 6-fold vs. 3-fold for severe deficiency), in line with previous research [5,25], although the observed differences in earlier studies may have been attenuated due to the exclusion of profoundly deficient participants. This supports the notion that skin pigmentation is not the only risk factor determined by ethnicity, and that other important differences may not have been captured in the present study.

The finding that the risk of profound deficiency is 17-fold increased following a period of the lowest ambient UVB radiation is striking. This suggests a very high potency of sunshine to protect against the most extreme vitamin D deficiency. Sunshine is known to be a key source of vitamin D for most humans and multiple population studies have reiterated the association between sun exposure and vitamin D status [5,8,26]. The importance of sunshine in this study was further supported by the significant 71 % increase in the risk of profound deficiency and 84 % increase in the risk of severe deficiency among individuals who avoid sun exposure. Similarly, risk was increased 78 % and 39 %, respectively, among those who spend less than an hour per day outside. These findings indeed support the need to increase dietary and supplemental vitamin D intake during the winter to avoid these clinically detrimental deficiency states. Additionally, sun exposure clinical trials in South Asian adults living in the UK emphasised the need for different exposure guidelines for this ethnic group to reach adequate vitamin D

Table 1
Baseline characteristics overall and by vitamin D status, based on the 25-hydroxyvitamin D (25OHD) concentration.

Variable [Median (IQR) / N (%)]	Entire cohort (N = 369,626)	< 10 nmol/L (N = 1,784, 0.48 %)	10–25 nmol/L (N = 47,226, 12.78 %)	25–50 nmol/L (N = 154,341, 41.76 %)	> 50 nmol/L (N = 166,275, 44.98 %)
25OHD (nmol/L)*	47.1 (32.6–62.7)	*NA*	19.9 (16.5–22.6)	38 (31.8–44)	64.5 (56.8–75.2)
Age	58 (50−63)	53 (47−60)	55 (48−61)	57 (50−63)	59 (51−64)
Sex					
Female	194819	912 (0.5 %)	24815 (12.7 %)	81076 (41.6 %)	88016 (45.2 %)
Male	174807	872 (0.5 %)	22411 (12.8 %)	73265 (41.9 %)	78259 (44.8 %)
Ethnicity					
White	352625	1069 (0.3 %)	40983 (11.6 %)	146854 (41.6 %)	163719 (46.4 %)
Asian	6086	556 (9.1 %)	2875 (47.2 %)	2144 (35.2 %)	511 (8.4 %)
Chinese	1057	8 (0.8 %)	278 (26.3 %)	589 (55.7 %)	182 (17.2 %)
Black	4959	74 (1.5 %)	1702 (34.3 %)	2439 (49.2 %)	744 (15 %)
Mixed	2076	24 (1.2 %)	505 (24.3 %)	978 (47.1 %)	569 (27.4 %)
Other	2823	53 (1.9 %)	883 (31.3 %)	1337 (47.4 %)	550 (19.5 %)
Vitamin D/fish oil supplement					
Yes	153497	268 (0.2 %)	9882 (6.4 %)	55824 (36.4 %)	87523 (57 %)
No	216129	1516 (0.7 %)	37344 (17.3 %)	98517 (45.6 %)	78752 (36.4 %)
Oily fish consumption					
≥2/week	66609	94 (0.1 %)	5650 (8.5 %)	26944 (40.5 %)	33921 (50.9 %)
1/week	140533	342 (0.2 %)	15489 (11 %)	58752 (41.8 %)	65950 (46.9 %)
<1/week	162484	1348 (0.8 %)	26087 (16.1 %)	68645 (42.2 %)	66404 (40.9 %)
UV protection (sunscreen)					
Never	36244	655 (1.8 %)	7894 (21.8 %)	15671 (43.2 %)	12024 (33.2 %)
Sometimes	123192	523 (0.4 %)	15634 (12.7 %)	52102 (42.3 %)	54933 (44.6 %)
Mostly	208165	560 (0.3 %)	22993 (11 %)	85664 (41.2 %)	98948 (47.5 %)
Avoid sun	2025	46 (2.3 %)	705 (34.8 %)	904 (44.6 %)	370 (18.3 %)
TV					
<1 hr/d	29400	194 (0.7 %)	3906 (13.3 %)	12563 (42.7 %)	12737 (43.3 %)
1–2 hr/d	147965	610 (0.4 %)	18082 (12.2 %)	61930 (41.9 %)	67343 (45.5 %)
≥3 hr/d	192261	980 (0.5 %)	25238 (13.1 %)	79848 (41.5 %)	86195 (44.8 %)
Computer					
<1 hr/d	176871	891 (0.5 %)	22081 (12.5 %)	72633 (41.1 %)	81266 (45.9 %)
1–2 hr/d	155963	617 (0.4 %)	18955 (12.2 %)	65280 (41.9 %)	71111 (45.6 %)
≥3 hr/d	36792	276 (0.8 %)	6190 (16.8 %)	16428 (44.7 %)	13898 (37.8 %)
Time outdoors in season of sample					
≥3 hr/d	160225	454 (0.3 %)	13684 (8.5 %)	59965 (37.4 %)	86122 (53.8 %)
1–2 hr/d	164291	826 (0.5 %)	23678 (14.4 %)	73343 (44.6 %)	66444 (40.4 %)
<1 hr/d	45110	504 (1.1 %)	9864 (21.9 %)	21033 (46.6 %)	13709 (30.4 %)
Night shift					
No	351174	1659 (0.5 %)	44263 (12.6 %)	146224 (41.6 %)	159028 (45.3 %)
Yes	18452	125 (0.7 %)	2963 (16.1 %)	8117 (44 %)	7247 (39.3 %)
Alcohol					
Never	27473	556 (2 %)	5926 (21.6 %)	11620 (42.3 %)	9371 (34.1 %)
Rare	81461	434 (0.5 %)	12692 (15.6 %)	36249 (44.5 %)	32086 (39.4 %)
1–2/week	95942	277 (0.3 %)	10804 (11.3 %)	40188 (41.9 %)	44673 (46.6 %)
3–4/week	87550	208 (0.2 %)	9029 (10.3 %)	35555 (40.6 %)	42758 (48.8 %)
Daily	77200	309 (0.4 %)	8775 (11.4 %)	30729 (39.8 %)	37387 (48.4 %)
Smoking					
Never	202238	988 (0.5 %)	24915 (12.3 %)	85252 (42.2 %)	91083 (45 %)
Previous	129325	375 (0.3 %)	14501 (11.2 %)	53018 (41 %)	61431 (47.5 %)
Current	38063	421 (1.1 %)	7810 (20.5 %)	16071 (42.2 %)	13761 (36.2 %)
Overall health rating					
Excellent	63041	142 (0.2 %)	5891 (9.3 %)	24527 (38.9 %)	32481 (51.5 %)
Good	215807	788 (0.4 %)	24756 (11.5 %)	89613 (41.5 %)	100650 (46.6 %)
Fair	75468	569 (0.8 %)	12801 (17 %)	33543 (44.4 %)	28555 (37.8 %)
Poor	15310	285 (1.9 %)	3778 (24.7 %)	6658 (43.5 %)	4589 (30 %)
Townsend Deprivation quartile					
Q1 (least deprivation)	95590	226 (0.2 %)	9125 (9.5 %)	38113 (39.9 %)	48126 (50.3 %)
Q2	94367	234 (0.2 %)	9443 (10 %)	38645 (41 %)	46045 (48.8 %)
Q3	92818	445 (0.5 %)	11853 (12.8 %)	39495 (42.6 %)	41025 (44.2 %)
Q4	86851	879 (1 %)	16805 (19.3 %)	38088 (43.9 %)	31079 (35.8 %)
BMI category					
Normal weight	116562	436 (0.4 %)	12286 (10.5 %)	43517 (37.3 %)	60323 (51.8 %)
Underweight	1905	41 (2.2 %)	322 (16.9 %)	683 (35.9 %)	859 (45.1 %)
Overweight	161379	607 (0.4 %)	18429 (11.4 %)	67385 (41.8 %)	74958 (46.4 %)
Obese	89780	700 (0.8 %)	16189 (18 %)	42756 (47.6 %)	30135 (33.6 %)
CW-D-UVB (kJ/m^2) quartile					
Q4 (most UVB)	91755	113 (0.1 %)	3007 (3.3 %)	27724 (30.2 %)	60911 (66.4 %)
Q3	92424	213 (0.2 %)	6663 (7.2 %)	37908 (41 %)	47640 (51.5 %)
Q2	93516	518 (0.6 %)	14866 (15.9 %)	44869 (48 %)	33263 (35.6 %)
Q1	91931	940 (1 %)	22690 (24.7 %)	43840 (47.7 %)	24461 (26.6 %)
CRP	1.3 (0.64–2.71)	1.81 (0.81–4.25)	1.53 (0.72–3.31)	1.36 (0.67–2.81)	1.2 (0.6–2.45)
Calcium	2.37 (2.32–2.43)	2.34 (2.27–2.4)	2.36 (2.3–2.42)	2.37 (2.31–2.43)	2.38 (2.32–2.44)
Cholesterol	5.6 (4.88–6.32)	5.5 (4.75–6.31)	5.64 (4.92–6.38)	5.65 (4.92–6.37)	5.54 (4.83–6.26)

Footnote: Participants with any missing data were excluded.
* 25OHD values below 10 nmol/L were below the UK Biobank assay detection limit.

** BMI categories were defined differently by ethnicity: for Asian and Chinese, normal weight ≥ 18.5 and ≤ 22.9 kg/m^2, overweight > 22.9 and ≤ 27.5 kg/m^2, and obese > 27.5 kg/m^2; for all other ethnic groups, ≥ 18.5 and ≤ 24.9 kg/m^2, overweight > 24.9 and ≤ 30 kg/m^2, and obese > 30 kg/m^2.
*** Overall CW-D-UVB range was 5.68–260.02 kJ/m^2 and Townsend deprivation index range −6.26–11.0.

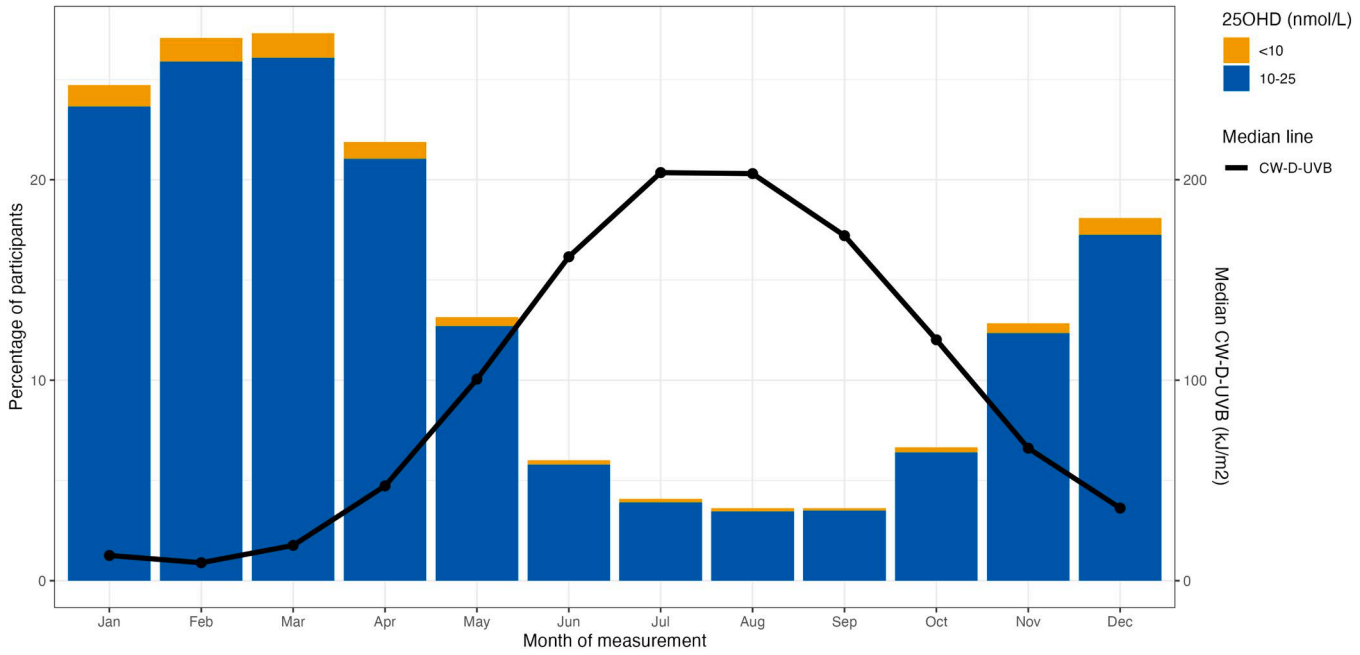

Fig. 1. The bars show the proportion of profoundly deficient (25OHD <10 nmol/L, orange) and severely deficient (10–25 nmol/L, blue) participants as a percentage of the analysis cohort. The black line shows median CW-D-UVB (kJ/m^2) in the cohort by month of blood sample.

concentrations at UK latitudes [27,28].

Sunshine. The synthesis of vitamin D is one of the most well-researched benefits of sunlight. Yet, sun exposure has been linked with numerous other health benefits such as the regulation of circadian rhythms, lowering blood pressure, and supporting immune function, which may also be compromised in those who avoid sunshine [29–31]. The strong relationship between ambient UVB and vitamin D deficiency suggests that those most deficient may also be losing out on these other benefits. Interestingly, we found that being older (58–73 vs. 38–57) reduced the risk of profound (by 26 %) and severe (by 16 %) deficiency. This was also reported by Darling et al. (2021), who hypothesise that "retirement may actually pose an opportunity for increased sunlight exposure" [6].

Public Health. Public health messages relevant to vitamin D deficiency include vitamin D supplementation and sun exposure guidelines. These guidelines tend to be general and ignore ethnicity or other personal characteristics, despite the notably lower risk of skin cancer and notably higher risk of vitamin D deficiency in Asian, Black, or Mixed ethnicities. For the most part, sun exposure guidelines are effectively skin cancer prevention guidelines [29,32]. Given the exceptionally strong relationship between sun exposure and profound vitamin D deficiency, it is likely that more balanced guidelines tailored to an individual (e.g. ethnicity) and their context (place of residence, time of year) have the potential to enhance overall health and well-being in a more balanced manner. For example, nuanced sun exposure guidelines were recently developed in Australia that assign individuals into three groups based on skin cancer risk, and recommend tailored levels of sun protection accorodingly [33].

Vitamin D guidelines are primarily focused on supplement intake and tend to discourage sun exposure as a method for meeting vitamin D requirements. Compared to the highest quartile (Q4) of ambient UVB, the risk of profound deficiency increased 2.36 (Q3), 7.49 (Q2), and 17.4 (Q1) times. In comparison, the risk was 4.42-fold higher if one was not taking vitamin D supplements. This highlights a significant role of sunshine in the prevention of vitamin D deficiency, even in a high-latitude region such as the UK, and consequently it is reasonable to expect that advising against sun exposure will impact vitamin D status, particularly in the absence of concomitant vitamin D supplementation. Previous research showed that time spent outdoors had less impact on reducing deficiency in Asians [25]. This may be due to biological or cultural factors, but in either case, it further supports the need to tailor sun exposure and vitamin D supplementation guidelines. A review from Lucas et al. [32] highlighted gaps in the available research including downstream functions of vitamin D, skin bleaching, risks versus benefits assessment, sun protection use, climate change, and interaction with air pollution. These gaps make it more challenging to address the imbalance between risks and benefits in sun exposure guidelines [32]. Furthermore, ambient solar radiation varies dramatically depending on season and location, even across a relatively narrow band of European latitudes [34]. Therefore, it is crucial to account for local climate conditions when considering sun exposure and vitamin D requirements.

Disease associations. The link between vitamin D and various diseases has been proposed and investigated through numerous research studies, including of the UK Biobank. We sought to evaluate whether the exclusion of individuals with very low 25OHD (i.e. below the assay detection limit of 10 nmol/L) would be consequential for disease association; in other words, whether the strength of the association with disease differs when comparing profoundly (<10 nmol/L) or severely (10–25 nmol/L) deficient with the referent group (25–50 nmol/L). Indeed, we found notable differences for some outcomes. For example, the risk of diabetes was 2.64-fold higher among profoundly deficient, but 1.48-fold in severely deficient; the risk of emphysema was 1.83-fold and 1.37-fold increased, respectively. Conversely, the risk of skin cancer was 47 % reduced among profoundly deficient and 17 % lower among severely deficient. Such findings are in keeping with many earlier studies that described relationships between the *degree* of vitamin D deficiency and disease risk [35,36]. Similarly, the benefit of supplementation is the strongest amongst those most deficient [37]. It is also

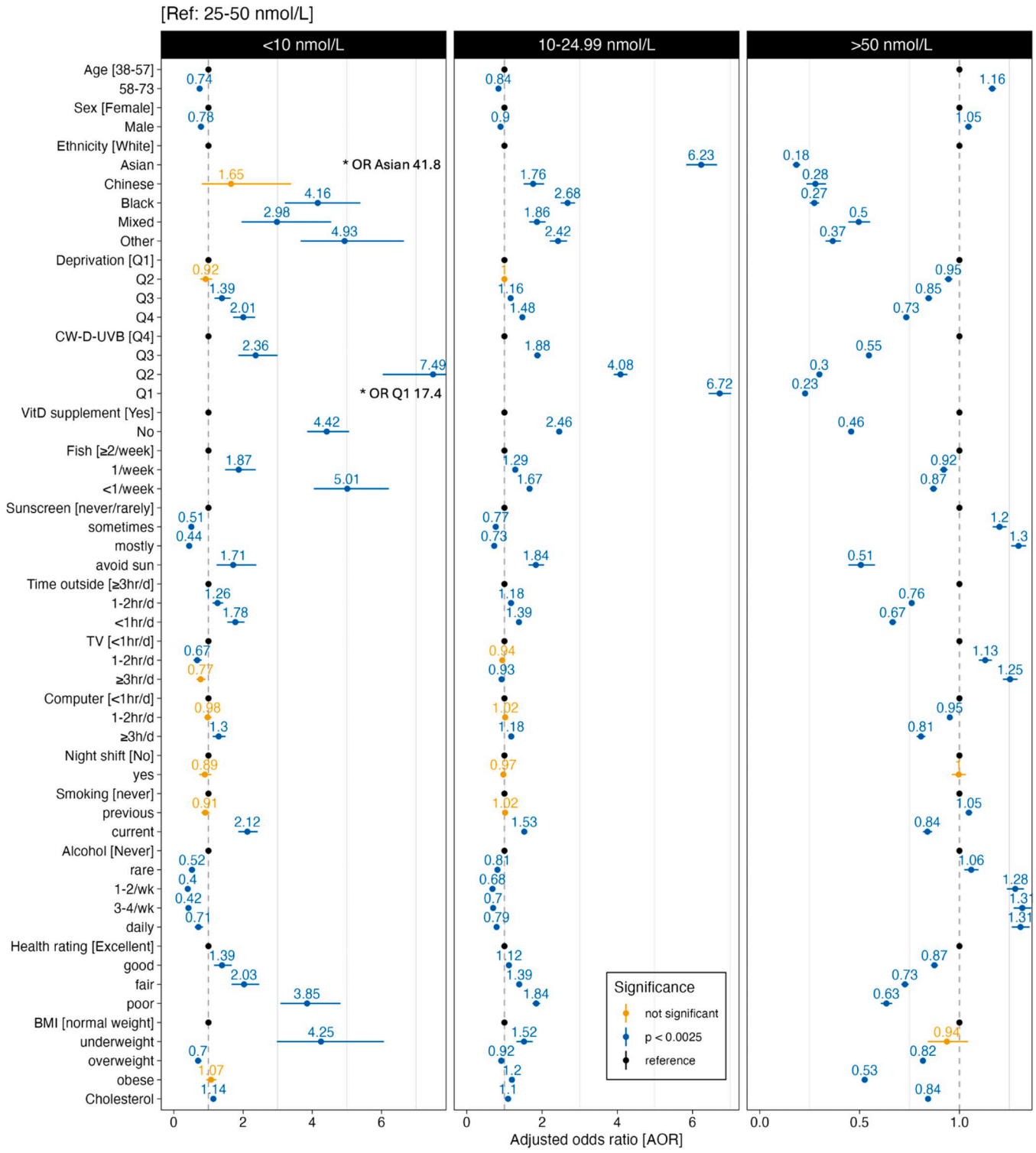

Fig. 2. Factors associated with vitamin D status estimated from a multinomial model in the complete case data (N = 369,626). The reference category is 25OHD 25–50 nmol/L. The dashed line represents an odds ratio of 1. Values shown in blue are significant at the Bonferroni-corrected p-value threshold $p < 0.05/20$ (see Table S2). The x-axis is limited for readability. Odds ratios outside the axis limit are noted on the plot: in the profoundly deficient panel, Ethnicity:Asian = 41.8 [CI: 36.0–48.5] and CW-D-UVB:Q1 = 17.4 [14–21.5], both were significant.

possible that severe vitamin D deficiency is a consequence rather than risk factor of disease, such as in pediatric coeliac disease [38]. Previous research suggests a bidirectional relationship for some outcomes, such as in cholesterol levels [39]. The UK Biobank is a key resource that many researchers turn to in order to estimate effect sizes describing the relationship between vitamin D status and other health outcomes. Regardless of the direction of the effect, the findings reported here suggest that the exclusion of profoundly deficient participants may diminish the strength of the association reported for certain health outcomes. On one hand, studies may underestimate the effect of disease on decreasing vitamin D levels. On the other hand, the exclusion may bias studies that seek to quantify the health, economic or other benefit of

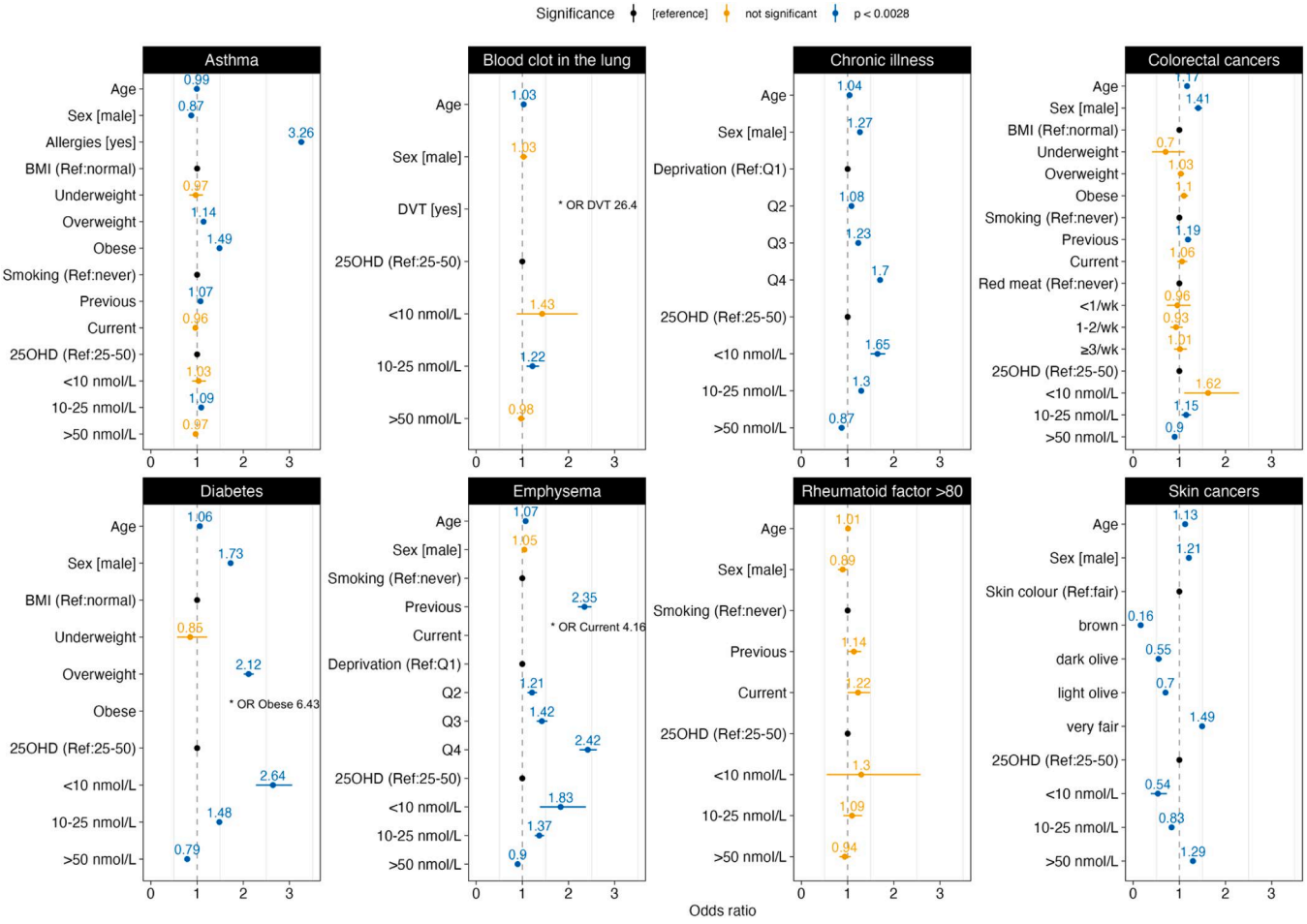

Fig. 3. Odds ratios are shown for the association between vitamin D status (reference 25–50 nmol/L) and selected health outcomes. All models were adjusted for age and sex (age at diagnosis for colorectal cancer [ICD10: C18, C19, C20] and skin cancer [ICD10: C43, C44]), and each model was additionally adjusted for key known modifiers. The dashed line represents an odds ratio of 1 and values shown in blue are significant at the Bonferroni-corrected p-value threshold $p < 0.05/18$. The x-axis is limited to 3.5 for readability. Odds ratios greater than 3.5 are noted on the plot, in blood clot in the lung, DVT:yes = 26.4 [CI: 24.3–28.6]; in diabetes, BMI: obese = 6.43 [CI: 6.12–6.76]; and in emphysema, Smoking:current = 4.16 [CI: 3.86–4.48].

vitamin D supplementation, or misinform sample size calculation when planning future studies [40].

Strengths and limitations. The UKBB provided a very large and diverse cohort for this research. Sample size ensured good statistical power, and the rich set of lifestyle and demographic variables enabled us to control for confounding. Unlike most other studies, we included the profoundly deficient individuals (N = 1,784), which allowed us to investigate this particularly vulnerable cohort. To account for ambient UVB radiation, we used a cumulative and weighted measure based on the participants' place of residence and date of blood sampling, thereby improving on the usual variables used to approximate solar radiation, such as season or latitude.

On the other hand, a "healthy volunteer" bias has been recognised in this cohort. The proportion of minority populations is lower than in the general population of the UK, meaning that groups found to be most deficient are underrepresented. Together, these suggest that the proportion of profoundly and severely deficient individuals is likely underestimated here. Unfortunately, vitamin D dose in supplements was not captured and the "fish oil supplement use" variable did not distinguish between fish oil and fish liver oil (the latter having a significantly higher vitamin D content). Similarly, we have no information about the time of day participants spent outdoors, or their clothing and other relevant habits. In terms of 25OHD assessment, Diasorin Liaison KL assay was used. This may have underestimated 25OHD, particularly at low concentrations and could have thus particularly impacted the profoundly/severely deficient cohort [41]. In some cases, a profoundly low 25OHD measurement (i.e. below the detection limit) may be a limitation of the assay itself or an interfering problem such as abnormal vitamin D-binding protein levels [42]. Further clinical studies and assessments in individuals at high risk of profound deficiency should consider various assays and analytical approaches to minimise measurement errors.

5. Conclusions

Prevalence of profound and severe vitamin D deficiency that requires intervention is high, particularly among Asian ethnicities. Thus, targeted, more personalised public health interventions are needed to address this. Asian ethnicity, low ambient UVB radiation, absence of vitamin D supplement use, low fish intake, and < 1 hr/day spent outdoors most strongly increase the risk of profound and severe deficiency. For some disease outcomes, profound vitamin D deficiency confers notably higher risk compared to severe deficiency, suggesting that current estimates of disease associations may only apply to severely or moderately deficient individuals.

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CRediT authorship contribution statement

Shraim Rasha: Writing – review & editing, Visualization, Validation, Supervision, Formal analysis. **Brennan Margaret M.:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **van Geffen Jos:** Writing – review & editing, Validation, Formal analysis, Data curation. **Zgaga Lina:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Conceptualization.

Declaration of Competing Interest

Authors have no conflict of interest to declare.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jsbmb.2025.106737.

Data availability

The authors do not have permission to share data.

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