Clinical Nutrition xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Differences and determinants of vitamin D deficiency among UK biobank participants: A cross-ethnic and socioeconomic study

Joshua P. Sutherland [a, *], Ang Zhou [a], Matthew J. Leach [b], Elina Hyppönen [a, c, **]

[a] Australian Centre for Precision Health, Unit of Clinical and Health Sciences, University of South Australia, Adelaide, Australia
[b] National Centre for Naturopathic Medicine, Southern Cross University, East Lismore, Australia
[c] South Australian Health and Medical Research Institute, Adelaide, Australia

ARTICLE INFO

Article history:
Received 14 July 2020
Accepted 17 November 2020

Keywords:
Vitamin D
Vitamin D deficiency
Nutritional status
Public health
Socioeconomic factors
Ethnic groups

SUMMARY

Background: The public health relevance of true vitamin D deficiency is undisputed, although controversy remains regarding optimal vitamin D status. Few contemporary cross-ethnic studies have investigated the prevalence and determinants of very low 25-hydroxyvitamin D [25(OH)D] concentrations.
Methods: We conducted cross-ethnic analyses on the prevalence and determinants of vitamin D deficiency (25(OH)D $\leq$ 25 nmol/L) using data from 440,581 UK Biobank participants, of which 415,903 identified as White European, 7880 Asian, 7602 Black African, 1383 Chinese, and 6473 of mixed ancestry. Determinants of vitamin D deficiency were examined by logistic regression.
Results: The prevalence of vitamin D deficiency was highest among participants of Asian ancestry (57.2% in winter/spring and 50.8% in summer/autumn) followed by those of Black African ancestry (38.5% and 30.8%, respectively), mixed (36.5%, 22.5%), Chinese (33.1%, 20.7%) and White European ancestry (17.5%, 5.9%). Participants with higher socioeconomic deprivation were more likely to have 25(OH)D deficiency compared to less deprived participants ($P = <1 \times 10^{-300}$); this pattern was more apparent among those of White European ancestry and in summer ($P_{interaction} \leq 6.4 \times 10^{-5}$ for both). In fully-adjusted analyses, regular consumption of oily fish was associated with reduced odds of vitamin D deficiency across all ethnicities, while outdoor-time in summer was less effective for Black Africans (OR 0.89, 95% CI 0.70, 1.12) than White Europeans (OR 0.40, 95% CI 0.38, 0.42).
Conclusions: Severe vitamin D deficiency remains an issue throughout the UK, particularly in lower socioeconomic areas. In some groups, levels of deficiency are alarmingly high with one-half of Asian and one-third of Black African ancestry populations affected across seasons.
Key messages: The prevalence of vitamin D deficiency in the UK is alarming, with certain ethnic and socioeconomic groups considered particularly vulnerable.

1. Introduction

Vitamin D is a hormone precursor synthesized in the skin during exposure to UVB radiation. The active hormone regulates widespread biological functions, with receptors for vitamin D located throughout the body [1,2]. A primary role of the hormonal vitamin D system is the mediation of osteogenic-related mineral absorption and utilisation [2], with skeletal development and maintenance constituting principal foci of public health strategies [3].

25-hydroxyvitamin D [25(OH)D] is the primary circulating vitamin D metabolite. As 25(OH)D reflects both dietary intake and sunlight-induced synthesis, it is often used as an indicator for nutritional vitamin D status [4]. Severe skeletal diseases, such as rickets, arise when 25(OH)D concentrations fall too low [3], with symptoms of skeletal maldevelopment and degradation becoming evident when serum concentrations fall below 25 nmol/L [5]. To this end, the scientific community broadly accepts <25 nmol/L as the cutoff point for overt vitamin D deficiency [6].

Since the National Academy of Medicine (NAM) (formerly Institute of Medicine) released their 2010 update on vitamin D dietary reference intakes, a decade of varied, and sometimes controversial commentary has ensued regarding optimal 25(OH)D serum concentrations for an increasing range of health issues

* Corresponding author.
** Corresponding author.
E-mail addresses: joshua.sutherland@mymail.unisa.edu.au (J.P. Sutherland), elina.hypponen@unisa.edu.au (E. Hyppönen).

https://doi.org/10.1016/j.clnu.2020.11.019
0261-5614/

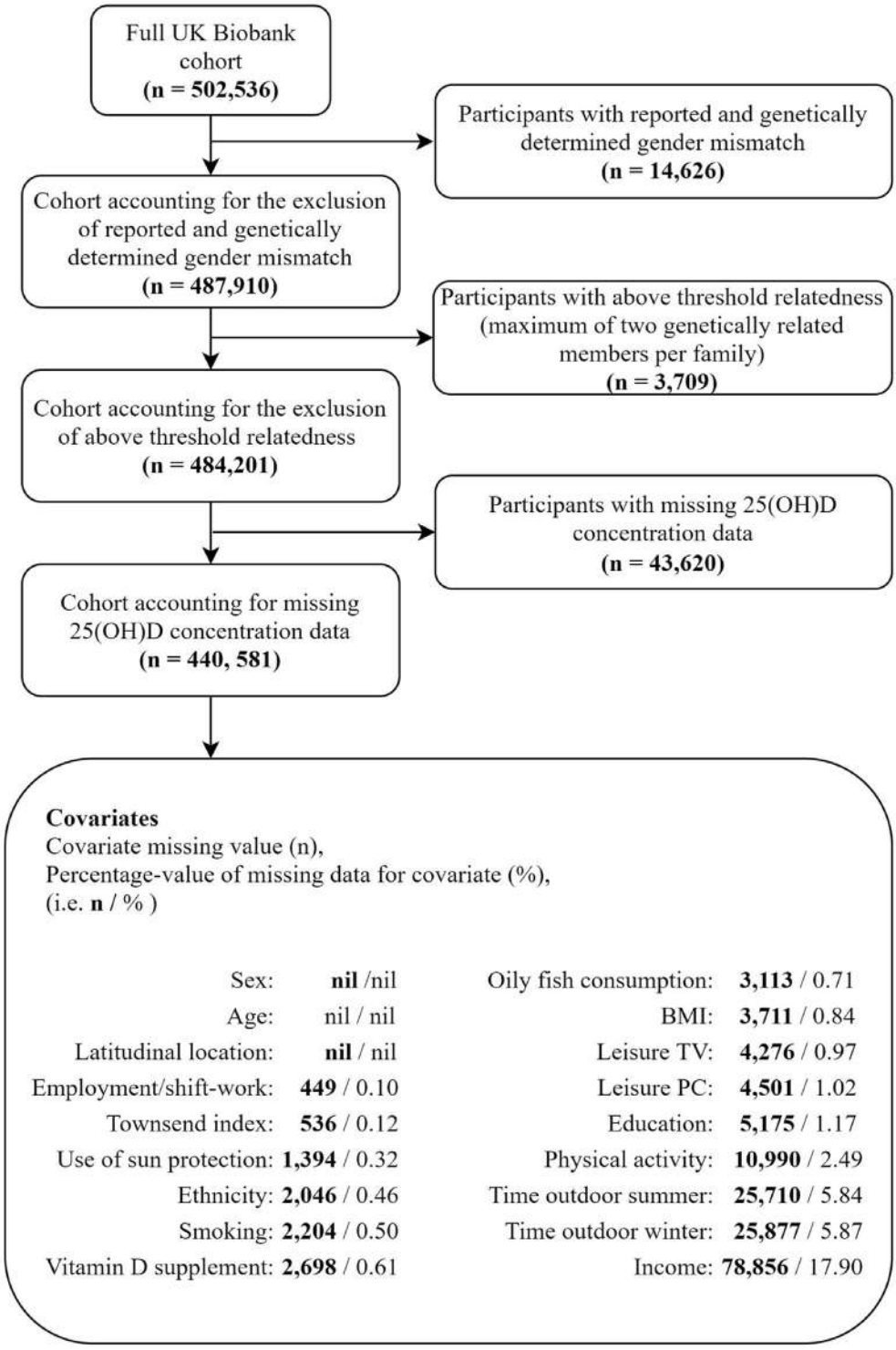


Fig. 1. Study population and participant inclusion criteria.

[7–10]. Although debate and exploration of these matters are essential, such dialogue should not overshadow the continuing reality of severe deficiency, as evidenced by the persistence of rickets in the twenty-first century, with 2011 rickets-attributable hospitalization rates in the UK being the highest in 50 years [11].

There are long-held concerns regarding vitamin D deficiency in the UK, both at the population level and within particular at-risk groups, such as South Asians and other immigrant populations [12–15]. In contrast to many other high-latitude Western countries, there is no mandatory vitamin D food fortification program in the UK that is designed to mitigate deficiency at a population level [16], aside from the small additions of vitamin D to margarine. Not surprisingly, recent reviews indicate that the UK has lower overall vitamin D status when compared to much of Western Europe [17], in addition to having the lowest level of adherence to infant vitamin D supplementation guidelines [18]. In this study, we examine

Table 1
Demographic characteristics of UK Biobank participants.

N =	N (%)	25(OH)D	Vitamin D supplementation[a]		Oily Fish[b]		Use of sun protection[c]		Outdoor time winter[d]		Outdoor time summer[e]	
		Geometric mean	No	Yes	Never	>1 per wk	Avoid sun	Mostly	>1hr	≥3hrs	>1hr	≥3hrs
		440,581	355,990	81,893	47,748	79,138	2,646	245,498	82,698	96,553	18,424	267,912
		Mean (95% CI)	%	%	%	%	%	%	%	%	%	%
All	440,581 (100)	43.8 (43.8, 43.9)	80.80	18.59	10.91	18.09	0.60	55.90	19.94	23.28	4.44	64.58
Sex												
Men	204,927 (46.5)	43.7 (43.6, 43.8)	81.56	18.44	11.22	17.66	0.53	43.96	15.65	30.19	3.63	67.94
Women	235,654 (53.5)	44.0 (43.9, 44.0)	75.58	24.42	10.65	18.46	0.67	66.26	23.76	17.15	5.17	61.58
P[g]		0.01		4.33×10^{-261}		3.81×10^{-31}		$<1.0 \times 10^{-300}$		$<1.0 \times 10^{-300}$		$<1.0 \times 10^{-300}$
Age												
<60	250,909 (57.0)	42.0 (41.9, 42.1)	78.62	21.38	13.11	14.98	0.57	57.13	23.95	19.25	5.56	56.98
≥60	189,672 (43.1)	46.4 (46.3, 46.5)	78.21	21.79	8.01	22.20	0.65	54.27	14.60	28.66	2.96	74.64
P[g]		$<1.0 \times 10^{-300}$		0.40		$<1.0 \times 10^{-300}$		1.21×10^{-41}		$<1.0 \times 10^{-300}$		$<1.0 \times 10^{-300}$
Ethnicity												
White European	415,903 (94.4)	44.9 (44.9, 45.0)	78.82	21.18	10.75	17.86	0.53	57.78	19.64	23.09	4.19	64.95
Chinese	1,383 (0.3)	32.1 (31.3, 32.8)	72.50	27.50	4.34	18.69	2.41	27.21	43.04	13.52	19.51	36.15
Asian	7,880 (1.8)	24.3 (24.0, 24.5)	73.37	26.63	27.01	14.58	2.08	16.42	28.27	22.96	11.10	50.14
Black African	6,896 (1.6)	30.3 (29.9, 30.6)	66.82	33.18	5.17	30.59	2.02	14.83	21.47	35.45	6.89	67.95
mixed ethnicity	6,473 (1.5)	32.9 (32.5, 33.3)	72.03	27.97	9.61	22.39	1.47	33.01	23.69	26.08	7.25	60.42
Missing	2,046 (0.5)	36.0 (35.1, 36.8)	79.18	20.82	10.60	24.59	1.79	41.33	20.82	24.90	5.64	62.93
P[g]		$<1.0 \times 10^{-300}$		7.18×10^{-88}		$<1.0 \times 10^{-300}$		$<1.0 \times 10^{-300}$		1.17×10^{-120}		1.52×10^{-201}
BMI[f]												
Lowest 25%	109,184 (24.8)	46.8 (46.7, 46.9)	76.10	23.90	10.56	18.52	0.45	60.48	21.27	19.15	4.62	60.46
Middle 50%	218,453 (49.6)	45.1 (45.0, 45.2)	78.65	21.35	10.22	18.13	0.47	55.64	18.65	24.32	3.84	66.06
Highest 25%	109,233 (24.8)	39.1 (39.0, 39.3)	80.28	19.72	12.57	17.47	0.97	52.22	21.06	25.35	5.41	65.82
Missing	3,711 (0.8)	35.0 (34.4, 35.6)	78.66	21.34	13.60	22.11	2.21	42.14	25.11	24.10	7.24	61.33
P[g]		$<1.0 \times 10^{-300}$		6.85×10^{-32}		7.25×10^{-59}		9.93×10^{-159}		1.17×10^{-15}		2.93×10^{-52}
Latitudinal location												
≤51°	155,928 (35.4)	44.8 (44.7, 44.9)	76.76	23.24	9.57	18.32	0.64	54.11	19.94	21.59	4.70	61.64
52°–53°	201,429 (45.7)	44.2 (44.1, 44.3)	79.05	20.95	11.17	18.51	0.59	56.36	20.34	23.87	4.40	65.75
54°- ≥55°	83,224 (18.9)	41.3 (41.2, 41.5)	80.05	19.95	12.82	16.63	0.56	58.12	18.98	25.04	4.04	67.33
P[g]		6.67×10^{-181}		6.11×10^{-47}		3.02×10^{-107}		1.14×10^{-109}		9.97×10^{-41}		1.91×10^{-156}
Smoking												
Non-smokers	240,002 (54.5)	44.0 (43.9, 44.1)	78.11	21.89	10.76	17.71	0.60	57.82	21.38	21.03	4.84	61.40
Ex-smokers	152,475 (34.6)	45.4 (45.3, 45.5)	78.27	21.73	9.62	19.35	0.51	55.78	18.18	25.03	3.80	67.84
Current smokers	45,900 (10.4)	38.7 (38.5, 38.9)	80.75	19.25	15.94	15.79	0.91	46.41	18.35	28.95	4.52	70.04
Missing	2,204 (0.5)	39.2 (38.3, 40.1)	79.54	20.46	14.43	20.14	0.87	50.84	17.90	34.01	4.41	73.53
P[g]		$<1.0 \times 10^{-300}$		5.87×10^{-20}		3.18×10^{-136}		1.03×10^{-305}		3.93×10^{-169}		8.31×10^{-299}
Physical activity												
Low	132,941 (30.2)	40.4 (40.3, 40.5)	82.72	17.28	12.27	14.76	0.91	54.00	32.84	14.79	8.07	54.17
Moderate	212,201 (48.2)	44.9 (44.8, 45.0)	80.81	19.19	9.78	18.72	0.43	57.84	16.43	20.76	3.06	64.52
High	84,449 (19.2)	48.3 (48.1, 48.4)	79.82	20.18	10.68	22.18	0.34	55.35	7.17	42.25	1.30	80.97
Missing	10,990 (2.5)	36.2 (35.8, 36.5)	85.09	14.91	18.94	14.35	2.32	44.77	47.15	18.91	17.11	53.06
P[g]		$<1.0 \times 10^{-300}$		1.48×10^{-86}		$<1.0 \times 10^{-300}$		2.21×10^{-167}		$<1.0 \times 10^{-300}$		$<1.0 \times 10^{-300}$

(*continued on next page*)

Table 1 (*continued*)

N =	N (%)	25(OH)D	Vitamin D supplementation[a]		Oily Fish[b]		Use of sun protection[c]		Outdoor time winter[d]		Outdoor time summer[e]	
		Geometric mean	No	Yes	Never	>1 per wk	Avoid sun	Mostly	>1hr	≥3hrs	>1hr	≥3hrs
	440,581		355,990	81,893	47,748	79,138	2,646	245,498	82,698	96,553	18,424	267,912
		Mean (95% CI)	%	%	%	%	%	%	%	%	%	%
Townsend index												
Q1 – least deprivation	110,010 (25.0)	47.0 (46.9, 47.1)	78.43	21.57	8.38	17.76	0.33	59.83	21.11	20.36	3.86	64.40
Q2	110,006 (25.0)	46.2 (46.1, 46.4)	78.67	21.33	9.50	18.01	0.38	58.65	20.16	22.04	3.83	65.76
Q3	109,998 (25.0)	43.8 (43.7, 44.0)	78.32	21.68	11.19	17.74	0.54	56.02	19.53	23.47	4.32	64.27
Q4 – most deprivation	110,031 (25.0)	38.8 (38.7, 38.9)	78.37	21.63	14.2	18.86	1.16	49.05	18.92	27.41	5.79	63.89
Missing	536 (0.1)	42.7 (41.0, 44.5)	76.76	23.24	14.53	14.34	0.94	52.82	20.99	22.77	6.75	56.35
P[g]		$<1.0 \times 10^{-300}$		0.23		$2.05 \times 10\text{-}67$		$<1.0 \times 10^{-300}$		$<1.0 \times 10^{-300}$		5.56×10^{-11}

[a] Missing n = 2698 (0.61%).
[b] Once per week or less n = 310,582 (70.49%), missing n = 3113 (0.71%).
[c] Never/rarely/sometimes n = 191,043 (43.36%), missing n = 1394 (0.32%).
[d] 1–2 h n = 235,453 (53.44%), missing n = 25,877 (5.87%).
[e] 1–2 h n = 128,535 (29.17%), missing n = 25,710 (5.84%).
[f] Constructed using ethnic specific BMI quartiles.
[g] All models were weighed by 1-kinship coefficient, and adjusted for sex, age, latitude, month and year of measurement, aliquot and fasting upon serum acquisition.

ethnic and social distributions in the prevalence of vitamin D deficiency (25(OH)D < 25nml/L) using data from over 440,000 UK participants.

2. Methods

The UK Biobank is a large-scale prospective cohort containing an expansive collection of phenotypic and genotypic data. The study was established to provide high-quality data to the scientific community for the betterment of the public's health [19]. The UK Biobank recruited 502,316 men and women aged 40–69 years (10% response rate) [20], from within the United Kingdom (England, Scotland and Wales), between March 2006 and July 2010 [19]. Participants had to reside within 10 miles of a UK Biobank assessment centre, and were requested to take part in questionnaire surveys and physical assessments, and to provide biological samples [21]. The present analysis was limited to UK Biobank participants with data on serum 25(OH)D concentration (n = 440,581) (Fig. 1).

2.1. Measurement of vitamin D status

Serum 25(OH)D concentration was measured using the LIAISON XL 25(OH)D assay (DiaSorin, Stillwater, USA), from blood samples (hours of fasting time: mean 3.8, SD 2.4) collected at baseline. The LIAISON XL is a fully automated chemiluminescence immunoassay device with magnetic microparticle separation technology for the direct measurement of 25(OH)D from human serum [22]. Functional sensitivity, the concentration at which coefficient of variation (CV) exceeds 20%, was ≤4.0 ng/ml, as determined over multiple runs in accordance with the Clinical Laboratory and Standards Institute (CLSI) EP17-A protocols [22]. Assay precision (CLSI EP5-A2), conducted using 6 samples and 2 controls gave CV 2.3% (intra-run) and CV 7.8% (total) [22]. Due to unexpected issues with sample dilution [23], we conducted sensitivity analyses restricting to the sample which were not affected by related problems (430,413 participants, 9960 excluded).

2.2. Covariates

Covariates were chosen for their relevance to outdoor exposure (latitude, use of sun protection, outdoor time - winter/summer, employment/shiftwork, and leisure time - TV/PC use) [2], vitamin D intake (vitamin D supplementation and oily fish consumption) [24,25], or their independent potential to affect 25(OH)D concentrations (smoking, body mass index [BMI] and physical activity) [26,27]. All covariates were self-reported at baseline, with the exception of latitude and socioeconomic status, which were derived from assessment center location and residential data, respectively.

Socioeconomic status was assessed using the Townsend deprivation index [28]. Each participant was assigned a score corresponding to socioeconomic data attributed to their postcode; this was derived from the preceding UK census of population and housing [29]. Ethnicity was self-reported at baseline and the data collapsed into five primary ethnic groups, namely 1) White European (White, British, Irish, and any other White background), 2) Chinese, 3) Asian (Asian British, Indian, Pakistani, Bangladeshi, and any other Asian background), 4) Black African (Black British, Caribbean, African, and any other Black background), and 5) mixed ("Other" ethnic group, White and Black Caribbean, White and Black African, White and Asian, and any other mixed background). Season was determined based on month of blood sampling and determined as summer (July–Sept), autumn (Oct–Nov), winter (Jan–March) and spring (April–June).

Body mass index was assessed at baseline from height and weight measures (calculated as body weight [kilograms] divided by height squared [meters]) [30]. For our study, we divided the cohort

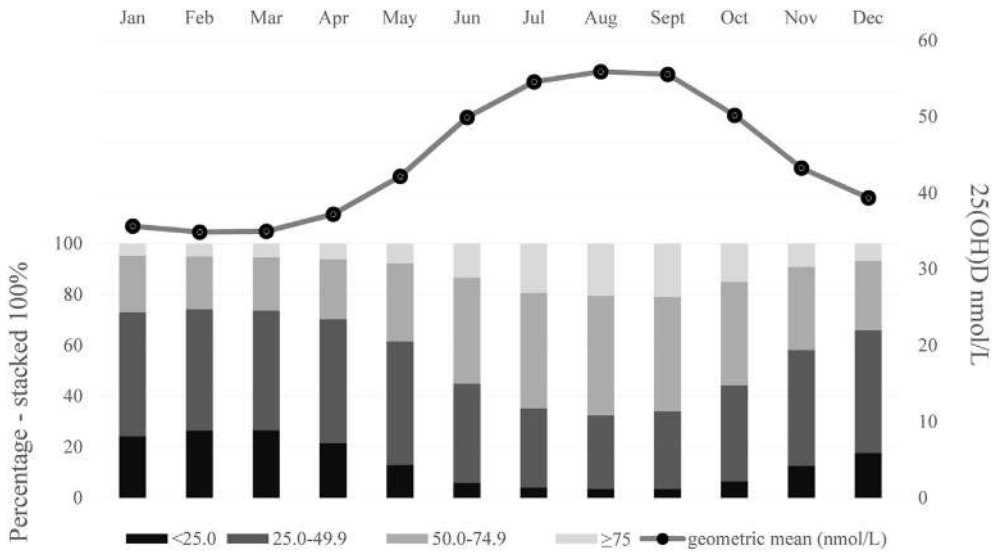


Fig. 2. Distribution of categorical 25(OH)D concentration (stacked bar chart) and geometric mean of 25(OH)D concentration (line chart) by months.

into ethnicity-specific BMI quartiles, with data presented for lowest 25%, middle 50% and highest 25% (ethnic-specific BMI ranges: White European 12.1–24.09, 24.1–29.8, 29.8–74.7 kg/m^2, Chinese 16.3–21.6, 21.7–26.1, 26.2–45.7 kg/m^2, Asian 14.9–24.19, 24.2–29.4, 29.4–60.0 kg/m^2, Black African 16.2–25.8, 25.8–32.2, 32.2–68.1 kg/m^2, and mixed 14.6–24.1, 24.1–30.3, 30.3–56.8 kg/m^2).

2.3. Statistical methods

Serum 25(OH)D concentration was categorized as <25.0, 25.0–49.9, 50.0–74.9, and ≥75.0 nmol/L. For analyses using 25(OH)D as a continuous indicator, we used natural logarithmic transformation to adjust for skewed distribution. Linear and logistic regression models were fitted to examine the associations of log 25(OH)D and risk for vitamin D deficiency with individual, dietary and lifestyle indicators. All models were weighed by 1 − kinship coefficient [31] to account for relatedness, and adjusted for age, sex, smoking, physical activity, month of measurement, assessment centre, Townsend index, sample aliquots for 25(OH)D measurement and fasting. For each dietary or lifestyle indicator, we further examined if the association pattern with log 25(OH)D varied by seasons by introducing dietary/lifestyle-indicator-by-season interaction terms to the model. Evidence of interaction was examined using the likelihood ratio test comparing the log-likelihood of nested models with and without the interaction term(s). The same interaction analysis was performed for latitudinal locations and ethnic groups, followed by stratified analyses where relevant. Sensitivity analyses were conducted, but as this had no implications on the results, data are presented for the full sample. STATA, version 14.1 (StataCorp LP, College Station, Texas, USA) was used for all analyses.

2.4. Ethics

Ethics approval for the UK Biobank was granted by the National Information Governance Board for Health and Social Care and North West Multicenter Research Ethics Committee (11/NW/0382) [32]. The present analysis operates under UK Biobank application 20,175.

3. Results

Of the 440,581 participants included in this analysis, 415,903 (94.4%) were White European, 1383 (0.3%) Chinese, 7880 (1.8%) Asian, 6896 (1.6%) Black African, and 6473 (1.5%) mixed ethnicity (Table 1). The overall mean 25(OH)D concentration was 43.8 nmol/L, with 7.5% of participants in summer/autumn and 18.8% in winter/spring having 25(OH)D < 25 nmol/L. There were large differences in the average 25(OH)D concentration by ethnic group, ranging from 44.9 nmol/L in White Europeans to 24.3 nmol/L in Asian ancestry participants. Asian participants tended to consume less oily fish and use vitamin D supplements less frequently compared to other ethnicities, while intakes of both oily fish and vitamin D supplementation were highest in Black African participants (Table 1).

Serum 25(OH)D concentrations followed a seasonal pattern, with a trough in February–March and peak in August–September (Fig. 2). Season modified the associations between all covariates and 25(OH)D concentrations (Table 2, all $P_{interaction} \leq 0.01$). There was a clear seasonal contrast in the prevalence of vitamin D deficiency among White Europeans, with smaller differences in other ethnic groups. From the Asian participants, more than one-half were affected throughout the year. A consistently high rate was also seen in Black African participants of whom a minimum of 30.78% were affected throughout the year. For the most affluent group, the contrast in the prevalence of vitamin D deficiency between winter and summer was larger, while the most socioeconomically deprived group showed smaller differences.

Greater time-spent-outdoors was associated with higher 25(OH)D concentrations in summer months, with a similar but weaker trend seen in winter (Fig. 3, all $P_{interaction} \leq 0.05$). The seasonal differences in 25(OH)D concentrations were smaller in participants who used vitamin D supplements and who ate oily fish regularly compared to others ($P_{interaction} \leq 7.04 \times 10^{-35}$ for both comparisons).

There was a strong north-south gradient in the prevalence of vitamin D deficiency across the seasons (Fig. 4, $P_{interaction}$ 7.10×10^{-32}). Nearly one-third of participants living ≥55° latitude (Edinburgh and Glasgow assessment centers) had 25(OH)D concentrations <25 nmol/L in winter, while 7.38% of participants also remained deficient during the summer. Lower income was associated with higher prevalence of vitamin D deficiency in all ethnic groups except for Black Africans, while educational status was

Table 2
25(OH)D concentration in UK Biobank participants, by season and demographic characteristics.

	Subjects N (%)	Summer and Autumn 25(OH)D Concentrations					Winter and Spring 25(OH)D Concentrations				
		<25.0%	25.0–49.9%	50.0–74.9%	>75.0%	Geometric mean (95% CI)	<25.0%	25.0–49.9%	50.0–74.9%	>75. % 0	Geometric mean
All	440,581 (100)	7.50	36.59	40.32	15.59	49.8 (49.7, 49.9)	18.83	46.45	27.36	7.36	39.3 (39.2, 39.4)
Sex											
Male	204,927 (46.5)	7.43	35.86	40.52	16.19	50.2 (50.1, 50.4)	19.20	47.18	26.88	6.74	38.8 (38.7, 39.0)
Female	235,654 (53.5)	7.57	37.23	40.14	15.06	49.5 (49.4, 49.6)	18.51	45.81	27.77	7.90	39.7 (39.6, 39.8)
P[b]					7.24×10^{-28}	6.28×10^{-26}				1.31×10^{-29}	3.29×10^{-33}
Age											
<60	250,909 (57.0)	8.99	38.10	38.12	14.79	48.3 (48.2, 48.5)	21.89	47.72	24.13	6.26	37.3 (37.2, 37.4)
≥60	189,672 (43.1)	5.53	34.59	43.24	16.64	51.9 (51.8, 52.1)	14.80	44.77	31.62	8.81	42.1 (42.0, 42.3)
P[b]					1.09×10^{-242}	$< 1.0 \times 10^{-300}$				$< 1.0 \times 10^{-300}$	$< 1.0 \times 10^{-300}$
Ethnicity											
White European	415,903 (94.4)	5.90	35.98	41.79	16.33	51.3 (51.2, 51.4)	17.45	46.62	28.26	7.68	40.1 (40.0, 40.2)
Chinese	1,383 (0.3)	20.68	59.13	18.58	1.62	34.6 (33.5, 35.7)	33.12	53.14	12.57	1.18	30.1 (29.2, 31.1)
Asian	7,880 (1.8)	50.80	39.93	8.19	1.08	25.2 (24.8, 25.6)	57.18	34.21	7.48	1.13	23.4 (23.0, 23.7)
Black African	6,896 (1.6)	30.78	52.41	14.14	2.67	31.8 (31.3, 32.3)	38.47	47.62	12.10	1.80	29.1 (28.7, 29.6)
mixed ethnicity	6,473 (1.5)	22.48	49.38	23.47	4.67	36.4 (35.8, 37.0)	36.53	46.25	14.81	2.42	30.2 (29.8, 30.7)
Missing	2,046 (0.5)	20.29	41.56	27.63	10.53	39.5 (38.2, 40.9)	30.07	45.86	19.14	4.94	33.3 (32.3, 34.4)
P[b]					$< 1.0 \times 10^{-300}$	$< 1.0 \times 10^{-300}$				$< 1.0 \times 10^{-300}$	$< 1.0 \times 10^{-300}$
BMI[a]											
Lowest 25%	109,184 (24.8)	6.36	31.23	41.67	20.73	53.1 (52.9, 53.3)	16.83	42.63	30.34	10.20	41.7 (41.5, 41.8)
Middle 50%	218,453 (49.6)	6.29	35.07	42.43	16.21	51.2 (51.1, 51.3)	16.69	46.55	29.05	7.71	40.5 (40.4, 40.6)
Highest 25%	109,233 (24.8)	10.73	45.22	35.02	9.03	44.5 (44.3, 44.6)	24.51	50.01	21.47	4.02	35.2 (35.1, 35.4)
Missing	3,711 (0.8)	22.46	42.60	25.91	9.03	37.9 (36.9, 38.9)	31.88	43.69	19.37	5.05	33.0 (32.2, 33.7)
P[b]					$< 1.0 \times 10^{-300}$	$< 1.0 \times 10^{-300}$				$< 1.0 \times 10^{-300}$	$< 1.0 \times 10^{-300}$
Latitudinal location											
≤51°	155,928 (35.4)	7.01	35.71	41.60	15.68	50.4 (50.3, 50.6)	17.44	47.22	28.15	7.20	39.8 (39.7, 40.0)
52°-53°	201,429 (45.7)	7.19	36.13	40.71	15.97	50.2 (50.1, 50.4)	17.50	46.01	28.60	7.88	40.2 (40.1, 40.3)
54°- ≥55°	83,224 (18.9)	9.14	39.29	37.00	14.58	47.9 (47.7, 48.1)	24.95	46.22	22.58	6.25	36.0 (35.9, 36.2)
P[b]					2.01×10^{-31}	1.48×10^{-35}				1.25×10^{-131}	3.6×10^{-162}
Townsend index											
Q1 – least deprivation	110,010 (25.0)	4.37	33.05	44.69	17.89	53.5 (53.3, 53.7)	14.85	45.96	30.82	8.37	41.8 (41.6, 41.9)
Q2	110,006 (25.0)	4.88	34.30	43.35	17.46	52.7 (52.5, 52.8)	15.31	46.71	29.95	8.02	41.3 (41.1, 41.4)
Q3	109,998 (25.0)	7.37	37.39	39.94	15.30	49.7 (49.5, 49.9)	18.60	47.10	27.02	7.28	39.2 (39.0, 39.4)
Q4 – most deprivation	110,031 (25.0)	13.82	42.01	32.79	11.39	43.7 (43.5, 43.9)	26.21	46.02	21.92	5.85	35.4 (35.2, 35.5)
Missing	536 (0.1)	10.26	38.46	34.07	17.22	47.7 (45.2, 50.4)	20.15	47.53	26.24	6.08	38.0 (35.8, 40.3)
P[b]					$<1.0 \times 10^{-300}$	$<1.0 \times 10^{-300}$				$<1.0 \times 10^{-300}$	$<1.0 \times 10^{-300}$

[a] Constructed using ethnic specific BMI quartile ranges.
[b] All models were weighed by 1-kinship coefficient, and adjusted for sex, age, latitude, month and year of measurement, aliquot and fasting upon serum acquisition.

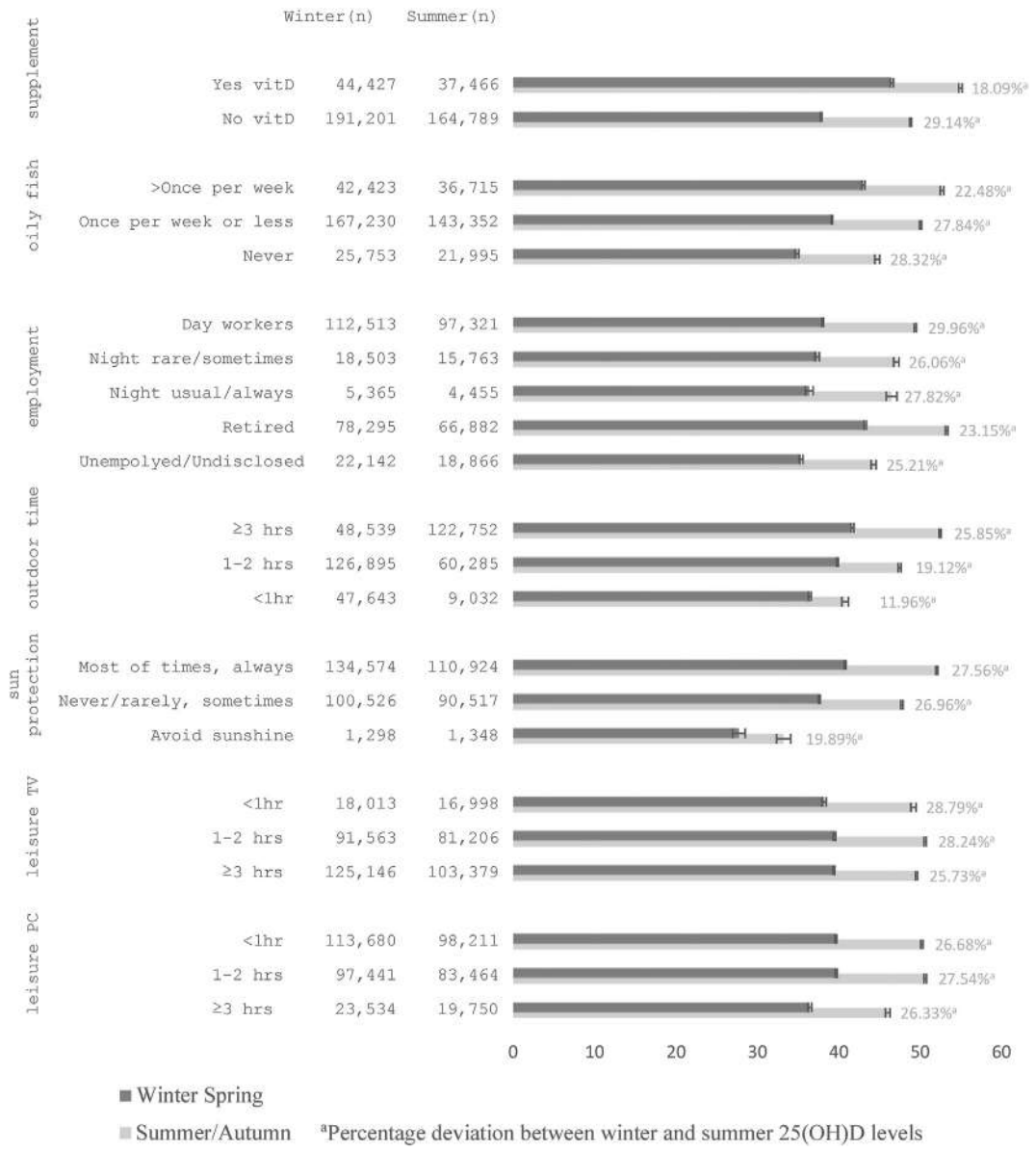


Fig. 3. Distribution of 25(OH)D concentration by seasons and socioeconomic, dietary, or lifestyle indicators.

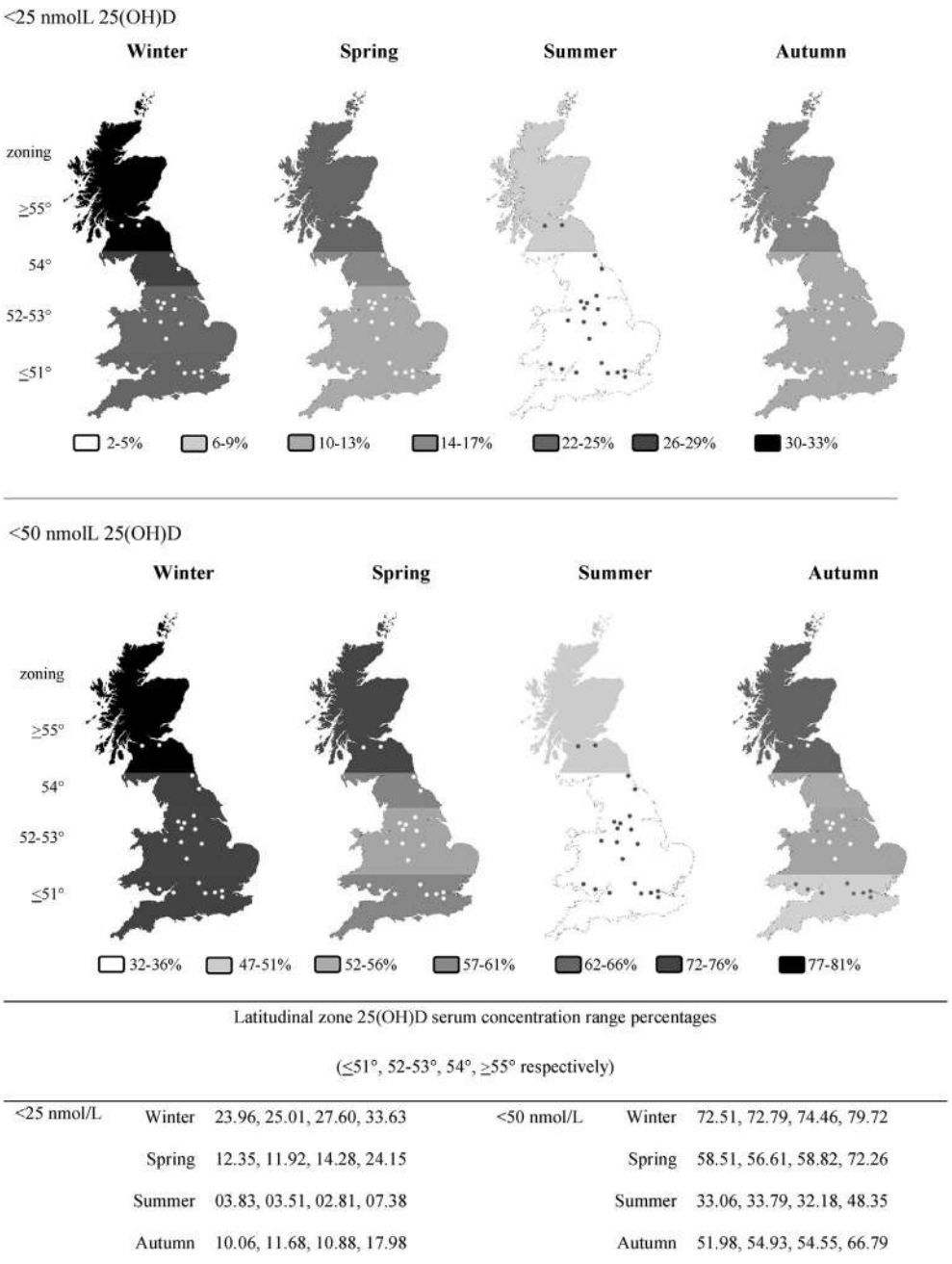
associated with deficiency in Asians but not in others (Fig. 5, all $P_{interaction} \leq 8.36 \times 10^{-7}$).

The associations between lifestyle factors and the odds of vitamin D deficiency varied by ethnic group ($P_{interaction} < 3 \times 10^{-5}$ for all comparisons, Table 3, Supplementary Table 1, appendix A). Similar patterns were observed at a 25(OH)D < 50 nmol/L cutoff ($P_{interaction} < 8.34 \times 10^{-3}$ for all comparisons, Supplementary Table 2, appendix A), while no ethnicity–covariate interactions were seen under 75 nmol/L (data not shown). Time spent outdoors, leisure time TV and PC use were all strongly associated with the odds of deficiency in White Europeans while weaker or no associations were seen for other ethnicities. Oily fish consumption and vitamin D supplementation were associated with the odds of deficiency across all ethnicities, with the estimates for regular oily fish consumption ranging from OR 0.29 (95% CI 0.23, 0.38) in Black Africans to OR 0.45 (95% CI 0.43, 0.47) in White Europeans, and for supplementation, from OR 0.36 (95% CI 0.35, 0.37) in White European to 0.45 (95% CI: 0.39, 0.51) in participants of Black African ancestry.

4. Discussion

The National Academy of Medicine and The Endocrine Society respectively recommend 25(OH)D concentrations should be at least 50 nmol/L [7] and 75 nmol/L [33] for maximal bone health. Our analysis showed that the average vitamin D status in the UK Biobank is below the more conservative of these recommendations, and uncovered striking rates of vitamin D deficiency. We confirmed the strong patterns by season and latitude [34] and also showed high rates of deficiency within certain socioeconomic subgroups. In line with previous research [13,14,35], we report very high risks of deficiency in non-White populations. Indeed, it was alarming to find >50% of Asian participants and >30% of Black African participants to have year-round vitamin D deficiency, which is a finding warranting urgent consideration and action.

Asian participants in our study were found to engage in vitamin D promoting behaviors the least, which is congruent with previous research and commentary [36,37]. However, with UK cross-ethnic qualitative analyses demonstrating relatively greater knowledge of



Latitudinal zone 25(OH)D serum concentration range percentages

(≤51°, 52-53°, 54°, ≥55° respectively)

<25 nmol/L	Winter	23.96, 25.01, 27.60, 33.63	<50 nmol/L	Winter	72.51, 72.79, 74.46, 79.72
	Spring	12.35, 11.92, 14.28, 24.15		Spring	58.51, 56.61, 58.82, 72.26
	Summer	03.83, 03.51, 02.81, 07.38		Summer	33.06, 33.79, 32.18, 48.35
	Autumn	10.06, 11.68, 10.88, 17.98		Autumn	51.98, 54.93, 54.55, 66.79

Fig. 4. Distribution of categorical 25(OH)D concentration, across seasons and UK latitudinal zoning.

vitamin D in Asian populations [36], our analysis may further indicate a possible disconnect between vitamin D awareness and action in this population. Our study also suggests environmental factors (i.e. time spent outdoors) may have less impact in reducing vitamin D deficiency among Asians. These findings emphasize the need to explore the psychocultural determinants of engaging in vitamin D promoting behaviors in Asian minority groups living in the UK.

The greater prevalence of vitamin D deficiency in higher latitude locations was anticipated due to the incrementally lower UVB exposure associated with increasing latitudinal degrees [38]; however, the extent of vitamin D deficiency (one-third) in the northernmost locations of the UK over winter was alarming. Alongside latitude, there may be other explanations for the strong north-south pattern in the prevalence of vitamin D deficiency in the UK. Northern England and Scotland have historically demonstrated higher socioeconomic deprivation [39,40], and in our analyses we observed social patterns in the prevalence of vitamin D deficiency. Our study also shows that participants from higher latitudinal locations engage in vitamin D supplementation and dietary-based behaviors to a lesser extent than people living in the southern parts of the UK, as might be expected with affordability and accessibility challenges [41]. These findings may offer some explanation for the consistently higher rates of mortality observed among UK northern populations [42]. Low 25(OH)D concentrations have been associated with increased mortality [43,44], which may in part contribute to regional health disparities between the southern and norther parts of the UK [45].

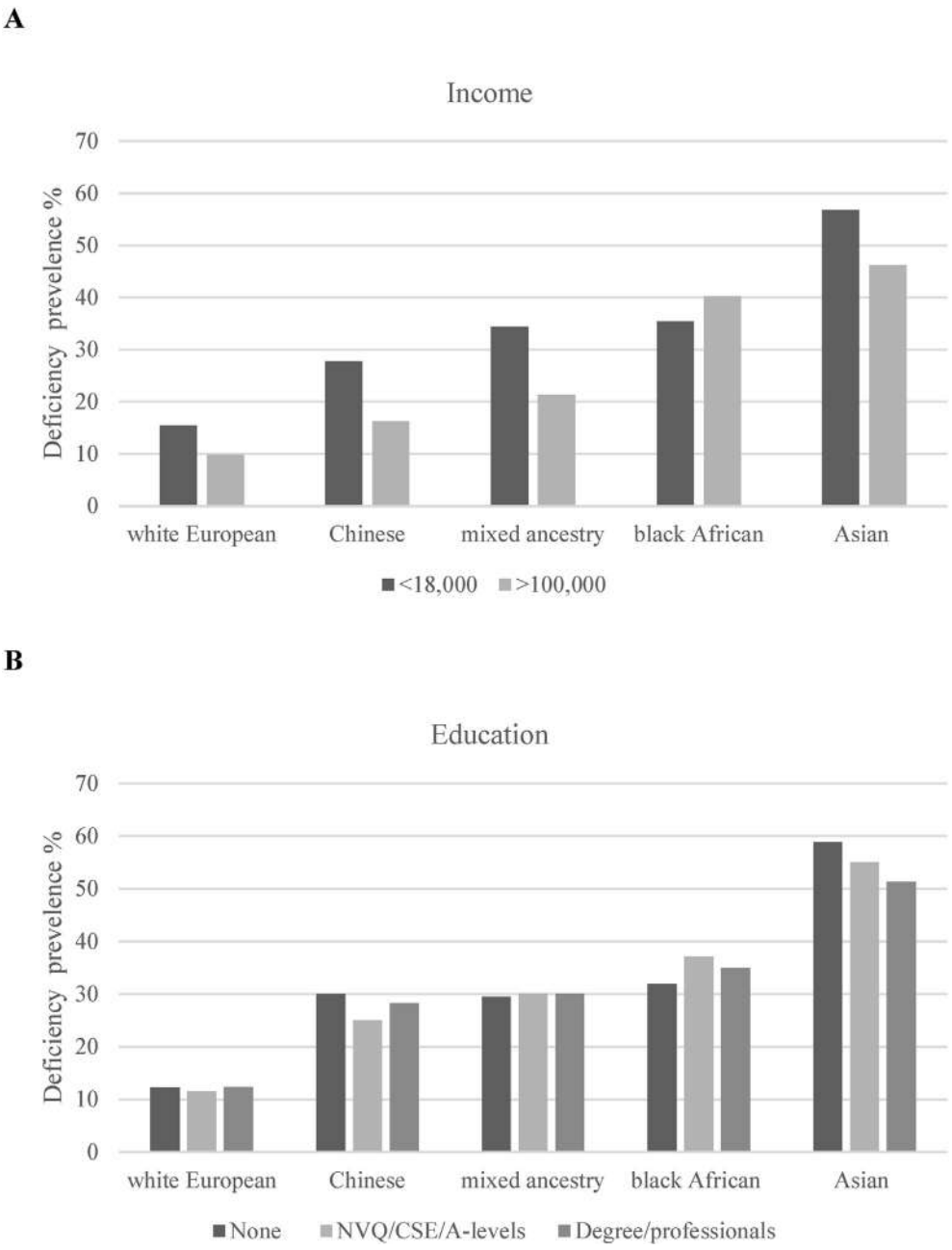


Fig. 5. Distribution of 25(OH)D deficiency (<25 nmol/L) by ethnic groupings and income (A) and by ethnic groupings and education (B). Educational level terms: National Vocational Qualification (NVQ), Certificate of Secondary Education (CSE), and A-levels (i.e. common name for the General Certificate of Education Advanced Level certificate.

Our research highlights the need for effective public health interventions to reduce the prevalence of vitamin D deficiency in the UK, at both the population level and within at-risk groups, specifically Asian populations. At the date of this publication, the topic of vitamin D fortification in the UK is gaining unprecedented traction, with calls for the fortification of wheat-flour [46]; in fact, some fortified bread products are now available to the UK public via limited high-end supermarkets. Dietary analysis of ethnic minorities in the UK, however, has highlighted that although some South Asian groups were found to consume wheat-based staples, in way of roti and chapattis, Indians from the Gujarat region and Bangladeshis tended to primarily use millet and rice, respectively [47]. The question therefore remains as to whether fortification of any single item alone would be enough to redress abject rates of severe vitamin D deficiency across ethnicities. As others have recently indicated, fortification measures in the UK will likely need to consider specific at-risk groups and vulnerable life stages, and proceed in conjunction with robust and accountable supplementation programs [48].

4.1. Strengths and limitations

Our study benefits from a large sample size with ethnic group diversity and the collection of comprehensive sociodemographic and lifestyle information. This level of granularity has allowed us to explore the determinants for a relatively severe form of vitamin D deficiency, defined as 25(OH)D < 25 nmol/L. A primary limitation of

Table 3
Association of 25(OH)D deficiency (<25 nmol/L) with selected risk factors by ethnic groups.

	Subjects N (%)	White Euro[a]	Chinese[b]	Asian[c]	Black African[d]	Mixed[e]
		OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
BMI[f,o]						
Lowest 25%	109,184 (24.78)	1.02 (1.00, 1.05)	0.53 (0.37, 0.75)	0.70 (0.62, 0.79)	1.13 (0.99, 1.28)	0.85 (0.73, 0.98)
Middle 50%	218,453 (49.58)	Reference	Reference	Reference	Reference	Reference
Highest 25%	109,233 (24.79)	1.67 (1.63, 1.71)	1.18 (0.86, 1.60)	1.26 (1.11, 1.42)	1.17 (1.03, 1.34)	1.35 (1.17, 1.55)
P		$<1.0 \times 10^{-300}$	2×10^{-4}	6.30×10^{-16}	0.04	1.37×10^{-7}
Latitudinal location						
≤51°	155,928 (35.39)	Reference	Reference	Reference	Reference	Reference
52°–53°	201,429 (45.72)	1.15 (1.12, 1.18)	1.08 (0.82, 1.44)	1.39 (1.25, 1.55)	1.33 (1.18, 1.49)	1.12 (0.99, 1.27)
54°- ≥55°	83,224 (18.89)	1.65 (1.60, 1.70)	1.19 (0.78, 1.80)	1.33 (1.07, 1.66)	1.64 (1.13, 2.37)	1.30 (1.04, 1.63)
P		1.33×10^{-286}	0.68	2.53×10^{-9}	8.26×10^{-7}	0.03
Vitamin D Supplements[g]						
No	355,990 (80.80)	Reference	Reference	Reference	Reference	Reference
Yes	81,893 (18.59)	0.36 (0.35, 0.37)	0.30 (0.21, 0.44)	0.40 (0.36, 0.46)	0.45 (0.39, 0.51)	0.52 (0.44, 0.60)
P		$<1.0 \times 10^{-300}$	9.53×10^{-10}	3.52×10^{-48}	1.84×10^{-32}	4.54×10^{-17}
Oily Fish[h]						
Never	47,748 (10.84)	Reference	Reference	Reference	Reference	Reference
1 per wk or less	310,582 (70.49)	0.67 (0.65, 0.69)	0.44 (0.24, 0.79)	0.71 (0.63, 0.80)	0.59 (0.46, 0.75)	0.81 (0.66, 0.99)
>1 per wk	79,138 (17.96)	0.45 (0.43, 0.47)	0.28 (0.14, 0.54)	0.41 (0.35, 0.49)	0.29 (0.23, 0.38)	0.50 (0.39, 0.63)
P		$<1.0 \times 10^{-300}$	7×10^{-4}	3.97×10^{-25}	1.08×10^{-32}	2.47×10^{-11}
Time Outdoor Summer[i]						
<1 hr	18,424 (4.18)	Reference	Reference	Reference	Reference	Reference
1–2 h	128,535 (33.36)	0.65 (0.62, 0.68)	0.95 (0.65, 1.38)	0.83 (0.7, 1.00)	0.97 (0.76, 1.25)	0.60 (0.47, 0.78)
≥3 hrs	267,912 (94.16)	0.40 (0.38, 0.42)	0.58 (0.39, 0.87)	0.72 (0.6, 0.86)	0.89 (0.70, 1.12)	0.62 (0.48, 0.79)
P		$<1.0 \times 10^{-300}$	4×10^{-3}	4×10^{-4}	0.31	2×10^{-4}
Time Outdoor Winter[j]						
<1 hr	82,698 (18.77)	Reference	Reference	Reference	Reference	Reference
1–2 h	235,453 (53.44)	0.80 (0.78, 0.82)	0.80 (0.59, 1.08)	0.86 (0.76, 0.97)	1.07 (0.92, 1.25)	0.87 (0.74, 1.01)
≥3hrs	96,553 (22.91)	0.65 (0.62, 0.67)	0.62 (0.38, 1.00)	0.81 (0.69, 0.94)	1.03 (0.88, 1.21)	0.90 (0.76, 1.08)
P		2.28×10^{-132}	0.10	0.01	0.64	0.20
Leisure TV[k]						
<1 hr	35,011 (7.95)	1.20 (1.16, 1.25)	0.99 (0.65, 1.51)	0.90 (0.75, 1.06)	0.86 (0.70, 1.06)	0.93 (0.76, 1.13)
1–2 h	172,769 (39.21)	1.02 (1.00, 1.04)	0.86 (0.64, 1.14)	1.08 (0.97, 1.20)	0.93 (0.82, 1.04)	1.05 (0.93, 1.20)
≥3hrs	228,525 (51.87)	Reference	Reference	Reference	Reference	Reference
P		3.74×10^{-19}	0.52	0.07	0.23	0.42
Leisure Computer[l]						
<1 hr	211,891 (48.09)	0.80 (0.77, 0.83)	0.83 (0.57, 1.20)	1.11 (0.96, 1.30)	0.92 (0.79, 1.08)	0.84 (0.71, 1.00)
1–2 h	180,905 (41.06)	0.79 (0.77, 0.82)	0.70 (0.49, 0.99)	0.97 (0.83, 1.13)	0.95 (0.82, 1.10)	0.94 (0.80, 1.11)
≥3hrs	43,284 (9.82)	Reference	Reference	Reference	Reference	Reference
P		4.24×10^{-40}	0.12	0.04	0.59	0.09
Use of Sun Protection[m]						
Avoid sunshine	2,646 (0.60)	3.63 (3.23, 4.08)	1.91 (0.82, 4.47)	1.18 (0.81, 1.70)	1.02 (0.68, 1.51)	1.62 (1.00, 2.63)
Never - sometimes	191,043 (43.36)	Reference	Reference	Reference	Reference	Reference
Mostly/always	245,498 (55.72)	0.76 (0.75, 0.78)	0.63 (0.46, 0.86)	0.88 (0.77, 1.00)	0.87 (0.74, 1.01)	0.84 (0.73, 0.95)
P		2.77×10^{-259}	3×10^{-3}	0.10	0.19	2×10^{-3}
Smoking[n]						
Non-smokers	240,002 (54.47)	0.54 (0.52, 0.56)	0.61 (0.38, 0.98)	0.99 (0.83, 1.17)	0.64 (0.54, 0.75)	0.73 (0.62, 0.86)
Ex-smokers	152,475 (34.61)	0.53 (0.51, 0.54)	0.60 (0.34, 1.05)	0.79 (0.64, 0.96)	0.79 (0.65, 0.96)	0.64 (0.53, 0.76)
Current smokers	45,900 (10.42)	Reference	Reference	Reference	Reference	Reference
P		$<1.0 \times 10^{-300}$	0.11	6×10^{-3}	6.36×10^{-8}	6.62×10^{-6}

Ethnicity N for: [a]415,903 (94.40%); [b]1,383 (0.31%); [c]7,880 (1.79%); [d]6,896 (1.57%); [e]6,473 (1.47%); Missing 2046 (0.46%).
Missing N for: [f]3,711 (0.84%); [g]2,698 (0.61%); [h]3,113 (0.71%); [i]25,710 (5.84%): [j]25,877 (5.87%); [k]4,276 (0.97%); [l]4,501 (1.02%); [m]1,394 (0.32%); [n]2,204 (0.50%).
[o]Constructed using ethnic specific BMI quartiles.
All models were weighed by 1−kinship coefficient, and adjusted for age, sex, latitudinal location, 25(OH)D acquisition month, 25(OH)D aliquot, fasting upon serum acquisition, Townsend deprivation index, BMI, physical activity, smoking.

our study is the lack of representativeness between the UK Biobank and the general UK population, with variations across a range of physical, sociodemographic, lifestyle and health-related characteristics underpinning an established 'healthy volunteer' bias [49,50]. This type of bias may explain why older participants appeared to be more active and spend more time outdoors than their general population counterparts [51] or indeed, the working-aged individuals within the UK Biobank cohort. However, possible preferential self-selection of healthy volunteers to the cohort suggests that the abject deficiency rates reported in our analysis may be even greater in magnitude within the general population. Furthermore, previous work suggests that despite the lack of representativeness with respect to disease prevalence and incidence rates, the UK Biobank can yield valid assessment of exposure–outcome relationships [49].

Additionally, although our analyses looked at ethnic differences in health behaviors and their association with vitamin D deficiency, we lacked explicit insight regarding culturally specific eating habits, which if available, could have bolstered inferences made from dietary analyses. Furthermore, the use of a single test of serum 25(OH)D concentration may raise some questions about the reliability of the vitamin D measurements, with repeat measures otherwise being able to afford greater insight into individual changes over time. The UK Biobank's sample dilution issues [23] were not seen to pose concern for our study, with sensitivity analysis demonstrating no notable differences in the primary findings.

5. Conclusion

Vitamin D deficiency remains a major public health issue throughout the UK, particularly in lower socioeconomic areas and Asian and Black African populations. These findings justify the provision of effective and targeted public health measures aimed at reducing vitamin D deficiency at a population level, and in vulnerable subgroups.

Funding

The study was supported by the National Health and Medical Research Council (NHMRC), Australia, grant number 11123603. Joshua P Sutherland studentship is funded by Australian Research Training Program Scholarship.

Availability of data and material

This research has been conducted using the UK Biobank resource under application number 20175. All data is available to approved users upon application to the UK Biobank.

Author contributions

EH conceived the study and designed the research question. JS wrote the first draft and analyzed the data with guidance from EH and AZ. All authors revised the paper, interpreted results and approved the final manuscript.

Conflict of interest

The authors declare that they have no competing interests.

Acknowledgements

We thank all UK Biobank participants involved and Dr Anwar Mulugeta (University of South Australia) for support in data management.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2020.11.019.

References

[1] Bikle DD. Extraskeletal actions of vitamin D. Ann N Y Acad Sci 2016;1376(1):29–52. https://doi.org/10.1111/nyas.13219.
[2] Nair R, Maseeh A. Vitamin D: the “sunshine” vitamin. J Pharmacol Pharmacother 2012;3(2):118. https://doi.org/10.4103/0976-500X.95506.
[3] Wheeler BJ, Snoddy AME, Munns C, Simm P, Siafarikas A, Jefferies C. A brief history of nutritional rickets. Front Endocrinol 2019;10. https://doi.org/10.3389/fendo.2019.00795.
[4] Mula-Abed W-A. 25- hydroxyvitamin D: explosion in clinical interest and laboratory requests. Oman Med J 2009. https://doi.org/10.5001/omj.2009.49.
[5] Cashman KD. Vitamin D in childhood and adolescence. Postgrad Med 2007;83(978):230–5. https://dx.doi.org/10.1136%2Fpgmj.2006.052787.
[6] Pilz S, Zittermann A, Trummer C, Theiler-Schwetz V, Lerchbaum E, Keppel MH, et al. Vitamin D testing and treatment: a narrative review of current evidence. Endocr Connect 2019;8(2):R27–43. https://dx.doi.org/10.1530%2FEC-18-0432.
[7] Heaney RP, Holick MF. Why the IOM recommendations for vitamin D are deficient. J Bone Miner Res 2011;26(3):455–7. https://doi.org/10.1002/jbmr.328.
[8] Minisola S, Ferrone F, Danese V, Cecchetti V, Pepe J, Cipriani C, et al. Controversies surrounding vitamin D: focus on supplementation and cancer. Int J Environ Res Publ Health 2019;16(2):189. https://dx.doi.org/10.3390%2Fijerph16020189.
[9] Tanner SB, Harwell SA. More than healthy bones: a review of vitamin D in muscle health. Ther Adv Musculoskelet Dis 2015;7(4):152–9. https://dx.doi.org/10.1177%2F1759720X15588521.
[10] Pfotenhauer KM, Shubrook JH. Vitamin D deficiency, its role in health and disease, and current supplementation recommendations. J Am Osteopath Assoc 2017;117(5):301. https://doi.org/10.7556/jaoa.2017.055.
[11] Goldacre M, Hall N, Yeates DGR. Hospitalisation for children with rickets in England: a historical perspective. Lancet 2014;383(9917):597–8. https://doi.org/10.1016/s0140-6736(14)60211-7.
[12] Hyppönen E, Power C. Hypovitaminosis D in British adults at age 45 y: nationwide cohort study of dietary and lifestyle predictors. Am J Clin Nutr 2007;85(3):860–8. https://doi.org/10.1093/ajcn/85.3.860.
[13] Lowe NM, Bhojani I. Special considerations for vitamin D in the south Asian population in the UK. Ther Adv Musculoskelet Dis 2017. https://doi.org/10.1177%2F1759720X17704430.
[14] Preece M, McIntosh W, Tomlinson S, Ford J, Dunnigan M, O'Riordan J. Vitamin-D deficiency among Asian immigrants to Britain. Lancet 1973;301(7809):907–10. https://doi.org/10.1016/S0140-6736(73)91361-5.
[15] Bivins R. Ideology and disease identity: the politics of rickets, 1929-1982. Med Humanit 2014;40(1):3–10. https://dx.doi.org/10.1136%2Fmedhum-2013-010400.
[16] Itkonen S, Erkkola M, Lamberg-Allardt C. Vitamin D fortification of fluid milk products and their contribution to vitamin D intake and vitamin D status in observational studies—a review. Nutrients 2018;10(8):1054. https://dx.doi.org/10.3390%2Fnu10081054.
[17] Lips P, Cashman KD, Lamberg-Allardt C, Bischoff-Ferrari HA, Obermayer-Pietsch B, Bianchi ML, et al. Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: a position statement of the European Calcified Tissue Society. Eur J Endocrinol 2019:P23–54. https://doi.org/10.1530/EJE-18-0736.
[18] Uday S, Kongjonaj A, Aguiar M, Tulchinsky T, Högler W. Variations in infant and childhood vitamin D supplementation programmes across Europe and factors influencing adherence. Endocr Connect 2017;6(8):667–75. https://dx.doi.org/10.1530%2FEC-17-0193.
[19] Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 2015;12(3). https://doi.org/10.1371/journal.pmed.1001779.
[20] Watts G. UK Biobank gets 10% response rate as it starts recruiting volunteers. BMJ 2007;334(7595):659. https://dx.doi.org/10.1136%2Fbmj.39167.407616.DB.
[21] UK Biobank. UK Biobank: protocol for a large-scale prospective epidemilogical resource - protocol No: UKBB-PROT-09-06. 2007. https://www.ukbiobank.ac.uk/wp-content/uploads/2011/11/UK-Biobank-Protocol.pdf.
[22] DiaSorin. LIAISON - 25 OH vitamin D TOTAL assay. 2019. https://www.diasorin.com/sites/default/files/allegati_prodotti/ese_brochure_25_oh_vit._d_total_low.pdf.
[23] UK Biobank. Biomarker assay quality procedures: approaches used to minimise systematic and random errors (and the wider epidemiological implications). 2019. http://biobank.ndph.ox.ac.uk/showcase/showcase/docs/biomarker_issues.pdf.
[24] Macdonald HM, Wood AD, Tang JC, Fraser WD. Comparison of vitamin D2 and vitamin D3 supplementation in increasing serum 25-hydroxyvitamin D status: a systematic review and meta-analysis. Am J Clin Nutr 2012;96(5):1152–3. https://doi.org/10.3945/ajcn.112.046110.
[25] L ehmann U, Gjessing HR, Hirche F, Mueller-Belecke A, Gudbrandsen OA, Ueland PM, et al. Efficacy of fish intake on vitamin D status: a meta-analysis of randomized controlled trials. Am J Clin Nutr 2015;102(4):837–47. https://doi.org/10.3945/ajcn.114.105395.
[26] Nwosu BU, Kum-Nji P. Tobacco smoke exposure is an independent predictor of vitamin D deficiency in US children. PloS One 2018;13(10). https://dx.doi.org/10.1371%2Fjournal.pone.0205342.
[27] Bertrand KA, Giovannucci E, Liu Y, Malspeis S, Eliassen AH, Wu K, et al. Determinants of plasma 25-hydroxyvitamin D and development of prediction models in three US cohorts. Br J Nutr 2012;108(10):1889–96. https://dx.doi.org/10.1017%2FS0007114511007409.
[28] Townsend P, Phillimore P, Beattie A. Health and deprivation: inequality and the. North: Routledge; 1988. https://doi.org/10.1016/0168-8510(88)90006-1.
[29] Vickers D, Rees P. Creating the UK National Statistics 2001 output area classification. J Roy Stat Soc 2007;170(2):379–403. https://doi.org/10.1111/j.1467-985X.2007.00466.x.
[30] Nuttall FQ. Body mass index. Nutr Today 2015;50(3):117–28. https://dx.doi.org/10.1097%2FNT.0000000000000092.
[31] Manichaikul A, Mychaleckyj JC, Rich SS, Daly K, Sale M, Chen W-M. Robust relationship inference in genome-wide association studies. Bioinformatics 2010;26(22):2867–73. https://doi.org/10.1093/bioinformatics/btq559.
[32] UK Biobank. The Ethics and governance Council. 2019. https://www.ukbiobank.ac.uk/the-ethics-and-governance-council/.
[33] Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2011;96(7):1911–30. https://doi.org/10.1210/jc.2011-0385.
[34] Kroll MH, Bi C, Garber CC, Kaufman HW, Liu D, Caston-Balderrama A, et al. Temporal relationship between vitamin D status and parathyroid hormone in the United States. PloS One 2015;10(3):e0118108. https://doi.org/10.1371/journal.pone.0118108.

[35] Shaw NJ. Vitamin D deficiency in UK Asian families: activating a new concern. Arch Dis Child 2002;86(3):147–9. https://doi.org/10.1136/adc.86.3.147.
[36] Webb A, Aseem S, Kift R, Rhodes L, Farrar M. Target the message: a qualitative study exploring knowledge and cultural attitudes to sunlight and vitamin D in Greater Manchester, UK. Br J Dermatol 2016;175(6):1401–3. https://doi.org/10.1111/bjd.14800.
[37] Kift R, Berry JL, Vail A, Durkin MT, Rhodes LE, Webb AR. Lifestyle factors including less cutaneous sun exposure contribute to starkly lower vitamin D levels in U.K. South Asians compared with the white population. Br J Dermatol 2013;169(6):1272–8. https://doi.org/10.1111/bjd.12518.
[38] Engelsen O, Brustad M, Aksnes L, Lund E. Daily duration of vitamin D synthesis in human skin with relation to latitude, total ozone, altitude, ground cover, aerosols and cloud thickness. Photochem Photobiol 2005;81(6):1287. https://doi.org/10.1562/2004-11-19-rn-375.
[39] Addison M, Kaner E, Johnstone P, Hillier-Brown F, Moffatt S, Russell S, et al. Equal North: how can we reduce health inequalities in the North of England? A prioritization exercise with researchers, policymakers and practitioners. J Publ Health 2019;41(4):652–64. https://dx.doi.org/10.1093%2Fpubmed%2Ffdy170.
[40] Yousaf S, Bonsall A. UK Townsend deprivation scores from 2011 census. Economic and Social Research Council (ESRC), UK Data Service; 2017. http://s3-eu-west-1.amazonaws.com/statistics.digitalresources.jisc.ac.uk/dkan/files/Townsend_Deprivation_Scores/UK%20Townsend%20Deprivation%20Scores%20from%202011%20census%20data.pdf.
[41] Corscadden L, Levesque JF, Lewis V, Strumpf E, Breton M, Russell G. Factors associated with multiple barriers to access to primary care: an international analysis. Int J Equity Health 2018;17(1). https://doi.org/10.1186/s12939-018-0740-1.
[42] Schofield L, Walsh D, Munoz-Arroyo R, McCartney G, Buchanan D, Lawder R, et al. Dying younger in Scotland: trends in mortality and deprivation relative to england and Wales, 1981–2011. Health Place 2016;40:106–15. https://doi.org/10.1016/j.healthplace.2016.05.007.
[43] Melamed ML, Michos ED, Post W, Astor B. 25-Hydroxyvitamin D levels and the risk of mortality in the general population. Arch Intern Med 2008;168(15):1629–37. https://doi.org/10.1001/archinte.168.15.1629.
[44] Afzal S, Brøndum-Jacobsen P, Bojesen SE, Nordestgaard BG. Genetically low vitamin D concentrations and increased mortality: mendelian randomisation analysis in three large cohorts. BMJ 2014;349:g6330. https://doi.org/10.1136/bmj.g6330.
[45] Bambra C, Barr B, Milne E. North and South: addressing the English health divide. J Publ Health 2014;36(2):183–6. https://doi.org/10.1093/pubmed/fdu029.
[46] Aguiar M, Andronis L, Pallan M, Högler W, Frew E. The economic case for prevention of population vitamin D deficiency: a modelling study using data from England and Wales. Eur J Clin Nutr 2019. https://doi.org/10.1038/s41430-019-0486-x.
[47] Leung G, Stanner S. Diets of minority ethnic groups in the UK: influence on chronic disease risk and implications for prevention. Nutr Bull 2011;36(2):161–98. https://doi.org/10.1111/j.1467-3010.2011.01889.x.
[48] Uday S, Fratzl-Zelman N, Roschger P, Klaushofer K, Chikermane A, Saraff V, et al. Cardiac, bone and growth plate manifestations in hypocalcemic infants: revealing the hidden body of the vitamin D deficiency iceberg. BMC Pediatr 2018;18(1). https://doi.org/10.1186/s12887-018-1159-y.
[49] UK Biobank. Access matter: representativeness of the UK Biobank resource. 2017. http://www.ukbiobank.ac.uk/.
[50] Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, et al. Comparison of sociodemographic and health-related characteristics of UK biobank participants with those of the general population. Am J Epidemiol 2017;186(9):1026–34. https://doi.org/10.1093/aje/kwx246.
[51] Stamatakis E, Ekelund U, Wareham NJ. Temporal trends in physical activity in england: the health survey for england 1991 to 2004. Prev Med 2007;45(6):416–23. https://doi.org/10.1016/j.ypmed.2006.12.014.