British Journal of Nutrition (2024), 132, 40–49 doi:10.1017/S0007114524000862

Vitamin D status of pregnant women with obesity in the UK and its association with pregnancy outcomes: a secondary analysis of the UK Pregnancies Better Eating and Activity Trial (UPBEAT) study

Karen M. O'Callaghan[1]†, Katarzyna G. Nowak[2,3]†, Kathryn V. Dalrymple[1], Lucilla Poston[3], Jessica Rigutto-Farebrother[4], Ola F. Quotah[2,5], Sara L. White[3,6]†, Angela C. Flynn[1,7]*† and UPBEAT Consortium

[1]*Department of Nutritional Sciences, School of Life Course and Population Sciences, King's College London, London, UK*
[2]*Department of Nutrition and Dietetics, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK*
[3]*Department of Women and Children's Health, School of Life Course and Population Sciences, King's College London, London, UK*
[4]*Human Nutrition Laboratory, Institute of Food, Nutrition and Health, ETH Zurich, Zurich, Switzerland*
[5]*Department of Clinical Nutrition, Faculty of Applied Medical Science, King Abdulaziz University, Jeddah, Saudi Arabia*
[6]*Department of Diabetes and Endocrinology, Guy's and St Thomas' Hospitals NHS Foundation Trust, London, UK*
[7]*School of Population Health, Royal College of Surgeons in Ireland, Dublin, Ireland*

(Submitted 5 December 2023 – Final revision received 26 February 2024 – Accepted 21 March 2024 – First published online 18 April 2024)

Abstract

Prenatal vitamin D deficiency is widely reported and may affect perinatal outcomes. In this secondary analysis of the UK Pregnancies Better Eating and Activity Trial, we examined vitamin D status and its relationship with selected pregnancy outcomes in women with obesity (BMI ≥ 30 kg/m^2) from multi-ethnic inner-city settings in the UK. Determinants of vitamin D status at a mean of 17 ± 1 weeks' gestation were assessed using multivariable linear regression and reported as percent differences in serum 25-hydroxyvitamin D (25(OH)D). Associations between 25(OH)D and clinical outcomes were examined using logistic regression. Among 1089 participants, 67 % had 25(OH)D < 50 nmol/l and 26 % had concentrations < 25 nmol/l. In fully adjusted models accounting for socio-demographic and anthropometric characteristics, 25(OH)D was lower among women of Black (% difference = −33; 95 % CI: −39, −27), Asian (% difference = −43; 95 % CI: −51, −35) and other non-White (% difference = −26; 95 % CI: −35, −14) ethnicity compared with women of White ethnicity (*n* 1086; $P < 0{\cdot}001$ for all). In unadjusted analysis, risk of gestational diabetes was greater in women with 25(OH)D < 25 nmol/l compared with ≥ 50 nmol/l (OR = 1·58; 95 % CI: 1·09, 2·31), but the magnitude of effect estimates was attenuated in the multivariable model (OR = 1·33; 95 % CI: 0·88, 2·00). There were no associations between 25(OH)D and risk of preeclampsia, preterm birth or small for gestational age or large-for-gestational-age delivery. These findings demonstrate low 25(OH)D among pregnant women with obesity and highlight ethnic disparities in vitamin D status in the UK. However, evidence for a greater risk of adverse perinatal outcomes among women with vitamin D deficiency was limited.

Keywords: 25-hydroxyvitamin D: Vitamin D: Pregnancy outcomes: Perinatal health: High BMI: Obesity: Gestational diabetes: Hyperglycaemia

Low vitamin D status, as reflected by a circulating 25-hydroxyvitamin D (25(OH)D) concentration < 50 nmol/l[(1)], is a global public health issue that is widely prevalent among pregnant women across all WHO world regions[(2,3)]. In the UK, where vitamin D deficiency is defined as a 25(OH)D concentration < 25 nmol/l[(4)], the most recently available data from the National Diet and Nutrition Survey (years 9–11; 2016–2017 and 2018–2019) estimated 15 % of women aged 19–64 years have a vitamin D status that falls below this threshold[(5)]; however, there is a lack of recent nationally representative data on vitamin D status among pregnant women in the UK.

Reported relationships between prenatal vitamin D status and maternal and offspring health outcomes are inconsistent, thereby challenging the concept of pregnancy-specific targeted

Abbreviations: GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; UPBEAT, UK Pregnancies Better Eating and Activity Trial; 25(OH)D, 25-hydroxyvitamin D.

* **Corresponding author:** Angela C. Flynn, email angela.flynn@kcl.ac.uk

† These authors contributed equally to this work.

thresholds for 25(OH)D[6]. Recent and pooled data from observational studies suggest an association between low maternal 25(OH)D and increased risk of adverse outcomes including gestational diabetes mellitus (GDM)[7–9], preeclampsia[10] and both preterm[11] and small-for-gestational age at birth[11]. Although the benefits of routine prenatal vitamin D supplementation remain unclear[6,12], maternal vitamin D status is a modifiable determinant of neonatal 25(OH)D[13], and hence maternal vitamin D deficiency is a known risk factor for neonatal vitamin D deficiency.

Compared with a BMI within the 'healthy' range, a greater prevalence of vitamin D deficiency has been reported among individuals with obesity[14,15], including pregnant populations[16,17]. The inverse relationship between 25(OH)D and BMI has been attributed to both volumetric dilution and sequestration of vitamin D in adipose tissue[18,19], meaning a greater vitamin D intake may be required among individuals with overweight and obesity to achieve target 25(OH)D thresholds. Limited data from randomised trials suggest an inverse relationship between BMI and achieved 25(OH)D following intervention with vitamin D[20], such that greater BMI attenuates the slope of the vitamin D intake-25(OH)D response relationship during pregnancy[13,21]. In line with worldwide trends in overweight and obesity, the rising incidence of women who enter pregnancy with a BMI ≥ 30 kg/m^2 is a global concern[22,23]. In England and Wales, 23 % of women with a recorded BMI were classified as having obesity at the first antenatal appointment in the years 2018–19[24]. Earlier audit data (years 2015–2017) found variations in BMI across the main ethnic categories in the UK, with severe obesity (BMI ≥ 35 kg/m^2) reported to be more common among women of White and Black ethnicity[25]. However, the vitamin D status of pregnant women with obesity in the UK is not well characterised. Data are specifically lacking among ethnically diverse cohorts, despite previous reports from other European cohorts that clearly highlight lower vitamin D status in women of non-White ethnicity[26–29]. Understanding of the distribution of 25(OH)D and prevalence of deficiency is therefore required to inform evidenced-based guidelines for vitamin D intake in pregnant women and identify populations who would benefit most from targeted public health campaigns.

Among a large UK-based cohort, this study aimed to assess the vitamin D status of a multi-ethnic cohort of pregnant women with obesity and to examine the relationship between vitamin D status and perinatal outcomes.

Methods

Study design and setting

This study was a secondary analysis utilising biological samples and data from the UK Pregnancies Better Eating and Activity Trial (UPBEAT), a complex lifestyle intervention aiming to prevent GDM and reduce risk of large-for-gestational-age birth in 1554 pregnant women with obesity[30]. UPBEAT was conducted in eight hospitals in inner-city settings across the UK. Ethical approval was obtained from UK IRAS (reference 09/H0802/5), and the trial was registered prospectively (ISRCTN89971375). The intervention, which encouraged improved dietary and physical activity behaviours, did not reduce risk of GDM or large-for-gestational-age birth[31], and for the purposes of this investigation, the trial was treated as a cohort study as there were also no differences in the 25(OH)D concentration between the intervention and standard care arms (online Supplementary Fig. 1).

Study participants

In the UPBEAT study, eligible participants were identified in antenatal clinic from general practitioner or midwife referrals. Women aged > 16 years with a BMI ≥ 30 kg/m^2, singleton pregnancy and gestational age between 15^{+0} and 18^{+6} weeks were invited to participate. Women were excluded if unwilling or unable to provide informed consent, or if they had pre-existing diabetes, hypertension, renal disease, systemic lupus erythematous, antiphospholipid syndrome, sickle cell disease, thalassemia, coeliac disease, thyroid disease, current psychosis or currently prescribed metformin. Verbal and written information was provided to eligible women, and written consent was obtained[30]. Inclusion in the present study was restricted to women for whom a baseline blood sample was available for measurement of serum 25(OH)D.

Demographic, clinical and pregnancy outcome data

Socio-demographic information was recorded at study entry, as collected through interview-administered questionnaires. Ethnicity was self-reported. Socio-economic status was assessed by Index of Multiple Deprivation (IMD), for which scores were calculated for the region of residence and presented as quintiles. The following anthropometric data were collected using standardised methods[30]: maternal weight (kg) and height (cm); maternal hip, waist and thigh circumferences (cm) and maternal triceps (mm), biceps (mm), suprailiac (mm) and subscapular (mm) thicknesses, which were used to calculate the sum of four skinfold thickness (mm). Neonatal length and weight were measured within 72 h of birth. Customised birthweight centiles were calculated using Gestation Related Optimal Weight (GROW) software version 6·7·5·1 (Gestation Network, Perinatal Institute, Birmingham, UK; www.gestation.net), and large-for-gestational-age and small for gestational age delivery were defined as ≥ 90th and ≤ 10th percentile, respectively[30].

As per the UPBEAT protocol, diagnosis of GDM was defined according to the International Association of Diabetes and Pregnancy Study Groups criteria as one or more of the following: fasting capillary glucose concentrations of ≥ 5·1 mmol/l and/or 1 h venous glucose of ≥ 10·0 mmol/l and/or 2 h venous glucose of ≥ 8·5 mmol/l following an oral glucose tolerance test (OGTT). The UPBEAT protocol restricted diagnosis of GDM to participants who had an OGTT conducted between 27^{+0} and 28^{+6} weeks' gestation; however, the present analysis pragmatically extended the timeframe to any OGTT performed between 23^{+2} and 30^{+0} weeks' gestation in order to maximise the sample size for this outcome. Pre-eclampsia was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg or both, on at least two occasions 4 h apart, with

proteinuria ≥ 300 mg/24 h or spot urine protein:creatinine ratio ≥ 30 mg/mmol or urine dipstick protein ≥ 2+.

Non-fasting venous blood samples were collected at the first study visit (second trimester), processed to serum within 2 h and stored at −80°C until analysis. The meteorological season of blood draw was assigned based on the date of the sample collection as follows: Winter – December, January, February; Spring – March, April, May; Summer – June, July, August; Autumn – September, October, November[32].

Laboratory analysis

Maternal HbA1c was measured at the University of Glasgow using a turbidimetric inhibition immunoassay on the Roche, Cobas c311 as previously described[33]; low and high CV were 1·3 % and 1·4 %, respectively. Total 25(OH)D (sum of 25(OH)D_2 and 25(OH)D_3) was measured at the Institute of Cardiovascular and Medical Sciences at the University of Glasgow using an electrochemiluminescence-based automated clinical assay (Vitamin D Total assay kit #05894913 190, Roche Diagnostics, Mannheimm Germany) on a Cobas e411 analyser using the manufacturer's standards and quality control material. This automated immunoassay method has been standardised against LC–MS/MS, which has been standardised to National Institute of Standardization and Technology (NIST) standard reference material[34,35]. The assay limit of detection was 7·5 nmol/l; values below this threshold (*n* 27/1089; 2·5 %) were imputed at the level of the limit of detection. The low and high inter-assay CV were 11·2 % and 9·2 %, respectively.

In the present study, vitamin D deficiency and low vitamin D status were defined as a 25(OH)D concentration < 25 nmol/l and between ≥ 25 – < 50 nmol/l, respectively, to facilitate comparison with previous studies exploring maternal vitamin D status[2,21].

Statistical analysis

Data distributions were assessed using histograms and kernel density plots and summarised as mean ± SD or median (25th, 75th percentile), as appropriate. For categorical data, number (*n*) and percentage (%) are reported. Variables following a skewed distribution were either natural (ln)-log transformed or transformed to their base 2 log to approximate normality in regression analysis. The association between each maternal socio-demographic, clinical and anthropometric characteristic of interest and serum 25(OH)D in the second trimester was first examined using simple linear regression with $\log_2$-transformed 25(OH)D as the outcome variable given the right-skewed distribution of 25(OH)D. To create a parsimonious multivariable model, variables with $P < 0{\cdot}20$ in the unadjusted analyses were entered into a general linear model and adjusted for IMD, ethnicity, maternal BMI at first study visit, maternal age at first study visit, season at blood sampling, gestational age at sampling and educational attainment, as appropriate to account for confounding of the exposure-vitamin D status relationship. The multivariable model included adjustment for BMI only, to avoid multicolinearity between BMI and other body size measures (i.e. weight and sum of skinfold thickness), whereby Pearson's $r \geq 0{\cdot}5$ was used to define collinearity between pairs of continuous variables. Effect estimates were back-transformed and reported as mean percent differences with 95 % CI.

To facilitate meaningful comparison of effect sizes when examining the association between 25(OH)D and blood glucose measurements, both the independent (maternal 25(OH)D in second trimester) and dependent (HbA1c, fasting glucose and glucose measures at 1- and 2-h post OGTT) variables were standardised using a Fisher–Yates transformation to create a normally distributed variable with a mean of zero and an SD of one[36] before use in regression models; as such, the standardised regression can be interpreted as SD change in the outcome variables per SD change in serum 25(OH)D. Logistic regression was used for categorical outcome data and presented as OR with 95 % CI, using 25(OH)D ≥ 50 nmol/l as the reference catergory and 25(OH)D < 25 nmol/l and between ≥ 25 and < 50 nmol/l as the comparators. Multivariable models included adjustment for the intervention arm assigned at enrolment to the UPBEAT trial, as well as known demographic characteristics to be associated with 25(OH)D; ethnicity, educational attainment, maternal BMI at first visit, maternal age at first visit, season at blood sampling, gestational age at blood sampling and gestational age at delivery, as appropriate. In post hoc exploratory analysis, we created similar regression models fitted to data stratified by ethnic group to examine whether the magnitude of the effect estimates for the association between 25(OH)D and pregancy outcomes differed by ethnicity. Stratified analysis was conducted among women of White and Black ethnicity only, given the very low sample size in the other non-White ethnic groups.

Statistical analysis was conducted using Stata v17.0 (StataCorp, College Station), with significance set at $P < 0{\cdot}05$.

Results

Population characteristics

Of 1091 participants with available 25(OH)D data in the UPBEAT cohort, two participants were excluded from the present analysis due to an early OGTT (13 weeks' gestation) (*n* 1) and lack of information on the date of blood sample collection (*n* 1). Hence, 1089 participants were included in the present study, representing 70 % of the primary UPBEAT study cohort. The population characteristics of the full study cohort and stratified by thresholds of vitamin D status are shown in Table 1. The mean age of participants at enrolment was 30·5 ± 5·6 years and median BMI was 35·2 (32·7, 38·7) kg/m^2. Over 75 % of participants were classified as having a relatively low socio-economic status based on the two highest quintiles of IMD. One-third of women identified as non-White ethnicity (33 %). The majority of participants lived in London (42 %), of which 43 % came from the most deprived areas, and just under two-thirds did not hold a university degree or equivalent (Table 1).

There was an even distribution of blood samples drawn across all four seasons (Table 1). The median serum 25(OH)D concentration was 38·9 (24·5, 56·4) nmol/l. In total, 727 (67 %) women were classed as having low a vitamin D status (25(OH)D < 50 nmol/l) and more than one-quarter of women (26 %) had a 25(OH)D concentration < 25 nmol/l. The prevalence of vitamin

British Journal of Nutrition

Table 1. Maternal characteristics by vitamin D status assessed in the second trimester of pregnancy

	Whole cohort		25(OH)D < 25 nmol/l		25(OH)D ≥ 25–< 50 nmol/l		25(OH)D ≥ 50 nmol/l	
	n 1089		*n* 286		*n* 441		*n* 362	
	n	%	*n*	%	*n*	%	*n*	%
25(OH)D, nmol/l								
Median	38·9		17·6		37·0		65·6	
25th, 75th percentile	24·5, 56·4		12·0, 21·8		31·1, 43·4		56·4, 81·9	
Age, years								
Mean	30·5		30·1		30·3		30·9	
SD	5·6		5·7		5·7		5·2	
Gestational age, weeks								
Mean	17		17·1		17·0		16·9	
SD	1·1		1·1		1·0		1·1	
Deprivation status*								
1 (Least deprived)	57	5·3	11	19·3	23	40·4	23	40·4
2	83	7·6	18	21·7	35	42·2	30	36·1
3	121	11·1	20	16·5	49	40·5	52	43·0
4	359	33·1	88	24·5	148	41·2	123	34·3
5 (Most deprived)	466	42·9	148	31·8	186	39·9	132	28·3
Educational attainment								
University degree	435	39·9	102	23·5	180	41·4	153	35·2
Centre†								
St Thomas', London	361	33·1	101	28·0	165	45·7	95	26·3
Newcastle	225	20·7	63	28·0	85	37·8	77	34·2
Glasgow	252	23·1	39	15·5	95	37·7	118	46·8
Manchester	117	10·7	33	28·2	48	41·0	36	30·8
Bradford	40	3·7	25	62·5	11	27·5	4	10·0
St Georges, London	94	8·6	25	26·6	37	39·4	32	34·0
Ethnicity								
Asian	73	6·7	38	52·1	23	31·5	12	16·4
Black	228	20·9	85	37·3	111	48·7	32	14·0
White	732	67·2	144	19·7	285	38·9	303	41·4
Other	56	5·1	19	6·6	22	5·0	15	4·1
Season								
Winter	244	22·4	76	31·2	96	39·3	72	29·5
Spring	292	26·8	91	31·2	122	41·8	79	27·0
Summer	265	24·3	45	17·0	113	42·6	107	40·4
Autumn	288	26·5	74	25·7	110	38·2	104	36·1
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Anthropometry								
Weight, kg	98·3	15·5	99·2	16·2	98·9	16·2	96·7	14·0
Hip circumference‡, cm	122·8	10·7	123·8	11·6	123·1	10·9	121·7	9·7
Waist circumference‡, cm	108·1	10·8	109·1	11·5	108·4	10·7	107·0	10·1
Thigh circumference‡, cm	69·0	6·8	69·4	7·4	69·6	7·0	68·1	6·6
Triceps skinfold§, mm	32·3	8·6	31·8	8·7	32·8	8·9	32·1	8·2
Biceps skinfold‖, mm	21·4	7·6	22·2	8·0	21·6	7·8	20·6	7·1
Suprailiac skinfold‖, mm	33·1	10·9	34·6	11·8	33·4	11·1	31·6	9·7
Subscapular skinfold‖, mm	35·8	10·5	37·5	11·6	36·0	10·7	34·4	9·1
Sum of skinfolds¶,**, mm	122·7	27·6	126·1	29·7	123·8	28·5	118·7	24·0
BMI, kg/m^2								
Median	35·2		36·1		35·0		34·8	
25th, 75th percentile	32·7, 38·7		32·8, 39·9		32·9, 38·8		32·5, 37·8	
	n	%	*n*	%	*n*	%	*n*	%
WHO BMI classification††								
Obesity class I	528	49	123	23·3	217	41·1	188	35·6
Obesity class II	359	33	92	25·6	140	39·0	127	35·4
Obesity class III	202	19	71	35·1	84	41·6	47	23·3
GDM‡‡,§§	272	29	79	29·0	120	44·1	73	26·8

25(OH)D, 25-hydroxyvitamin D; GDM, gestational diabetes mellitus.
* *n* = 1086 due to missing data.
† Serum 25(OH)D measurements were unavailable for UPBEAT study participants recruited from community clinics or Sunderland City Hospitals Foundation Trust, and hence were not included in the present analysis.
‡ *n* = 1084 due to missing data.
§ *n* = 1080 due to missing data.
‖ *n* = 1079 due to missing data.
¶ *n* = 1077 due to missing data.
** Calculated by sum of biceps, triceps, suprailiac, and subscapular skinfold thicknesses.
†† Obesity class I – BMI 30·0–34·9 kg/m^2, Obesity class II – BMI 35·0–39·9 kg/m^2, Obesity class III – BMI ≥ 40·0 kg/m^2.
‡‡ *n* = 993 due to missing data.
§§ GDM diagnosis at 22^{+0}–30^{+0} weeks' gestation by oral glucose tolerance test.

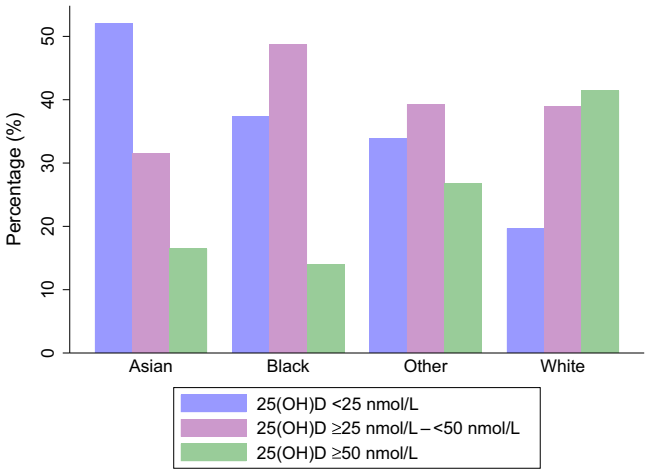

Fig. 1. Maternal 25(OH)D concentration (nmol/l) in second trimester (mean: 17 ± 1 weeks' gestation). 25(OH)D; 25-hydroxyvitamin D. *n* 73, 228, 56 and 732 for participants of Asian, Black, other non-White and White ethnicity, respectively.

Table 2. Determinants of maternal serum 25-hydroxyvitamin D assessed in the second trimester of pregnancy (15–18^{+6} weeks' gestation)

		Unadjusted				Adjusted†		
Maternal characteristics	*n*	% difference*	95 % CI	*P*	*n*	% difference*	95 % CI	*P*
Age (years)	1089	0·74	0·07, 1·42	0·03	1086	0·88	0·21, 1·54	0·01
Deprivation status								
5 (Most deprived)	466	Reference		–	466	Reference		–
4	359	9·5	0·5, 19	0·039	259	2·9	–5·2, 12	0·50
3	121	27	12, 44	<0·001	121	15	2·6, 30	0·017
2	83	22	5·1, 41	0·009	83	5·9	–7·9, 22	0·42
1 (Least deprived)	57	24	4·8, 48	0·013	57	1·8	–14, 20	0·84
Education								
No university degree	654	Reference		–	651	Reference		–
University degree	435	8·4	0·5, 17	0·037	435	8·3	0·40, 17	0·039
Ethnicity								
White	732	Reference		–	730	Reference		–
Asian	73	–41	–49, –32	<0·001	73	–43	–51, –35	<0·001
Black	228	–33	–39, –27	<0·001	227	–33	–39, –27	<0·001
Other	56	–23	–34, –9·0	0·002	56	–26	–37, –13	<0·001
Season								
Summer	265	Reference		–	265	Reference		–
Winter	244	–16	–25, –6·4	0·002	243	–15	–23, –5·6	0·002
Spring	292	–18	–26, –8·7	<0·001	290	–15	–23, –6·0	0·001
Autumn	288	–7·0	–16, 3·3	0·18	288	–6·1	–15, 3·6	0·21
Anthropometry								
Weight (kg)	1089	–0·29	–0·53, –0·05	0·02	1086	–0·38	–0·61, –0·15	0·001
BMI (kg/m2)	1089	–33	–46, –18	<0·001	1086	–1·4	–2·1, –0·74	<0·001
Sum of skinfolds (mm)	1077	–0·26	–0·39, –0·12	<0·001	1074	–0·16	–0·29, 0·03	0·017

* Effect estimates represents the percent difference in serum 25-hydroxyvitamin D per 1-unit increase in the predictor variable (continuous variables) or in comparison to the reference category (categorical variables).
† Adjusted for: Index of Multiple Deprivation, ethnicity, season of blood sampling, BMI, age, gestational age at blood sampling, educational attainment (university degree obtained or not). Adjustment for BMI was not included for anthropometric outcomes due to multicollinearity with weight and sum of skinfold thickness.

D deficiency was highest among women of Asian ethnicity and lowest among women who identified as White (Table 1, Fig. 1).

Association of maternal characteristics with 25-hydroxyvitamin D concentrations. In both unadjusted and multivariable-adjusted linear regression models, maternal age was positively associated with serum 25(OH)D in the second trimester (Table 2). Participants who held a university degree had a greater 25(OH)D concentration than those without. Women living in the most deprived area had a lower 25(OH)D concentration compared with women with an IMD score < 5; however, effect estimates were attenuated in adjusted analysis such that the percent difference between IMD quintiles only remained significant for comparison between the third and fifth quintiles (Table 2). Compared with White women, 25(OH)D was lower among women of non-White ethnicity, for which the percent difference was greatest for women of Asian ethnicity (percent difference = 41 %; 95 % CI: −49, −31; $P < 0{\cdot}001$); inferences were unchanged upon adjustment for covariates. Greater weight, BMI and skinfold thickness were associated with

Table 3. Occurrence of selected perinatal outcomes by categories of maternal vitamin D status in the second trimester*

			Unadjusted model			Adjusted model‡		
	n†	%	OR	95 % CI	*P*	OR	95 % CI	*P*
GDM								
25(OH)D ≥ 50 nmol/l	73/304	24	Reference			Reference		
25(OH)D > 25–< 50 nmol/l	120/390	31	1·4	1·00, 1·98	0·049	1·28	0·89, 1·82	0·18
25(OH)D < 25 nmol/l	79/273	33	1·58	1·09, 2·31	0·02	1·33	0·88, 2·00	0·18
Pre-eclampsia								
25(OH)D ≥ 50 nmol/l	22/347	6·3	Reference			Reference		
25(OH)D > 25–< 50 nmol/l	31/424	7·3	1·17	0·66, 2·05	0·60	1·10	0·61, 1·99	0·75
25(OH)D < 25 nmol/l	15/278	5·4	0·84	0·43, 1·66	0·62	0·81	0·39, 1·68	0·57
Preterm birth								
25(OH)D ≥ 50 nmol/l	24/353	6·8	Reference			Reference		
25(OH)D > 25–< 50 nmol/l	23/429	5·4	0·78	0·43, 1·40	0·40	0·64	0·34, 1·18	0·15
25(OH)D < 25 nmol/l	22/281	7·8	1·16	0·64, 2·12	0·62	0·86	0·44, 1·67	0·66
SGA								
25(OH)D ≥ 50 nmol/l	35/353	9·9	Reference			Reference		
25(OH)D > 25–< 50 nmol/l	50/429	12	1·20	0·76, 1·89	0·44	1·23	0·77, 1·96	0·40
25(OH)D < 25 nmol/l	40/281	14	1·51	0·93, 2·45	0·10	1·63	0·97, 2·73	0·07
LGA								
25(OH)D ≥ 50 nmol/l	33/353	9·4	Reference			Reference		
25(OH)D > 25–< 50 nmol/l	35/429	8·2	0·86	0·52, 1·42	0·56	0·81	0·48, 1·36	0·43
25(OH)D < 25 nmol/l	30/281	11	1·16	0·69, 1·95	0·58	1·13	0·64, 2·00	0·68

* OR represents the probability of occurrence of the event in each category of vitamin D status compared to 25(OH)D ≥ 50 nmol/l. 25(OH)D, 25-hydroxyvitamin D; GDM, gestational diabetes mellitus; LGA, large for gestational age; OR, odds ratio; SGA, small for gestational age.
† Represents total number and percentage of women with outcome of interest.
‡ Adjusted for: ethnicity, season of blood sampling, BMI, maternal age, assigned UPBEAT intervention arm, gestational age at blood sampling and educational attainment (university degree obtained or not).

Table 4. Association between maternal second trimester ($15–18^{+6}$ weeks' gestation) serum 25-hydroxyvitamin D and blood glucose measurements*

		Unadjusted model				Adjusted model†		
	n	Difference in SD/SD*	95 % CI	*P*	*n*	Difference in SD/SD*	95 % CI	*P*
Maternal measures								
HbA1c	1014	–0·02	–0·09, 0·04	0·44	1014	0·06	0·001, 0·13	0·045
Fasting glucose‡	931	–0·05	–0·12, 0·01	0·10	931	–0·03	–0·10, 0·03	0·33
1 h glucose‡	882	–0·02	–0·09, 0·05	0·57	882	–0·04	–0·11, 0·04	0·33
2 h glucose‡	930	–0·08	–0·15, –0·02	0·01	930	–0·07	–0·14, –0·003	0·04

* The dependent and independent variables have been Fisher-Yates transformed to a normally distributed variables with a mean of zero and a standard deviation of one[36]. The regression coefficients have been standardised and can be interpreted as SD change in the outcome variables per SD change in serum 25(OH)D. 25(OH)D, 25-hydroxyvitamin D.
† Adjusted for: ethnicity, season, BMI, maternal age, assigned UPBEAT intervention arm, gestational age at sampling and educational attainment (university degree obtained or not).
‡ Measurements taken as part of standard oral glucose tolerance test between 23^{+2} and 30^{+0} weeks' gestation.

a lower 25(OH)D concentration in both unadjusted and adjusted models, but effect estimates were minor. Serum 25(OH)D was lower among women whose blood sample was taken in winter and spring compared with the summer months (Table 2).

Association between maternal 25-hydroxyvitamin D and maternal outcomes. Compared with women with 25(OH)D concentrations ≥ 50 nmol/l in the second trimester, the occurrence of preeclampsia, preterm birth and both small for gestational age and large-for-gestational-age birth was similar in women with low vitamin D status (25(OH)D ≥ 25 – < 50 nmol/l), and vitamin D deficiency (25(OH)D < 25 nmol/l) (Table 3). In unadjusted analysis, the odds of developing GDM were greater in women with 25(OH)D < 25 nmol/l *v.* ≥ 50 nmol/l, but effect estimates were attenuated and rendered non-significant upon adjustment for maternal socio-demographic characteristics (Table 3). There was a minor negative association between 25(OH)D concentration and blood glucose measured at the 2-h OGTT time point that was attenuated albeit remained statistically significant in multivariable-adjusted analysis, such that each SD increase in 25(OH)D was associated with a 0·07 SD decrease in blood glucose (95 % CI: –0·14, –0·003; $P = 0·042$; n 931) (Table 4), which is equivalent to –0·11 mmol/l (95 % CI: –0·21, –0·005). Associations between 25(OH)D and either HbA1c or fasting glucose were not observed (Table 4).

In subgroup analysis stratified by ethnicity, the magnitude and direction of effect estimates differed between White and Black women for most outcomes; however, the odds of having an adverse outcome at 25(OH)D < 50 nmol/l were not statistically significant in either ethnic group such that inferences from primary analysis were unchanged (online Supplementary Table 1). The relatively small sample size for Black women resulted in a low absolute number of diagnosed adverse outcomes which resulted in wide confidence intervals surrounding effect

estimates and precluded estimation of the odds of preeclampsia and small for gestational age using 25(OH)D ≥ 50 nmol/l as the reference category. The negative association between 25(OH)D and blood glucose measured at the 2-h OGTT time point was not statistically significant in multivariable models in either White (mean difference = –0·07 SD/SD; 95 % CI: –0·16, 0·02; $P = 0·14$; n 631) or Black (mean difference = –0·13 SD/SD; 95 % CI: –0·29, 0·02; $P = 0·10$; n 187) women.

Discussion

Among an ethnically diverse cohort of pregnant women with obesity in the UK, our findings highlight an overall low vitamin D status, with more than two-thirds of women presenting with a 25(OH)D concentration < 50 nmol/l in the second trimester. While our findings do not support an association between maternal 25(OH)D in early-mid pregnancy and later clinical outcomes, we report a lower 25(OH)D among women of ethnic minority, highlighting a wide disparity in vitamin D status among population sub-groups within the UK. Of particular concern is the high prevalence of deficiency among women of Asian ethnicity, of whom > 50 % had a 25(OH)D concentration < 25 nmol/l, a threshold at which risk of nutritional rickets and osteomalacia is increased[1,4]. Given the resurgence in vitamin D-dependent rickets in recent decades, particularly among children of ethnic minority[37,38], prevention of maternal vitamin D deficiency is an important consideration for ensuring adequate neonatal vitamin D status and protection against rickets in early infancy[39].

Current dietary reference values for vitamin D are not pregnancy specific but rather based on 25(OH)D targets for the maintenance of bone health, and as such, there has been little change in dietary vitamin D intake recommendations for pregnant women in the UK[4,40,41]. Furthermore, there is no specific national guidance for pregnant women with overweight or obesity. Within a cohort limited to women with obesity (BMI ≥ 30 kg/m^2), we report an inverse association of 25(OH)D with BMI that remained significant after adjustment for selected maternal socio-demographic determinants of vitamin D status. The present study clearly shows a lower 25(OH)D among women at higher ends of the BMI distribution; only 23 % of women with severe obesity had a 25(OH)D concentration above the 50 nmol/l threshold. As neonatal 25(OH)D concentrations are dependent on maternal values in late gestation[13], and human breastmilk is typically low in vitamin D[42,43], the high prevalence of vitamin D deficiency among pregnant women with obesity is a concern, particularly in an era where nutritional rickets remains a public health issue, both in the UK[37,38] and globally[44].

The prevalence of vitamin D deficiency in our study population was higher in comparison to a previous UK pregnant cohort of BMI heterogenous women from Southampton[45], yet comparable with baseline trial data among women with overweight and obesity in Northern Ireland[21]. Our findings suggest current national guidelines in the UK, which recommend a vitamin D intake of 400 μg/d[4], may not be adhered to, and/or may not be adequate for preventing vitamin D deficiency. While pregnancy-specific thresholds for 25(OH)D may be required, trial-derived dose–response data is needed to determine whether the nutritional requirement for vitamin D to meet existing target thresholds is the same for pregnant women at both ends of the BMI distribution. Data from Ireland[46], New Zealand[47] and Canada[48] suggest a maternal 25(OH)D concentration of 50 nmol/l in late gestation is required to prevent neonatal vitamin D deficiency at the 25 nmol/l threshold. However, data from Northern Ireland has shown supplementation with 400 μg vitamin D_3/d is not sufficient to raise 25(OH)D concentration > 50 nmol/l in women with overweight and obesity[21]. A greater vitamin D dose than currently recommended is therefore likely required in this population, particularly among women who enter pregnancy with a low vitamin D status.

In line with previously published data[26–29], we report a greater prevalence of vitamin D deficiency among women of Black, Asian and non-White ethnicity compared with women who identify as White. As melanin hinders dermal synthesis of pre-vitamin D_3[49], darker skin pigmentation is a well-recognised risk factor for vitamin D deficiency for individuals living at northern latitudes[50,51]. While ethnic differences in vitamin D status are unlikely to be explained by variations in cutaneous production alone[52], our findings reiterate the need for targeted public health messaging to prevent vitamin D deficiency among the populations who are most at risk. Given the limited sample size in the Asian and non-White ethnic groups, our post hoc analysis stratified by ethnicity was limited to White and Black women only. While 25(OH)D < 50 nmol/l was not associated with a greater odds of adverse outcomes in either ethnic group, we acknowledge imprecision of the effect estimates owing to the reduced sample size, and hence such findings should be considered as exploratory only.

We report a greater 25(OH)D among women with a university degree, yet the impact of socio-economic status on vitamin D status was less clear once additional socio-demographic factors were considered in the multivariable model. Despite the availability of funding schemes for low-income households, it was previously estimated that < 10 % of those eligible obtained free vouchers for vitamin D supplements for children and pregnant women in the UK[53]. Barriers such as complex ordering and reimbursement systems and limited locations from which supplements can be acquired have been reported[54]. Despite efforts to increase micronutrient intake among pregnant women of lower socio-economic status, such barriers to supplement use may therefore have contributed to a lower uptake and continued low vitamin D status among certain subgroups at the time blood samples were drawn for the present study.

The potential impact of vitamin D intervention on blood glucose regulation and its role in prevention of diabetes has been discussed in recent years[55–57]. At present, pooled trial data show promising albeit conflicting evidence for an effect of vitamin D supplementation on prevention of GDM among generally healthy pregnancies[58,59]. However, limited evidence from populations with obesity suggests little benefit of vitamin D supplementation. In the multicentre DALI vitamin D study[60], the authors report a reduction in fasting plasma glucose in late

gestation following a daily dose of 1600 μg vitamin D, but this did not translate to a reduction in GDM. The high frequency of personal micronutrient supplement use and high mean 25(OH)D concentration (> 50 nmol/l) at baseline limits generalisability of these findings to women with vitamin D deficiency[60]. Expression of the vitamin D receptor in pancreatic islet cells suggests a direct role for $1,25(OH)_2D$ in glucose regulation. *In vitro* studies of mouse and human tissues provide mechanistic evidence linking vitamin D-mediated gene transcription to insulin secretion in response to glucose exposure. Specifically, $1,25(OH)_2D$ upregulates the expression of voltage-gated calcium channels causing increased Ca influx to the cell, in turn stimulating insulin secretion from pancreatic β-cells[61]. As with others, we did not find strong evidence for an association between 25(OH)D and glucose regulation[62]; compared with women with 25(OH)D ≥ 50 nmol/l, lower vitamin D status was not associated with an increased odds of developing GDM in the present study after adjusting for relevant confounders. Furthermore, while higher serum 25(OH)D was associated with a lower blood glucose concentration measured at the OGTT 2-h timepoint, the effect estimate was minor and unlikely to be clinically meaningful, and we acknowledge the possibility of type 1 errors owing to multiple testing. Given the lack of an association between 25(OH)D and fasting glucose, as well as glucose at the OGTT 1-h time point, we caution interpretation of these findings.

Strengths of this study include the large well characterised and ethnically diverse cohort of pregnant women with obesity and high levels of socio-economic deprivation, who are a high-risk group for adverse pregnancy outcomes. However, several limitations should be acknowledged. As the present study utilised data and biological samples from a previously reported intervention trial[31], the sample size was limited to participants with existing data, and we recognise that the study population may not be representative of the general UK population within the UK. We assessed 25(OH)D at a single time point during the second trimester and did not specifically collect data on dietary vitamin D intake or personal vitamin D supplementation use; 25(OH)D reflects habitual vitamin D intake from both cutaneous synthesis and dietary intake; however, 25(OH)D followed a skewed distribution in all ethnic groups and we therefore expect some participants to have taken supplemental vitamin D either alone or as part of a prenatal multiple micronutrient supplementation regimen. It is possible that the 25(OH)D measured at this time point is not reflective of changes in vitamin D intake later in pregnancy, which may impact pregnancy outcomes. Variability in the quality of 25(OH)D data across analytical methods has been discussed at length in the literature. We used a well-recognised automated immunoassay that was available at the time of 25(OH)D assessment. However, we acknowledge potential bias of this method due to cross-reactivity with other vitamin D metabolites, including the C3-epimer of 25(OH)D[63]. While only 2·5 % of samples were at or below the assay limit of detection of 7·5 nmol/l, this possible bias and relatively high limit of detection may have influenced precision of the effect estimates when modelling determinants of 25(OH)D. We used a statistical-based approach to select variables for covariate adjustment in multivariable models. While empirical methods are valid approaches for covariate selection, we acknowledge the advantages and increasing movement towards illustrative-based approaches (e.g. direct acyclic graphs) to identify confounding relationships[64]. Lastly, while parathyroid hormone concentrations were not available for this cohort, the interactive effects of low 25(OH)D and elevated parathyroid hormone, representing functional vitamin D deficiency, may be a more meaningful indicator to explore rather than 25(OH)D alone[65]. As the limited evidence relating functional vitamin D deficiency to an increased risk of hypertensive disorders and restricted fetal growth is mixed[65–68], the possibility of a greater risk of adverse perinatal outcomes is worth further exploration in diverse cohorts.

Conclusion

In this cohort of women at high risk of pregnancy complications, our findings do not support a greater risk of GDM, pre-eclampsia, preterm birth or abnormal fetal growth among women with 25(OH)D concentrations below the conventional threshold of 50 nmol/l. However, our findings add to the increasing evidence that low vitamin D status is widespread among pregnant women with obesity in the UK, for which women of ethnic minority are most at risk. To meet current recommended thresholds for 25(OH)D, future dose–response trials are required to inform guidance for vitamin D intakes among pregnant women with obesity.

Acknowledgements

The authors thank all staff in the UPBEAT consortium and the participants in the trial for their patience, time, interest and goodwill.

This research was funded/supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas' The National Health Service Foundation Trust and King's College London and/or the NIHR Clinical Research Facility. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. The UPBEAT study was funded by UK's National Institute for Health Research (RP-PG-0407-10452) and the Chief Scientist Office, Scottish Government Health Directorates (Edinburgh) (CZB/A/680), Guys and St Thomas' Charity (1060508), Tommy's Charity (SC039280), the NIHR Biomedical Research Centre at Guy's and St Thomas' The National Health Service Foundation Trust and King's College London. Medical Research Council UK provided additional funding for the biomarker study (MR/L002477/1). The views expressed are those of the author(s) and not necessarily those of The National Health Service, the NIHR or the Department of Health.

A. C. F., S. L. W. and K. G. N. conceptualised and designed this study. K. G. N., O. F. Q., K. M. O'C. and K. V. D. analysed the data. A. C. F., K. G. N., K. M. O'C., K. V. D., L. P., J. R-F. and S. L. W. interpreted the findings. K. M. O'C., K. G. N. and A. C. F. wrote the manuscript. A. C. F. and S. L. W. have primary responsibility for final content. All authors have read and approved the manuscript.

The authors declare no conflict of interest.

The UPBEAT Scientific Advisory Committee accepts applications for use of data from this study upon request (www.medscinet.net/upbeat/).

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114524000862

References

1. Institute of Medicine (2011) *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: National Academies Press (US).
2. Saraf R, Morton SMB, Camargo CA Jr, *et al.* (2016) Global summary of maternal and newborn vitamin D status – a systematic review. *Matern Child Nutr* **12**, 647–668.
3. van der Pligt P, Willcox J, Szymlek-Gay EA, *et al.* (2018) Associations of maternal vitamin D deficiency with pregnancy and neonatal complications in developing countries: a systematic review. *Nutrients* **10**, 640.
4. Scientific Advisory Committee on Nutrition (2016) *Vitamin D and Health*. London: Scientific Advisory Committee on Nutrition (SACN).
5. National Diet and Nutrition Survey (2020) NDNS: Results from Years 9 to 11 (combined) – Data Tables. –https://www.gov.uk/government/statistics/ndns-results-from-years-9-to-11–2016-to-2017-and-2018-to-2019 (accessed November 2023).
6. Kiely ME, Wagner CL & Roth DE (2020) Vitamin D in pregnancy: where we are and where we should go. *J Steroid Biochem Mol Biol* **201**, 105669.
7. Sadeghian M, Asadi M, Rahmani S, *et al.* (2020) Circulating vitamin D and the risk of gestational diabetes: a systematic review and dose-response meta-analysis. *Endocrine* **70**, 36–47.
8. Vivanti AJ, Monier I, Salakos E, *et al.* (2020) Vitamin D and pregnancy outcomes: overall results of the FEPED study. *J Gynecol Obstet Hum Reprod* **49**, 101883.
9. Agüero-Domenech N, Jover S, Sarrión A, *et al.* (2021) Vitamin D deficiency and gestational diabetes mellitus in relation to body mass index. *Nutrients* **14**, 102.
10. Rouhani P, Mokhtari E, Lotfi K, *et al.* (2023) The association between circulating 25-hydroxyvitamin D levels and preeclampsia: a systematic review and dose-response meta-analysis of epidemiologic studies with GRADE assessment. *Nutr Rev* **81**, 1267–1289.
11. Zhao R, Zhou L, Wang S, *et al.* (2022) Effect of maternal vitamin D status on risk of adverse birth outcomes: a systematic review and dose-response meta-analysis of observational studies. *Eur J Nutr* **61**, 2881–2907.
12. Bialy L, Fenton T, Shulhan-Kilroy J, *et al.* (2020) Vitamin D supplementation to improve pregnancy and perinatal outcomes: an overview of 42 systematic reviews. *BMJ Open* **10**, e032626.
13. Levy B, O'Callaghan KM, Qamar H, *et al.* (2021) Basal vitamin D status and supplement dose are primary contributors to maternal 25-hydroxyvitamin D response to prenatal and postpartum cholecalciferol supplementation. *J Nutr* **151**, 3361–3378.
14. Vimaleswaran KS, Berry DJ, Lu C, *et al.* (2013) Causal relationship between obesity and vitamin D status: bi-directional Mendelian randomization analysis of multiple cohorts. *PLoS Med* **10**, e1001383.
15. Pereira-Santos M, Costa PR, Assis AM, *et al.* (2015) Obesity and vitamin D deficiency: a systematic review and meta-analysis. *Obes Rev* **16**, 341–349.
16. McAree T, Jacobs B, Manickavasagar T, *et al.* (2013) Vitamin D deficiency in pregnancy – still a public health issue. *Matern Child Nutr* **9**, 23–30.
17. Bodnar LM, Catov JM, Roberts JM, *et al.* (2007) Prepregnancy obesity predicts poor vitamin D status in mothers and their neonates. *J Nutr* **137**, 2437–2442.
18. Drincic AT, Armas LA, Van Diest EE, *et al.* (2012) Volumetric dilution, rather than sequestration best explains the low vitamin D status of obesity. *Obesity (Silver Spring)* **20**, 1444–1448.
19. Walsh JS, Bowles S & Evans AL (2017) Vitamin D in obesity. *Curr Opin Endocrinol Diabetes Obes* **24**, 389–394.
20. Moon RJ, Harvey NC, Cooper C, *et al.* (2016) Determinants of the maternal 25-hydroxyvitamin D response to vitamin D supplementation during pregnancy. *J Clin Endocrinol Metab* **101**, 5012–5020.
21. Alhomaid RM, Mulhern MS, Strain J, *et al.* (2021) Maternal obesity and baseline vitamin D insufficiency alter the response to vitamin D supplementation: a double-blind, randomized trial in pregnant women. *Am J Clin Nutr* **114**, 1208–1218.
22. Devlieger R, Benhalima K, Damm P, *et al.* (2016) Maternal obesity in Europe: where do we stand and how to move forward?: A scientific paper commissioned by the European Board and College of Obstetrics and Gynaecology (EBCOG). *Eur J Obstet Gynecol Reprod Biol* **201**, 203–208.
23. Chen C, Xu X & Yan Y (2018) Estimated global overweight and obesity burden in pregnant women based on panel data model. *PLoS One* **13**, e0202183.
24. NMPA Project Team (2022) *National Maternity and Perinatal Audit: Clinical Report 2022. Based on births in NHS maternity services in England and Wales between 1 April 2018 and 31 March 2019*. London: RCOG.
25. Relph S & NMPA Project Team (2021) *National Maternity and Perinatal Audit: NHS Maternity Care for Women with a Body Mass Index of 30 kg/m^2 or Above. Births between 1 April 2015 and 31 March 2017 in England, Wales and Scotland*. London: RCOG.
26. Richard A, Rohrmann S & Quack Lötscher KC (2017) Prevalence of vitamin D deficiency and its associations with skin color in pregnant women in the first trimester in a sample from Switzerland. *Nutrients* **9**, 260.
27. Vinkhuyzen AAE, Eyles DW, Burne TH, *et al.* (2016) Prevalence and predictors of vitamin D deficiency based on maternal mid-gestation and neonatal cord bloods: the Generation R Study. *J Steroid Biochem Mol Biol* **164**, 161–167.
28. Kiely ME, Zhang JY, Kinsella M, *et al.* (2016) Vitamin D status is associated with uteroplacental dysfunction indicated by pre-eclampsia and small-for-gestational-age birth in a large prospective pregnancy cohort in Ireland with low vitamin D status. *Am J Clin Nutr* **104**, 354–361.
29. Eggemoen ÅR, Falk RS, Knutsen KV, *et al.* (2016) Vitamin D deficiency and supplementation in pregnancy in a multiethnic population-based cohort. *BMC Pregnancy Childbirth* **16**, 7.
30. Briley AL, Barr S, Badger S, *et al.* (2014) A complex intervention to improve pregnancy outcome in obese women; the UPBEAT randomised controlled trial. *BMC Pregnancy Childbirth* **14**, 74.
31. Poston L, Bell R, Croker H, *et al.* (2015) Effect of a behavioural intervention in obese pregnant women (the UPBEAT study): a multicentre, randomised controlled trial. *Lancet Diabetes Endocrinol* **3**, 767–777.
32. The Met Office (2021) When Does Summer Start? https://www.metoffice.gov.uk/weather/learn-about/weather/seasons/summer/when-does-summer-start (accessed January 2022).

33. White SL, Lawlor DA, Briley AL, *et al.* (2016) Early antenatal prediction of gestational diabetes in obese women: development of prediction tools for targeted intervention. *PLoS One* **11**, e0167846.
34. Emmen JM, Wielders JP, Boer AK, *et al.* (2012) The new Roche Vitamin D Total assay: fit for its purpose? *Clin Chem Lab Med* **50**, 1969–1972.
35. Bjerg LN, Halgreen JR, Hansen SH, *et al.* (2019) An evaluation of total 25-hydroxyvitamin D assay standardization: where are we today? *J Steroid Biochem Mol Biol* **190**, 224–233.
36. Armitage P, Berry G & Matthews JNS (2008) *Statistical Methods in Medical Research*. John Wiley & Sons.
37. Goldacre M, Hall N & Yeates DG (2014) Hospitalisation for children with rickets in England: a historical perspective. *Lancet* **383**, 597–598.
38. Julies P, Lynn RM, Pall K, *et al.* (2020) Nutritional rickets under 16 years: UK surveillance results. *Arch Dis Child* **105**, 587.
39. Munns CF, Shaw N, Kiely M, *et al.* (2016) Global consensus recommendations on prevention and management of nutritional rickets. *J Clin Endocrinol Metab* **101**, 394–415.
40. Department of Health (1998) *Nutrition and Bone Health: With Particular Reference to Calcium and Vitamin D. Report on the Subgroup on Bone Health, Working Group on the Nutritional Status of the Population of the Committee on Medical Aspects of Food and Nutrition Policy. Report on Health and Social Subjects 49*. London: TSO.
41. National Institute for Health and Care Excellence (NICE) (2014) Vitamin D: Supplement Use in Specific Population Groups. https://www.nice.org.uk/guidance/ph56 (accessed November 2023).
42. Specker BL, Tsang RC & Hollis BW (1985) Effect of race and diet on human-milk vitamin D and 25-hydroxyvitamin D. *Am J Dis Child* **139**, 1134–1137.
43. Hollis BW, Roos BA, Draper HH, *et al.* (1981) Vitamin D and its metabolites in human and bovine milk. *J Nutr* **111**, 1240–1248.
44. Creo AL, Thacher TD, Pettifor JM, *et al.* (2017) Nutritional rickets around the world: an update. *Paediatr Int Child Health* **37**, 84–98.
45. Crozier SR, Harvey NC, Inskip HM, *et al.* (2012) Maternal vitamin D status in pregnancy is associated with adiposity in the offspring: findings from the Southampton Women's Survey. *Am J Clin Nutr* **96**, 57–63.
46. O'Callaghan KM, Hennessy Á, Hull GLJ, *et al.* (2018) Estimation of the maternal vitamin D intake that maintains circulating 25-hydroxyvitamin D in late gestation at a concentration sufficient to keep umbilical cord sera ≥ 25–30 nmol/l: a dose-response, double-blind, randomized placebo-controlled trial in pregnant women at northern latitude. *Am J Clin Nutr* **108**, 77–91.
47. Grant CC, Stewart AW, Scragg R, *et al.* (2014) Vitamin D during pregnancy and infancy and infant serum 25-hydroxyvitamin D concentration. *Pediatrics* **133**, e143–153.
48. March KM, Chen NN, Karakochuk CD, *et al.* (2015) Maternal vitamin D_3 supplementation at 50 μg/d protects against low serum 25-hydroxyvitamin D in infants at 8 weeks of age: a randomized controlled trial of 3 doses of vitamin D beginning in gestation and continued in lactation. *Am J Clin Nutr* **102**, 402–410.
49. Clemens TL, Adams JS, Henderson SL, *et al.* (1982) Increased skin pigment reduces the capacity of skin to synthesise vitamin D3. *Lancet* **1**, 74–76.
50. Cashman KD, Dowling KG, Škrabáková Z, *et al.* (2016) Vitamin D deficiency in Europe: pandemic? *Am J Clin Nutr* **103**, 1033–1044.
51. Martin CA, Gowda U & Renzaho AM (2016) The prevalence of vitamin D deficiency among dark-skinned populations according to their stage of migration and region of birth: a meta-analysis. *Nutrition* **32**, 21–32.
52. O'Callaghan KM & Kiely ME (2018) Ethnic disparities in the dietary requirement for vitamin D during pregnancy: considerations for nutrition policy and research. *Proc Nutr Soc* **77**, 164–173.
53. Jessiman T, Cameron A, Wiggins M, *et al.* (2013) A qualitative study of uptake of free vitamins in England. *Arch Dis Child* **98**, 587–591.
54. McFadden A, Green JM, McLeish J, *et al.* (2015) Healthy start vitamins—a missed opportunity: findings of a multimethod study. *BMJ Open* **5**, e006917.
55. Yaribeygi H, Maleki M, Sathyapalan T, *et al.* (2020) The molecular mechanisms by which vitamin D improve glucose homeostasis: a mechanistic review. *Life Sci* **244**, 117305.
56. Lips P, Eekhoff M, van Schoor N, *et al.* (2017) Vitamin D and type 2 diabetes. *J Steroid Biochem Mol Biol* **173**, 280–285.
57. Mirhosseini N, Vatanparast H, Mazidi M, *et al.* (2017) The effect of improved serum 25-hydroxyvitamin D status on glycemic control in diabetic patients: a meta-analysis. *J Clin Endocrinol Metab* **102**, 3097–3110.
58. Palacios C, Kostiuk LK & Peña-Rosas JP (2019) Vitamin D supplementation for women during pregnancy. *Cochrane Database Syst Rev 2019* issue 7, CD008873.
59. Roth DE, Leung M, Mesfin E, *et al.* (2017) Vitamin D supplementation during pregnancy: state of the evidence from a systematic review of randomised trials. *BMJ* **359**, j5237.
60. Corcoy R, Mendoza LC, Simmons D, *et al.* (2020) The DALI vitamin D randomized controlled trial for gestational diabetes mellitus prevention: no major benefit shown besides vitamin D sufficiency. *Clin Nutr* **39**, 976–984.
61. Kjalarsdottir L, Tersey SA, Vishwanath M, *et al.* (2019) 1,25-Dihydroxyvitamin D(3) enhances glucose-stimulated insulin secretion in mouse and human islets: a role for transcriptional regulation of voltage-gated calcium channels by the vitamin D receptor. *J Steroid Biochem Mol Biol* **185**, 17–26.
62. Mendoza LC, Harreiter J, Desoye G, *et al.* (2022) The weak relationship between vitamin D compounds and glucose homeostasis measures in pregnant women with obesity: an exploratory sub-analysis of the DALI study. *Nutrients* **14**, 3256.
63. Carter GD, Jones JC, Shannon J, *et al.* (2016) 25-Hydroxyvitamin D assays: potential interference from other circulating vitamin D metabolites. *J Steroid Biochem Mol Biol* **164**, 134–138.
64. Digitale JC, Martin JN & Glymour MM (2022) Tutorial on directed acyclic graphs. *J Clin Epidemiol* **142**, 264–267.
65. Hemmingway A, Kenny LC, Malvisi L, *et al.* (2018) Exploring the concept of functional vitamin D deficiency in pregnancy: impact of the interaction between 25-hydroxyvitamin D and parathyroid hormone on perinatal outcomes. *Am J Clin Nutr* **108**, 821–829.
66. Davis S, Lyles E, Shary JR, *et al.* (2023) Post hoc analysis of national institute of child health and human development vitamin-D Pregnancy cohort and the role of functional vitamin-D deficiency in pregnancy. *Am J Perinatol* (Epublication ahead of print version 28 June 2023).
67. Scholl TO, Chen X & Stein TP (2014) Maternal calcium metabolic stress and fetal growth. *Am J Clin Nutr* **99**, 918–925.
68. Scholl TO, Chen X & Stein TP (2013) Vitamin D, secondary hyperparathyroidism, and preeclampsia. *Am J Clin Nutr* **98**, 787–793.

British Journal of Nutrition