

Original article

Serum 25-hydroxyvitamin D and IgE – a significant but nonlinear relationship

Background: Hormonal vitamin D system affects the determination of T-cell responses. It is unknown if there is an association between vitamin D status and allergic conditions. Our aim was to investigate differences in serum IgE concentrations by vitamin D status [measured by 25(OH)D] and by a genetic variation in a key vitamin D activation enzyme (CYP27B1) previously shown to be associated with type 1 diabetes.

Methods: 9377 participants in the 1958 British birth cohort completed a biomedical assessment at 45 years of age; 7288 eligible participants had data on 25(OH)D and IgE, with 6429 having further information on CYP27B1 genotype (–1260C > A).

Results: There was a nonlinear association between 25(OH)D and IgE (P -value for curvature = 0.0001). Compared with the reference group with the lowest IgE concentrations [25(OH)D 100–125 nmol/l], IgE concentrations were 29% higher (95% CI 9–48%) for participants with the 25(OH)D < 25 nmol/l, and 56% higher (95% CI 17–95%) for participants with 25(OH)D > 135 nmol/l (adjusted for sex, month, smoking, alcohol consumption, time spent outside, geographical location, social class, PC/TV time, physical activity, body mass index and waist circumference). CYP27B1 genotype was associated with both 25(OH)D (difference for A vs. C allele: 1.88%, 95% CI 0.37–3.4%, P = 0.01) and IgE concentrations (–6.59%, –11.6% to –1.42%, P = 0.01).

Conclusions: These data suggest that there may be a threshold effect with both low and high 25(OH)D levels associated with elevated IgE concentrations. The same CYP27B1 allele that is protective of diabetes was associated with increased IgE concentrations.

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Hormonal vitamin D system is known to be involved in immune regulation and the active form, 1,25-dihydroxyvitamin D [1,25(OH)₂D], is believed to affect dendritic cell maturation and subsequent determination of T-cell responses. There is accumulating experimental evidence and epidemiological data suggesting that vitamin D may reduce the risk of various immunological diseases including type 1 diabetes (1, 2), multiple sclerosis (3) and pre-eclampsia (4, 5), all of which are characterized by upregulation of T-helper type 1 (Th1) responses. Reduced secretion of Th1-type cytokines IL-2, and INF- γ , and an increase in Th2-type IL-4 has been observed in several experiments after treatment with 1,25(OH)₂D; hence, a shift in the Th1–Th2 polarization could provide one explanation for the reduced risks of Th1-dominated conditions (6, 7). Allergies are characterized by upregulation of Th2 responses (thereby presenting the opposite end of immune deviation compared with Th1-mediated conditions) (8). However, evidence for an association between vitamin D metabolism and allergic conditions is

inconsistent and both beneficial and detrimental influences have been suggested.

Direct support for involvement of vitamin D metabolism in the development of allergic conditions has been obtained from genetic studies showing an association between vitamin D receptor (VDR) gene polymorphisms with atopy and asthma (9–11). An interesting experiment in mice reported dual influences for 1,25(OH)₂D administration: 1,25(OH)₂D increased allergen-induced T-cell proliferation, IL-4 and IL-13 cytokine secretion and serum IgE production; however, airway eosinophilia (a key pathophysiological feature of asthma) was reduced, possibly suggesting beneficial influences through a reduced inflammatory response (6). Data from humans are sparse, with two recently published studies reporting reduced early childhood wheezing in offspring to mothers who had higher compared with lower vitamin D intakes (12, 13), while another was suggestive of a greater prevalence of early eczema and asthma in a sample of offspring to mothers with higher 25-hydroxyvitamin D

[25(OH)D, an indicator for vitamin D status] concentrations during pregnancy (14). There are also some observational data suggesting a greater prevalence of allergies in children who have received vitamin D supplements early in life (15). Earlier cross-sectional analyses on adults have reported an association between higher 25(OH)D concentrations with better lung function (16), but also with a higher prevalence of allergic rhinitis (17). The purpose of this study therefore was to investigate association between 25(OH)D with serum IgE concentrations, and to determine whether there is evidence for a threshold effect. Moreover, information was available for a genetic variation in the key vitamin D activation enzyme (namely CYP27B1 –1260C/A) which had previously been shown to be associated with the risk of type 1 diabetes (18). If this variant also influences IgE concentrations, it could point towards an important genetic regulation by the vitamin D metabolic system where some heredity has already been found (19).

Methods

Participants are from the 1958 British birth cohort, which included all births in England, Scotland and Wales during 1 week in March 1958 ($n = 16\,751$) (20). Between September 2002 and April 2004, at 45 years of age [44 (31.1%) to 46 years (0.4%)], a target population of 11 971 individuals currently living in Britain were contacted: 78% ($n = 9377$) completed a questionnaire and 7 591 (80%) also provided blood samples from which 25-hydroxyvitamin D was measured (20, 21). The 1958 cohort is largely a Caucasian population (98%); for these analyses 154 individuals of other ethnicity groups were excluded. We further excluded one participant who was pregnant at the time of survey and 148 participants with missing data on IgE at the age of 45 years. Main analyses were carried out among 7288 individuals with full data on 25-hydroxyvitamin D and IgE (age 45 years), of whom 6429 also had information on CYP27B1 genotype. Written consent for the use of information in medical studies was obtained from the cohort members. The 45-year biomedical survey was approved by the South-East Multi-Centre Research Ethics Committee (ref: 01/1/44).

Laboratory and genetic analyses

Venous blood samples were obtained without prior fasting and posted to collaborating laboratories. Total IgE was assayed using the HYTEC-automated enzyme immunoassay (22). Specific IgE to cat, grass and dust were also measured if total IgE was greater than 30 kU/l but automatically coded zero if total IgE was less than or equal to 30 kU/l (23). Specific IgE production was defined as at least one specific IgE greater than 0.3 kU/l. 25-hydroxyvitamin D was measured using automated application of the IDS OCEIA ELISA on the BEP2000 analyser (Dade-Behring, Marburg, Germany) and standardized according to the mean of the Vitamin D External Quality Assurance Survey (DEQAS) (24). CYP27B1 –1260C > A (rs10877012, located in the 5'-region) was genotyped using TaqMan (Assay-by-design; Applied Biosystems, Warrington, UK) (18). All genotypes were scored by two researchers independently to minimize error. There was no deviation from Hardy–Weinberg equilibrium above that expected at random ($P > 0.05$).

Demographic, lifestyle and social covariates

The time of year of blood sampling was categorized by month. Information on current (age 45 years) region of residence was based on Government Office Regions divided into sections as follows: southern (south-east, south-west, greater London), middle (east Anglia, Midlands and Wales), England (north, north-west, Yorkshire and Humber) and Scotland. Information on the frequency of physical activity (any type of sport or leisure activity including physical exercise) (25) was collected at 42 years, and coded as '< 2–3 times per month', 'once per week', '2–3 times per week' or '4–7 times per week'. Intensity of recreational activity was based on information collected at age 45 years [in MET (h/week): a MET (metabolic equivalent) is the ratio of the energy cost of an activity to resting metabolic rate]. An additional category was created for implausibly high values (participants with weekly recreation hours of 3 SD above the gender mean). Usual time spent outdoors in daylight hours and time spent watching a television/using a computer were reported at age 45 years and coded as '< 1 h', '1–2 h' and '≥ 3 h'. Smoking was recorded as 'none', 'ex-smoker', '1–19 cigarettes per day' and '≥ 20 cigarettes per day' based on smoking history at ages 23, 33 and 42 years. (26) Frequency and amount of alcohol consumption were reported at 45 years and coded as 'not in the last month', 'less than once per month', '2–4 times per month', '2–3 times per week', '> 4 times per week'; quantity was converted to standard drinks and coded as 'nondrinker', 'less than 7 drinks', '7–14 drinks', '14–21 drinks' and '≥ 21 drinks' per week. Socio-economic position at birth (1958) and at age 42 years was assessed using the Registrar General's occupational classification categorized as I and II (professional/managerial), III nonmanual, III manual and IV and V (unskilled manual). If information was missing from 42 years, it was supplemented with data collected at 33 years. Individuals who were institutionalized, retired or long-term unemployed were classified in a separate category. Waist circumference was measured by the nurse midway between the costal margin and iliac crest. Body mass index (BMI) was calculated from weight and height at 45 years of age.

Statistical analysis

Natural log transformation was used for 25(OH)D and IgE to achieve normal distributions and for calculating geometric means. Variations in continuous (log transformed) outcomes were evaluated by linear regression and in dichotomous outcomes for specific IgE production by logistic regression. If multiplied by 100, β coefficients from the linear regression analyses on log-transformed outcomes can be interpreted as percentage difference compared with the reference group (27). P -values are from likelihood ratio tests (LRT), tests for trend (LRT trend) and Pearson's chi-squared test where appropriate.

Initial analyses included graphical examination of data, evaluation of curvature for 25(OH)D and IgE through inclusion of quadratic terms and tests for interaction term between gender and 25(OH)D. In the analyses on CYP27B1 genotype and 25(OH)D, model of multiplicative allelic effects was assumed as this model was not significantly different from a full genotype model (LRT $P = 0.38$). For allele analysis, the slope of the genotype was used. In the models investigating effect modification by CYP27B1 genotype on the association between 25(OH)D and IgE/specific IgE production, 25(OH)D was included as a categorized indicator [< 25, 25–49.9, 50–74.9, 75–99.9, 100–124.9, 125–134.9 and 135–max nmol/l] to allow for the nonlinear association between 25(OH)D and IgE. Main modelling was performed in two phases: (i) adjusting for sex and month of measurement; (ii) adjusting for demographic, lifestyle, social confounders and obesity as indicated by BMI and waist circumference. Missing values

in lifestyle, social and obesity confounders were imputed after determining predictors of 'missingness'. All analyses were carried out using STATA, version 9.

Results

Prevalence of specific IgE production and average IgE concentrations were higher in men compared with that in women ($P < 0.001$ for both, Table 1). Of the lifestyle indicators, only smoking was associated with both average IgE concentration and specific IgE production, while alcohol consumption was associated with average IgE only. Higher family social class in 1958 was associated with a greater prevalence of specific IgE production. Some variation in the average and prevalence of low (< 25 nmol/l) 25(OH)D concentrations was observed by all lifestyle and background characteristics, while prevalence of a high concentration (> 135 nmol/l) was not associated with sex, smoking, physical activity or social class. Both 25(OH)D concentration and IgE showed evidence of seasonal variations, with the lowest concentrations in late winter/early spring and the highest in August to September (LRT for seasonal trend $P \leq 0.002$ for both, Fig. 1). CYP27B1 genotype (rs10877012) did not vary by geographical location or other characteristics shown in Table 1 ($P = 0.03$ for alcohol consumption, $P \geq 0.16$ for all other comparisons); the statistical association between CYP27B1 genotype and alcohol consumption reflecting an unexpectedly high proportion of CC carriers among participants consuming two to four times per month rather than any systematic differences (data not shown). There was an association between CYP27B1 genotype and 25(OH)D concentration (difference for A vs. C allele: 1.88%, 95% CI 0.37–3.40%, $P = 0.01$). However, there was a suggestion of effect modification by season ($P = 0.04$), and during summer/autumn 25(OH)D concentrations were on average 5% higher in CC compared with that in AA carriers (95% CI 1–8%, $P = 0.009$ after full adjustment), there was no association during winter/spring ($\beta -0.03$, -8% to 3% , $P = 0.64$).

There was a nonlinear association between vitamin D status and average IgE concentration (LRT curvature $P = 0.0001$, Fig. 2). There was little variation in IgE when 25(OH)D concentrations were between 30 and 120 nmol/l, while significant increases in IgE were observed both for participants with the lowest (< 25 nmol/l) and highest (> 135 nmol/l) 25(OH)D concentrations. In linear regression analyses, IgE concentrations were 29% higher (95% CI 9–48%) for participants with 25(OH)D < 25 nmol/l compared with the 100–125 nmol/l group (adjusted for sex, month, smoking, alcohol consumption, time spent outside, geographical location, social class, PC/TV time, physical activity, body mass index and waist circumference). Moreover, the small group of participants with 25(OH)D concentrations

> 135 nmol/l ($n = 58$) had after full adjustment 56% higher IgE concentrations (95% CI 17–95%) and an increased specific IgE production (OR 2.30, 95% CI 1.29–4.10).

CYP27B1 genotype was associated with IgE, and concentrations were 7% (95% CI 1–12%) lower in the carriers of the C allele compared with those in the carriers of the A allele ($P = 0.01$) (Table 2). No significant association, however, was observed between CYP27B1 and specific IgE production, although the risk was slightly reduced in homozygote CC carriers (OR 0.85; 0.71–1.01). Adjustment for 25(OH)D concentrations slightly attenuated the association between CYP27B1 and IgE, but did not fully explain it (adjusted $P = 0.03$, data not shown). We observed no evidence for effect modification by CYP27B1 genotype in the association between 25(OH)D and IgE serum concentrations or specific IgE production risk (LRT interaction $P > 0.3$ for all comparisons).

Discussion

Using information from the large nationwide 1958 British birth cohort, we report evidence for an association between current vitamin D status, genetic variation in the vitamin D activation enzyme CYP27B1 and serum IgE concentrations, which could suggest that both very low and very high vitamin D concentrations may be associated with aggravated allergic responses.

Vitamin D is a precursor to a hormone that is known to regulate the expression of up to 900 genes (28). Consequently, the metabolic effects of variations in vitamin D status and intake are believed to be wide-ranging and complex. Reduction in inflammation (29), influences on regulatory T-cell activity (and thereby the balance between Th1- and Th2-type immunological responses) (30) and influences on cell growth and proliferation (31) could all be involved in establishing the physiologic effects of vitamin D on allergy risk. Our novel finding for a U-shaped association between 25(OH)D concentrations with IgE and specific IgE production supports dual influences for vitamin D metabolism on allergy risk. Evidence for both benefits and potentially harmful influences has been obtained from a previous animal experiment where 1,25(OH)₂D administration reduced airway eosinophilia (suggesting beneficial influences through a reduced inflammatory response), while allergen-induced T-cell proliferation, IL-4 and IL-13 cytokine secretion, and serum IgE production were increased (6). Findings from previous studies in humans have been inconsistent; some have proposed an increased occurrence of allergies/atopy by higher concurrent (17) or maternal 25(OH)D concentrations (14), and by high-dose vitamin D supplementation early in life (15, 32), while others suggest that risk of

Table 1. 25-hydroxyvitamin D, immunoglobulin E and prevalence of atopy by sex, season, lifestyle and social factors in the 1958 British birth cohort ($n = 7288$)

	Number (%)	25-Hydroxyvitamin D (nmol/l)			IgE, geometric mean† (95% CI)	Specific IgE production‡, % (n)
		Geometric mean* (95% CI)	<25 nmol/l %* (n)	>135 nmol/l %* (n)		
Sex						
Men	3639 (49.9)	53.1 (52.4, 53.9)	6.5 (237)	0.7 (27)	38.2 (36.5, 40.0)	33.7 (1227)
Women	3649 (50.1)	51.1 (50.3, 51.9)	9.2 (336)	0.9 (31)	25.3 (24.2, 26.4)	23.5 (856)
P-value		0.0001	<0.0001	0.59	<0.0001	<0.0001
Season						
Dec–Feb	1270 (17.4)	40.8 (39.7, 41.9)	16.8 (213)	0.2 (3)	32.4 (30.0, 34.9)	28.4 (360)
Mar–May	1536 (21.1)	41.5 (40.6, 42.4)	14.0 (217)	0.1 (1)	29.0 (27.0, 31.2)	28.5 (437)
Jun–Aug	1717 (23.6)	57.2 (56.2, 58.3)	4.2 (72)	0.5 (9)	32.1 (30.1, 34.2)	27.8 (478)
Sep–Nov	2765 (37.9)	62.4 (61.5, 63.4)	2.6 (71)	1.6 (45)	31.0 (29.4, 32.7)	29.2 (808)
P-value		<0.0001	<0.0001	<0.0001	0.13	0.77
Time spent outdoors						
<1 h/day	1917 (26.3)	47.2 (46.3, 48.2)	9.6 (215)	0.3 (5)	29.1 (27.3, 30.9)	29.0 (555)
1–2 h/day	1901 (26.1)	51.4 (50.4, 52.3)	8.2 (154)	0.6 (12)	31.3 (29.4, 33.4)	28.5 (542)
≥3 h/day	2895 (39.7)	55.5 (54.6, 56.4)	6.2 (143)	1.3 (40)	31.8 (30.2, 33.4)	28.6 (827)
Unknown	575 (7.9)	50.4 (48.6, 52.3)	10.1 (61)	0.2 (1)	34.1 (30.5, 38.2)	27.7 (159)
P-value		<0.0001	0.003	0.004	0.11	0.10
Smoking						
None	3369 (46.2)	53.6 (52.9, 54.4)	6.5 (219)	0.9 (29)	28.3 (27.0, 29.6)	30.0 (1010)
Ex-smoker	1998 (27.4)	54.1 (53.2, 55.1)	5.7 (112)	0.5 (10)	28.9 (27.2, 30.8)	27.2 (544)
1–19 cigarettes per day	838 (11.5)	49.4 (47.9, 51.0)	10.7 (92)	1.3 (10)	41.9 (38.0, 46.2)	29.1 (244)
≥ 20 cigarettes per day	846 (11.6)	44.5 (43.2, 46.0)	15.8 (131)	1.1 (9)	38.8 (35.1, 42.9)	25.1 (212)
Unknown	237 (3.3)	51.1 (48.3, 53.9)	8.1 (19)	0 (0)	35.3 (29.7, 41.9)	30.8 (73)
P-value		<0.0001	<0.0001	0.49	<0.0001	0.006
Alcohol consumption						
Nondrinker	449 (6.2)	44.9 (43.0, 46.9)	12.2 (62)	0.2 (1)	31.1 (26.9, 35.8)	25.6 (115)
Light: < 7 drinks/week	3495 (48.0)	51.7 (51.0, 52.4)	7.7 (279)	0.5 (18)	29.2 (27.9, 30.6)	27.4 (957)
Moderate: 7–14 drinks/week	1824 (25.0)	54.9 (53.9, 56.0)	6.3 (111)	1.2 (21)	31.1 (29.2, 33.1)	29.6 (539)
Heavy: 14–21 drinks/week	808 (11.1)	55.1 (53.5, 56.7)	5.4 (43)	1.2 (9)	33.8 (30.6, 37.3)	30.2 (244)
Very heavy: > 21 drinks/week	681 (9.3)	49.3 (46.9, 51.7)	12.9 (73)	1.1 (8)	37.0 (32.5, 42.2)	32.2 (219)
Unknown	31 (0.4)	47.2 (41.3, 53.9)	12.7 (5)	3.8 (1)	37.8 (23.0, 62.0)	29.0 (9)
P-value		<0.0001	0.49	0.002	0.0001	0.44
Recreation MET hours						
1st quartile	1771 (24.3)	46.0 (45.0, 47.0)	12.1 (225)	0.4 (8)	31.4 (29.3, 33.7)	26.3 (465)
2nd quartile	1768 (24.3)	51.5 (50.6, 52.5)	7.4 (135)	0.8 (14)	30.3 (28.3, 32.3)	29.1 (514)
3rd quartile	1770 (24.3)	54.4 (53.3, 55.4)	6.1 (109)	0.8 (14)	30.0 (28.1, 32.1)	27.5 (487)
4th quartile	1768 (24.3)	56.6 (55.5, 57.7)	5.3 (84)	1.0 (20)	31.5 (29.5, 33.7)	31.0 (547)
Implausible§	90 (1.2)	59.2 (55.0, 63.8)	3.6 (3)	1.2 (1)	35.6 (27.1, 46.8)	38.9 (35)
Unknown	121 (1.7)	47.8 (43.9, 52.1)	13.3 (17)	0.8 (1)	36.6 (28.8, 46.6)	28.9 (35)
P-value		<0.0001	<0.0001	0.11	0.87	0.18
Adult social class (2000)						
I and II (high)	2955 (40.6)	52.6 (51.8, 53.5)	7.4 (214)	0.8 (22)	30.7 (29.1, 32.3)	30.5 (902)
III nonmanual	1503 (20.6)	52.4 (51.0, 53.8)	7.5 (121)	0.8 (10)	29.2 (26.9, 31.7)	25.2 (379)
III manual	1384 (19.0)	52.7 (51.2, 54.3)	8.4 (93)	1.4 (16)	32.2 (29.4, 35.4)	29.3 (406)
IV and V	1135 (15.6)	50.6 (49.3, 51.9)	8.6 (101)	0.7 (8)	34.1 (31.1, 37.3)	26.4 (300)
Other¶	311 (4.3)	46.8 (44.5, 49.3)	14.6 (44)	0.7 (2)	37.2 (32.0, 43.4)	30.9 (96)
P-value		0.0003	0.004	0.87	0.008	0.20

P-values from LR test for trend, from linear regression for continuous outcomes and from logistic regression for dichotomous outcomes, adjusted for month and sex.

*Standardized by sex and season.

†Standardized by sex.

‡Defined as at least one specific IgE (cat, grass or dust) greater than 0.3 kU/l.

§Participants with weekly recreation hours of 3 SD above the gender mean.

¶Includes cohort members who are institutionalized, retired, unemployed and others.

wheezing is reduced in offspring to mothers with higher maternal dietary vitamin D intake (12, 13). It could be argued that methodological limitations in these studies (loss to follow-up and residual confounding) may

explain the observed discrepancies; however, it is also possible that the inconsistency reflects dual influences of vitamin D on allergic conditions as suggested by the U-shaped relation reported in this study.

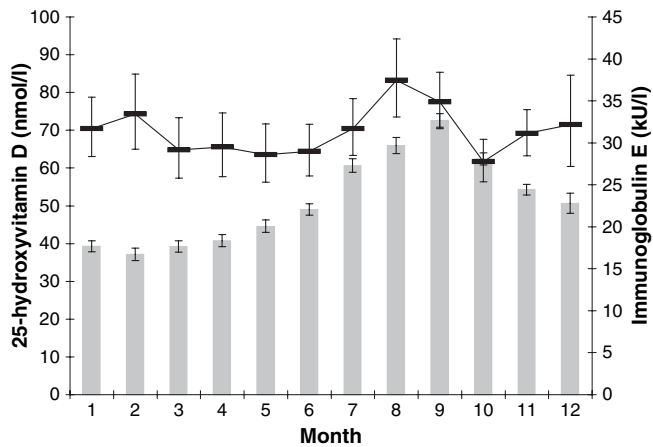


Figure 1. Seasonal variation in 25-hydroxyvitamin D (grey bars) and immunoglobulin E (tick marks) concentrations in the 1958 British cohort at the age of 45 years. Data are sex-adjusted geometric mean values, 95% confidence intervals given in error bars.

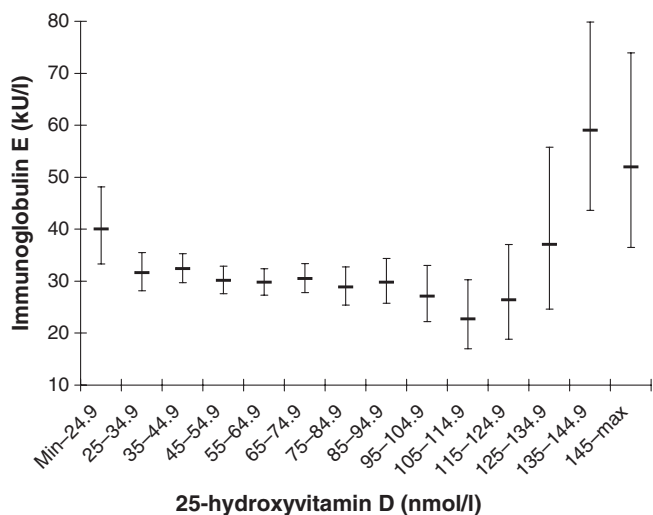


Figure 2. Variation in the average immunoglobulin E by 25-hydroxyvitamin D concentration in the 1958 British cohort at the age of 45 years. Data are season and sex-adjusted geometric mean values, 95% confidence intervals given in error bars.

U-shaped distributions are not uncommon in biological systems. The mutation–selection–drift balance is an example of an U-shaped distribution, which describes the frequency distribution of an allele in a model with two neutral alleles that mutate into each other – the ‘love it’ or ‘hate it’ effect. Analyses on CYP27B1 genotype showed that the same allele that has been found to be protective of type 1 diabetes (18) was also associated with higher IgE concentrations. This could indicate that the Th1/Th2 paradigm may explain some of the effects of vitamin D on the risk of allergy and type 1 diabetes, and be suggestive of a genetically coded vitamin D metabolism and/or

sensitivity. The observation for an association between CYP27B1 genotype and 25(OH)D concentration during summer/autumn (but not winter/spring) suggests that the expression of this gene may vary by season, perhaps reflecting different affinity to dietary/sunlight-derived vitamin D. Evidence for season-dependent heritability of 25(OH)D has been previously obtained from a study on asthma families, where in agreement with our observations, a genetic association with 25(OH)D was stronger in summer compared with that in winter (19). Interestingly, also the seasonal association in 25(OH)D and IgE concentrations seemed to reflect the period of active sun-induced synthesis (June to October), suggesting that effect modification by season on the influences of 25(OH)D deserves further study.

Methodological considerations

The main strength of the study lies in the large sample of participants with information available on 25-hydroxyvitamin D, IgE and a wide range of relevant lifestyle and social confounders. Due to the exceptional data available from this cohort, we were able to take multiple factors into account in our analyses and control for important potential confounders such as time spent outdoors and physical activity among other demographic, lifestyle and social variations. Our study was restricted to Caucasians thereby reducing problems of severe population stratification. However, our findings cannot be extrapolated to non-White ethnic groups, given possible heterogeneity by ethnic origin on the association between 25(OH)D and allergy (17). As recently described, some sample attrition has occurred during the survey and, although the present sample remains broadly representative of the surviving cohort, there is some under-representation of specific minority groups (33). A key feature with the current study is that it is based on cross-sectional data, and hence it is not possible to demonstrate causality for the observed elevations in IgE concentrations at the extremes of 25(OH)D concentrations. It can be argued that support for a causal relation between vitamin D metabolism and IgE concentrations was obtained from the observed association with CYP27B1 genotype (34); however, it is evident that the underlying mechanisms are complex and require further study.

In the current study, increases in IgE concentrations were observed at 25(OH)D concentrations of 135 nmol/l or higher. However, there is well-known variation in 25(OH)D concentrations measured by different methods, and the assay used in the current study (IDS EIA) is known to underestimate absolute 25(OH)D concentrations (24). Values were standardized to the mean of Vitamin D Quality Assessment Scheme, and, although this made the average concentrations (and the observed prevalence rates for hypovitaminosis D) comparable with those that would have been obtained by other commonly used methods (24), it is possible that at the extreme high

Table 2. Association of 25-hydroxyvitamin D concentration and CYP27B1 genotype with immunoglobulin E concentration and the prevalence of specific IgE production in the 1958 British birth cohort study

	Immunoglobulin E			Specific IgE production*		
	N	Adjusted for sex and month, β † (95% CI)	Fully adjusted‡, β † (95% CI)	N (%)	Adjusted for sex and month, OR (95% CI)	Fully adjusted‡, OR (95% CI)
25(OH)D						
<25	573	0.38 (0.18, 0.57)	0.29 (0.09, 0.48)	170 (29.7)	1.34 (0.98, 1.82)	1.34 (0.97, 1.85)
25–49.9	2475	0.16 (0.00, 0.32)	0.12 (–0.04, 0.28)	701 (28.2)	1.18 (0.91, 1.53)	1.15 (0.88, 1.51)
50–74.9	2613	0.11 (–0.04, 0.27)	0.10 (–0.05, 0.26)	751 (28.7)	1.17 (0.91, 1.51)	1.15 (0.89, 1.48)
75–99.9	1173	0.02 (–0.14, 0.19)	0.02 (–0.14, 0.18)	328 (28.0)	1.07 (0.82, 1.40)	1.06 (0.81, 1.39)
100–124.9	356	Reference	Reference	98 (27.5)	Reference	Reference
125–134.9	40	–0.12 (–0.58, 0.33)	–0.17 (–0.62, 0.29)	9 (22.5)	0.73 (0.34, 1.61)	0.74 (0.33, 1.62)
≥135	58	0.61 (0.22, 0.99)	0.56 (0.17, 0.95)	26 (44.8)	2.23 (1.26, 3.96)	2.30 (1.29, 4.10)
P-value§		<0.0001	0.002		0.06	0.05
CYP27B1						
Allele	6429	–0.07 (–0.12, –0.01)	–0.06 (–0.11, –0.01)	1854 (28.8)	0.94 (0.86, 1.02)	0.93 (0.86, 1.01)
P-value§		0.01	0.03		0.12	0.10
Genotype						
A/A	749	Reference	Reference	232 (31.7)	Reference	Reference
C/A	2814	–0.14 (–0.25, –0.03)	–0.13 (–0.24, –0.02)	786 (28.5)	0.87 (0.73, 1.03)	0.86 (0.72, 1.03)
C/C	2866	–0.17 (–0.28, –0.05)	–0.15 (–0.26, –0.04)	799 (28.4)	0.85 (0.71, 1.01)	0.84 (0.70, 1.00)
P-value§		0.01	0.03		0.18	0.15

*Defined as at least one specific IgE (cat, grass or dust) greater than 0.3 kU/l.

†When multiplied by 100, β coefficients can be interpreted as percentage difference compared with the reference group.

‡Adjusted for sex, month, smoking, alcohol consumption, time spent outside, geographical location, social classes, PC/TV time, physical activity, BMI and waist circumference.

§P-values from likelihood ratio test.

of 25(OH)D concentrations (> 135 nmol/l) values remain underestimated, and hence, the absolute cut-off needs to be interpreted with caution. Interestingly, also the earlier study suggesting an association between high maternal 25(OH)D concentrations of (> 75 nmol/l) and an increased atopy risk (14) used IDS EIA, which may explain the apparently very low threshold for the proposed adverse influences.

Finally, although high 25(OH)D (> 135 nmol/l) was associated with a 56% increase in IgE concentrations and over twofold greater prevalence of specific IgE production in our study, it could be argued that the observed elevations in IgE by increasing 25(OH)D are not clinically relevant. While these data do not demonstrate that the observed elevations in IgE concentrations in participants with the highest 25(OH)D levels are clinically relevant *per se*, supported by the association with CYP27B1 genotype and other evidence suggesting increases in allergy related responses (6, 14, 15, 17), these data highlight the importance of considering possible adverse influences on allergy risk in studies proposing to use high-dose vitamin D supplementation, especially in patient groups prone to allergic diseases.

Conclusions

Discussion on the optimal 25-hydroxyvitamin D concentrations is ongoing. In addition to many positive

effects of having a balanced 25-hydroxyvitamin D concentration, our data are in line with other studies suggesting 75–100 nmol/L as a lower threshold of an optimal serum level (35–38). Our results also suggest that there may be a threshold effect in relation to IgE concentrations with both extremely low and extremely high 25(OH)D concentrations, a finding requiring confirmation by prospective and experimental studies. Clinical trials using large-dose vitamin D supplementation should be monitored for possible increases in IgE concentrations and even allergic responses. Effects may be predicted by CYP27B1 genotypes, while the full network of interacting variants needs to be explored.

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