British Journal of Nutrition (2011), **106**, 1433–1440
doi:10.1017/S0007114511001991

Vitamin D status has a linear association with seasonal infections and lung function in British adults

Diane J. Berry, Kathryn Hesketh, Chris Power and Elina Hyppönen*

Centre for Paediatric Epidemiology and Biostatics and MRC Centre of Epidemiology for Child Health, UCL Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK

(Received 19 October 2010 – Revised 14 March 2011 – Accepted 17 March 2011 – First published online 6 June 2011)

Abstract

Higher vitamin D concentrations have been proposed as a protective 'seasonal stimulus' against influenza, and there are suggestions for associations with other aspects of respiratory health. The aim of the present study was to investigate the relationship of current vitamin D status (measured by 25-hydroxyvitamin D, 25(OH)D) with respiratory infections and lung function. We used cross-sectional data from 6789 participants in the nationwide 1958 British birth cohort who had measurements of 25(OH)D, lung function (forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC)) and respiratory infections available from the age of 45 years. In this population, the prevalence of respiratory infections had a strong seasonal pattern in the opposite direction to the pattern for 25(OH)D concentrations. Each 10 nmol/l increase in 25(OH)D was associated with a 7 % lower risk of infection (95 % CI 3, 11 %) after adjustment for adiposity, lifestyle and socio-economic factors. For FEV_1 and FVC, each 10 nmol/l increase in 25(OH)D was associated with 8 (95 % CI 3, 13) ml and 13 (95 % CI 7, 20) ml higher volume, respectively, after controlling for covariates. Associations of 25(OH)D with FEV_1 and FVC were only slightly attenuated after further adjustment for infection and other respiratory illness. In conclusion, vitamin D status had a linear relationship with respiratory infections and lung function. Randomised controlled trials are warranted to investigate the role of vitamin D supplementation on respiratory health and to establish the underlying mechanisms.

Key words: 25-Hydroxyvitamin D: Respiratory infections: Lung function

During the past decade, understanding of the actions of the hormonal vitamin D system has greatly improved, and there has been much interest in its potential role for respiratory health. Vitamin D is mostly obtained through UV-B sunlight-induced synthesis in the skin, and consequently, circulating serum concentrations of 25-hydroxyvitamin D (25(OH)D, a marker for nutritional vitamin D status) demonstrate strong seasonal patterns[1]. As such, it has been suggested that vitamin D may be a 'seasonal stimulus'[2] partly explaining wintertime peaks in the incidence of influenza[3]. The lungs are the first line of defence for airborne infections, and there is evidence that the epithelial cells in the lung convert inactive vitamin D to its active form as part of the immune response[4]. It is possible that the immune response to infections in the lung is dependent on adequate 25(OH)D concentrations.

The evidence from observational studies of a role for vitamin D in allergies and asthma appears to be equivocal. Some studies have shown a reduction in early childhood wheezing for offspring born to mothers with higher *v.* lower vitamin D intakes[5,6]. In contrast, higher maternal 25(OH)D concentrations[7] and high dose of vitamin D supplementation in infancy[8,9] have been associated with an increased risk of asthma and eczema later in life. Also, cross-sectional examinations in adults suggest increases in the prevalence of allergic rhinitis[10] and in the circulating IgE concentrations[11] with increases in 25(OH)D concentrations. However, a dose–response relationship between current 25(OH)D concentrations and lung function (measured by forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC)) has been suggested in a cross-sectional analysis in the Third National Health, Nutrition and Examination Survey III[12]. A recent study on this same population has also suggested a lower prevalence of respiratory infections by higher 25(OH)D concentrations[13]. These findings have yet to be replicated, particularly in studies that overcome the limitations of previous work by taking account of seasonal variations, related lifestyle or health factors potentially affecting the observed associations.

Therefore, the aim of the present study was to investigate the association of serum 25(OH)D concentrations with

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; CRP, C-reactive protein; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; RCT, randomised controlled trial; SEP, socio-economic position.

* **Corresponding author:** E. Hyppönen, fax +44 207 905 2793, email e.hypponen@ich.ucl.ac.uk

seasonal infections and lung function using information from a large, nationally representative cohort of British adults. The cohort has detailed information on relevant social and lifestyle factors, respiratory health and medications, and 25(OH)D measurements, which are distributed across the full seasonal range[1].

Participants and methods

Participants in the cohort are all births in England, Scotland and Wales during 1 week in March 1958 (*n* 17 416). A detailed description of the study has been provided elsewhere[14]. At the age of 45 years, a target population, 11 971 individuals currently living in Britain, were invited to participate in a biomedical assessment that took place between September 2002 and April 2004; of these, 78 % (*n* 9377) completed a questionnaire. The study participants were largely representative of the original cohort; however, as reported previously, certain minorities were under-represented[15]. We excluded individuals from non-Caucasian origin (*n* 188) and two participants who were pregnant at the time of the study. Blood samples for 25(OH)D measurements were obtained for 7431 participants, of whom 91 % also reported the prevalence of respiratory infection and had full data on lung function, leaving 6789 for the analyses. The 45-year biomedical survey was approved by the South-East Multi-Centre Research Ethics Committee, and written consent for the use of information in medical research studies was obtained from the participants.

The 25(OH)D concentrations were measured by an automated Immunodiagnostic Systems Ltd OCTEIA assay with a Dade-Behring BEP2000 analyser (Dade-Behring, Marburg, Germany) and standardised according to the mean vitamin D external quality assessment scheme[16]. C-reactive protein (CRP) was assayed by nephelometry (Dade Behring) on citrated plasma samples after one thaw cycle, and total IgE was assayed by the HYTEC automated enzyme immunoassay (HYCOR Biomedical Inc., Garden Grove, CA, USA). Spirometry was performed according to the criteria of the American Thoracic Society[17], in the standing position, without nose clips, using the Vitalograph Mirco spirometer (Vitalograph, Maids Moreton, UK). At least three (up to five) spirograms were captured until three satisfactory blows were obtained (assessed by best-test variation, where the sum of FEV_1 and FVC was <5 %). Readings with a best-test variation >10 % or values with standardised residuals $>\pm 3$ standard errors were excluded. The highest technically satisfactory values for FEV_1 and FVC from each set of spirograms were used in the analysis. Information on respiratory infections (influenza, pneumonia, bronchitis or severe cold) during the past 3 weeks, use of respiratory medication (British National Formulary (BNF) code 3) and antibiotics for the respiratory system (BNF codes 5.1.1–5.1.5, 5.1.7 and 5.1.9) were self-reported at the age of 45 years, when the participants also reported whether they had used an inhaler within the last 24 h. Past diagnoses of asthma, allergies and bronchitis were ascertained from reports at 42 years of 'ever' diagnosed or within the last 12 months.

Socio-economic position (SEP) was categorised using the Registrar General's Classification into the following classes: I and II, managerial and professional; III, non-manual; III, manual; IV and V, manual unskilled, including individuals who were institutionalised, retired or long-term unemployed. SEP in childhood was based on father's occupation at birth; in adulthood, it was based on occupation at the age of 42 years (or 33 years if data at the age of 42 years were missing). Smoking was based on smoking history recorded at ages 23, 33 and 42 years and coded as 'none', 'ex-smoker', '1–19 cigarettes' or '>20 cigarettes'/d. Factors reported at the age of 45 years included television watching, personal computer usage and time spent outdoors (coded as '<1', '1–2' and '>3 h'/d), oily fish consumption/week (never, less than weekly and weekly) and vitamin D or fish oil/cod-liver oil supplements (no/yes). Recreational metabolic equivalent of task hours were divided into quarters with an additional category for implausibly high values (participants with weekly recreation hours of three standard deviations above the sex mean) and vigorous activity (those who recorded an activity with a metabolic equivalent score ≥ 6). Alcohol consumption and frequency were converted to standard units and coded as '0', '<7', '7–14', '14–21', '>21 units' consumed per week. Geographical location was based on current region of residence, classified as Southern, Middle, Northern England, Scotland and Greater London. Waist circumference was measured midway between the costal margin and the iliac crest. BMI was calculated from weight and height measurements.

Statistical methods

Exploratory analyses of the data included histograms of the distributions of 25(OH)D and lung function. The natural log transformation was used for 25(OH)D to achieve normal distribution and for calculating the geometric mean. The differences in the means by lifestyle and background factors were evaluated by linear regression using the likelihood ratio test for trend. The prevalence of respiratory infections and geometric means of 25(OH)D were standardised for sex. Means for FEV_1 and FVC are presented standardised by sex and height. The associations of 25(OH)D with FEV_1 and FVC were modelled by linear regression, and with respiratory infection by logistic regression. Deviations from linearity were assessed by the likelihood ratio test of the quadratic term. Missing data for adiposity measurements, illness, SEP and lifestyle factors were imputed (ten times) using the multiple imputation chain of equations as implemented in STATA, version 10 (StataCorp LP, College Station, TX, USA). Final models presented are from the multiple imputed datasets. Analyses were repeated for participants with complete information, and results were similar. The four main models were adjusted for (1) sex; (2) sex, social and lifestyle factors (birth and adult SEP, smoking status, alcohol consumption, geographical location, recreation metabolic equivalent hours, vigorous activity and inactivity based on television/personal computer usage, oily fish consumption, vitamin D supplementation, time spent outside); (3) measurements of adiposity (BMI, waist circumference and quadratic terms for adiposity) in addition to indicators included in the previous model, and finally for FEV_1 and FVC only; (4) use of respiratory

British Journal of Nutrition

medication, inhaler use, antibiotics, respiratory infections, asthma, bronchitis, allergy, IgE and CRP concentrations as well as all covariates in models 1–3. The models on FEV_1 and FVC were also adjusted for the height of cohort member. Analyses on 25(OH)D and the prevalence of respiratory infections were repeated, adjusting for season. The 25(OH)D concentrations were categorised into 25 nmol/l groups with tails <25 and ≥ 100 nmol/l, as well as a continuous variable of per 10 nmol/l, for the ease of interpretation across common cut-off points and linear approximation with the outcomes.

Table 1. 25-Hydroxyvitamin D (25(OH)D) concentrations, respiratory infection and lung function by social and lifestyle characteristics*
(Mean values, numbers and percentages, *n* 6789)

	n	%	Mean 25(OH)D (nmol/l)†	Respiratory infection† *n*	Respiratory infection† %	Mean FEV_1 (ml)‡	Mean FVC (ml)‡
25(OH)D (nmol/l)							
<25	523	7·7	–	63	11·5	3179	4039
25–49	2282	33·6	–	246	10·8	3280	4153
50–74	2454	36·2	–	201	8·2	3331	4210
75–99	1112	16·4	–	80	7·2	3361	4258
≥ 100	418	6·2	–	25	5·9	3399	4348
P			–		<0·001	<0·001	<0·001
Sex							
Male	3389	49·9	53·2	302	8·9	3822	4857
Female	3400	50·1	51·3	313	9·2	2796	3530
P			0·001		0·67	<0·001	<0·001
Season							
Winter (December–February)	1183	17·4	40·9	188	15·9	3322	4221
Spring (March–May)	1410	20·8	41·7	136	9·7	3292	4175
Summer (June–August)	1602	23·6	57·1	66	4·1	3278	4142
Autumn (September–November)	2594	38·2	62·6	225	8·7	3331	4218
P			<0·001		<0·001	0·19	0·61
Smoking							
Never	3138	46·2	53·8	246	7·8	3373	4224
Ex-smoker	1864	27·5	54·1	159	8·5	3358	4239
1–19/d	781	11·5	49·7	106	13·7	3240	4162
≥ 20/d	791	11·7	44·9	88	11·4	3030	3982
Unknown	215	3·2	51·9	16	7·3	3154	4056
P			<0·001		<0·001	<0·001	<0·001
Vigorous activity							
No	3401	50·1	49·0	309	9·0	3253	4127
Yes	3292	48·5	56·1	297	9·0	3372	4268
Unknown	96	1·4	46·4	9	9·5	3191	4002
P			<0·001		0·95	<0·001	<0·001
Watches TV/uses PC (h/d)							
<1	769	11·3	56·7	65	8·8	3353	4258
1 to <3	3561	52·5	54·3	291	8·2	3337	4226
≥ 3	2166	31·9	48·3	229	10·7	3261	4134
Unknown	293	4·3	47·1	30	10·2	3190	4046
P			<0·001		0·008	<0·001	<0·001
Time spent outdoors (h/d)							
<1	1789	26·4	45·5	179	10·0	3335	4222
1 to <3	1783	26·3	51·8	152	8·5	3335	4226
≥ 3	2694	39·7	58·3	225	8·4	3278	4154
Unknown	523	7·7	49·7	59	11·2	3283	4175
P			<0·001		0·07	<0·001	<0·001
Vitamin D supplementation							
No	5550	81·7	50·8	497	9·0	3299	4181
Yes	1101	16·2	61·1	105	9·7	3370	4260
Unknown	138	2·0	46·5	13	9·5	3236	4100
P			<0·001		0·56	<0·001	<0·001
Adult social class							
Professional and managerial	2774	40·9	52·9	231	8·3	3360	4237
Skilled (non-manual)	1400	20·6	52·4	130	8·7	3307	4179
Skilled (manual)	2092	30·8	51·8	200	9·7	3261	4160
Unskilled and others§	523	7·7	49·1	54	10·6	3183	4094
P			0·008		0·07	<0·001	<0·001

FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; TV, television; PC, personal computer.
* LRT *P* for trend excluding unknown category adjusted for sex, in addition to FEV_1 and FVC adjusted for height.
† Geometric mean and proportion standardised by sex.
‡ Mean standardised by sex and height.
§ Includes cohort members who are institutionalised, retired, unemployed and others.

BJN British Journal of Nutrition

Additional parameters of nurse and the spirometer instrument number were investigated and not included in the final analysis due to the lack of impact on the 25(OH)D associations and preferable modelling criteria (Bayesian information criteria). Interactions between lifestyle, SEP, illness, medication and 25(OH)D with lung function and respiratory infections were tested in sex (and height)-adjusted models (twenty-four tests for lung function and twenty-three tests for respiratory infection). Since the interaction tests were performed on the numerous factors without pre-defined hypotheses, we controlled for chance findings by applying a strict Bonferroni correction on these analyses ($P \leq 0{\cdot}002$ considered significant). All analyses were carried out using STATA, version 10.

Results

Men had higher concentrations of 25(OH)D and better lung function compared with women (Table 1). Similarly, several of the lifestyle characteristics, including smoking, vigorous activity, time spent television watching/using a personal computer and supplement intake, showed trends in FEV_1 and FVC that were parallel to those for 25(OH)D concentrations. An important exception was time spent outdoors, where the trend in lung function was reverse to what was observed for 25(OH)D concentrations. Respiratory infections were associated with smoking and more frequent television watching/using a personal computer; lifestyle categories with high 25(OH)D had a lower prevalence of infections. There was no significant seasonal variation in FEV_1 and FVC (Table 1). However, both the prevalence of infections and circulating 25(OH)D concentrations showed strong seasonal patterns but in opposing directions (Fig. 1). Concentrations of 25(OH)D increased from February until September, when the mean 25(OH)D concentration was 72·5 nmol/l. For respiratory infections, the prevalence started to decrease in January (the highest point at 17·9 %) and continually dropped until its lowest point in late summer (August). From participants with 25(OH)D concentrations <25 nmol/l and from those with >100 nmol/l, 11·5 % and 6 %, respectively, had an infection during the preceding month.

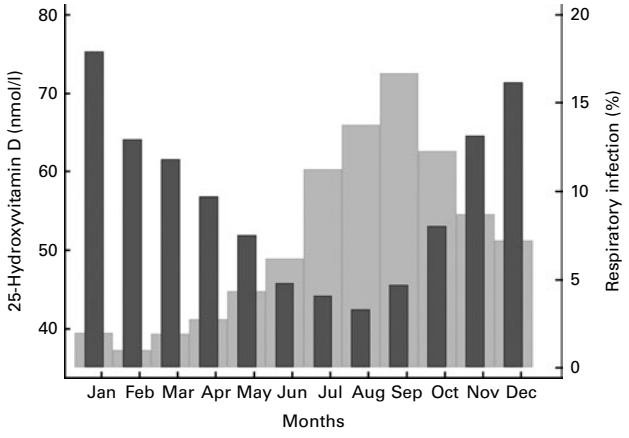

Fig. 1. Geometric mean of 25-hydroxyvitamin D (nmol/l, ▒) concentrations and the prevalence of respiratory infections (■) in the 1958 British birth cohort.

Circulating 25(OH)D concentrations were associated with the prevalence of infections, with the association being little affected by adjustment for measurements of adiposity, lifestyle and socio-economic factors (Table 2). After this adjustment, there was a 7 % reduction in the risk of infections by each 10 nmol/l increase in 25(OH)D (test for trend $P=0{\cdot}001$; Table 2). Across seasons, there was a steady decline in the prevalence of respiratory infections by increasing 25(OH)D concentrations, and especially so during winter, with the highest prevalence of infections (Fig. 2).

There was also an association for 25(OH)D with both FEV_1 and FVC, which persisted after controlling for adiposity, lifestyle and socio-economic factors: FEV_1 was 9 ml (95 % CI 4, 13, $P=0{\cdot}002$) and FVC was 14 ml (95 % CI 8, 24, $P<0{\cdot}001$) higher per 10 nmol/l increase in 25(OH)D. Further adjustment (for respiratory infections or medication, use of inhalers, asthma, allergy, IgE and CRP concentrations) only slightly attenuated the observed associations of 25(OH)D with FEV_1 and FVC.

We considered the interactions between 25(OH)D and a range of factors including socio-economic and lifestyle factors, adiposity, CRP, IgE, respiratory medication and illness. After applying a Bonferroni correction, we found evidence for modification of 25(OH)D association with FEV_1 by vigorous activity ($P=0{\cdot}002$), suggesting that individuals who did not engage in vigorous activity had a stronger association between 25(OH)D and lung function than individuals who did. For example, each 10 nmol/l increase in 25(OH)D was associated with a 10 ml increase in FEV_1 in the active participants (95 % CI 3, 16), while the association for those not engaged in vigorous activity was 24 ml (95 % CI 18, 31).

Discussion

The seasonal reduction in vitamin D synthesis in the skin has been suggested to be the 'seasonal stimulus'[2] behind the increase in the incidence of influenza infection, which penetrates the epithelial cells, in winter months[3]. Using data from the 1958 British birth cohort, we show a clear seasonal pattern in the prevalence of infections, and strikingly, how this mirrors variations in serum 25(OH)D concentrations. We further demonstrate a linear association between 25(OH)D and lung function. This relationship was not fully explained by infections or related factors, which may suggest that additional mechanisms play a role.

The most compelling evidence for a role of vitamin D in reducing the occurrence of seasonal infections has recently been come from a randomised controlled trial (RCT) on schoolchildren over the winter period, where there was a substantial reduction in the incidence of influenza A in those taking vitamin D_3 supplements of 1200 IU/d (30 μg equivalent)[18]. Furthermore, in a secondary analysis of a RCT, which reported a notable lack in the seasonal peak of infections in the group receiving the higher dosage of vitamin D, the control group infections showed the expected seasonal patterns[3,19]. In a Finnish study, a larger proportion of men

Table 2. Association of serum 25-hydroxyvitamin D with respiratory infections and lung function in the 1958 British birth cohort for imputed covariates
(Odds ratios or β coefficients and 95 % confidence intervals, *n* 6789)

	25-Hydroxyvitamin D (nmol/l)											
	<25	25–49·9		50–74·9		75–99·9		100–Max			Per 10 nmol/l increase		*P** for trend
		Estimate†	95 % CI	Estimate†	95 % CI	Estimate†	95 % CI	Estimate†	95 % CI	*P**	Estimate†	95 % CI	
Respiratory infections													
Adjusted for sex	1	0·88	0·66, 1·19	0·65	0·48, 0·88	0·57	0·40, 0·80	0·47	0·29, 0·76	<0·001	0·91	0·88, 0·94	<0·001
Adjusted for sex + lifestyle and socio-economic factors‡	1	0·94	0·70, 1·27	0·71	0·52, 0·97	0·61	0·42, 0·88	0·50	0·31, 0·83	0·001	0·92	0·88, 0·95	<0·001
Adjusted for sex + adiposity§	1	0·94	0·69, 1·27	0·74	0·54, 1·02	0·66	0·46, 0·96	0·57	0·34, 0·94	0·015	0·93	0·89, 0·97	0·001
FEV_1 (ml)													
Adjusted for sex and height	Ref	107	61, 154	157	111, 204	188	137, 238	211	149, 274	<0·001	20	15, 24	<0·001
Adjusted for sex and height + lifestyle and socio-economic factors‡	Ref	66	21, 112	98	51, 144	125	73, 176	150	87, 213	<0·001	14	10, 19	<0·001
Adjusted for sex and height + adiposity§	Ref	51	5, 96	66	20, 112	82	31, 133	93	30, 156	0·015¶	9	4, 13	0·001
Adjusted for sex and height + respiratory illness and medication‖	Ref	43	−1, 88	58	13, 103	74	24, 125	80	18, 142	0·036¶	8	3, 13	0·003
FVC (ml)													
Adjusted for sex and height	Ref	104	45, 163	161	102, 220	218	153, 282	281	201, 361	<0·001	27	21, 33	<0·001
Adjusted for sex and height + lifestyle and socio-economic factors‡	Ref	73	14, 132	115	56, 175	167	101, 234	226	144, 307	<0·001	22	16, 28	<0·001
Adjusted for sex and height + adiposity§	Ref	56	−2, 114	73	14, 132	108	42, 174	147	65, 228	0·002	14	8, 20	<0·001
Adjusted for sex and height + respiratory illness and medication‖	Ref	52	−6, 110	69	10, 128	103	38, 169	141	60, 222	0·004	13	7, 20	<0·001

FEV_1, forced expiratory volume in 1 s; Ref, reference; FVC, forced vital capacity.
* Multiply imputed parameter test *P*.
† For respiratory infections, the estimate is OR; for FEV_1 and FVC, the estimate is β.
‡ Includes smoking, alcohol consumption, time spent watching television or using personal computer, recreation metabolic equivalent hours, vigorous activity, time spent outside, oily fish consumption, use of vitamin D supplements, region and social class at birth and adulthood in addition to sex (and height for FEV_1 and FVC).
§ Includes adjustment for BMI and waist circumference, and their curvature terms in addition to social/lifestyle factors detailed above.
‖ Adjusted for the use of respiratory medication, antibiotics, inhalers, reported respiratory illness during the past 3 weeks, history of or current asthma or allergy, and serum measurements of C-reactive protein and IgE.
¶ In the analyses for the complete cases, the likelihood ratio test was not significant at the 5 % level: $P=0·059$, $P=0·11$.

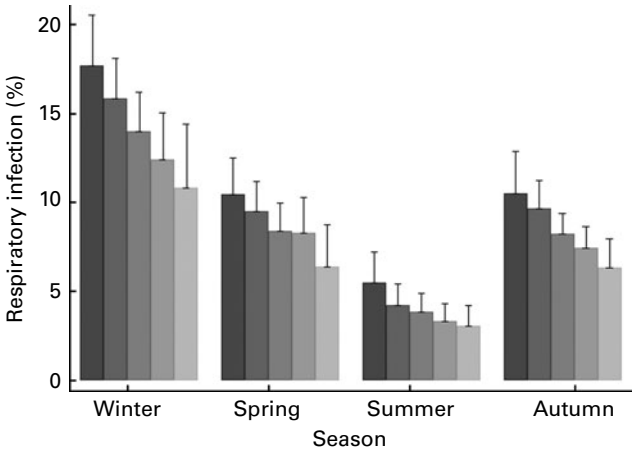

Fig. 2. Prevalence of respiratory infections with 95 % prediction intervals in the 25-hydroxyvitamin D categories of <25 nmol/l (■), 25–49·9 nmol/l (■), 50–74·9 nmol/l (■), 75–99·9 nmol/l (■) and >100 nmol/l (■) as predicted from a logistic regression model adjusted for factors of lifestyle, socio-economic position and adiposity, and season in the 1958 British birth cohort.

receiving vitamin D supplementation (400 IU/d; 10 μg equivalent) remained healthy throughout the 6-month study compared with men receiving placebos[20]. However, in that study, the intervention was not associated with the number of days absent from work due to acute respiratory tract infection or with the various symptoms of infections investigated. Evidence for an association between 25(OH)D and respiratory infections has also been obtained from observational studies. In one study, 25(OH)D concentrations of 95 nmol/l were identified as the break point differentiating between those who developed or did not develop viral infections of the respiratory tract[21]. Recent analyses in the Third National Health and Nutrition Examination Survey III also demonstrated an association between current vitamin D status and respiratory infections, with evidence for related seasonal variations[13]. In the present study, seasonal patterns both in 25(OH)D concentrations and in the prevalence of respiratory infections were impressive, including in the wintertime, a drop in the prevalence of respiratory infections over increasing 25(OH)D concentrations. However, reductions in infections preceded the raise in 25(OH)D and not vice versa as may have been expected. 25(OH)D is believed to be a good indicator for the combined intake of vitamin D from sunlight-induced synthesis and diet during the past 3–4 weeks[22], directly corresponding to the target period for the reporting of respiratory infections in the present study. Furthermore, the availability of sunlight for vitamin D production in the UK starts to increase from February[23], notably earlier than the observed accumulation of 25(OH)D (the circulating storage form). Hence, it appears logical that there is a delay in 25(OH)D accumulation, and if there is a causal association, it is likely that increases in vitamin D intake (due to greater vitamin D synthesis in the skin) would contribute to the reduced infection rates already before increases in the storage form 25(OH)D are observed. Previous studies have reported a dose–response relationship between 25(OH)D concentrations and pulmonary function in the general population[12] as well as in patients with asthma[24] and chronic obstructive pulmonary disease[25]. The present study confirms these associations and goes further by demonstrating that this observation of 25(OH)D association with lung function was robust to adjustment for measurements of adiposity or a wide range of lifestyle or socio-economic measures. It is of particular interest that the relationship of 25(OH)D with either FEV_1 or FVC was not markedly affected by adjustment for respiratory infections or medication, suggesting that mechanisms beyond immunological influences call for further investigation.

There is much debate regarding the optimal levels of 25(OH)D concentration for health[26,27]. The recent report from the Institute of Medicine[28] on vitamin D intake recommendations concluded that there is an increased risk of bone disease with 25(OH)D levels below 30 nmol/l, and that most of the population's needs are met at 25(OH)D levels of 50 nmol/l. Also in the present observational study, the steepest associations between 25(OH)D and measurements of lung function were observed before 50 nmol/l; however, the positive trend continued up to 100 nmol/l.

The presence of vitamin D receptors in a range of organs and tissues of the body (including lung epithelial cells and macrophages among others)[29] supports the wide-ranging health effects proposed for vitamin D. It is notable that $1,25(OH)_2D$ is known to regulate the expression of over 900 different genes[30], including those related to apoptosis and cellular proliferation[31]. The available evidence suggests that the influences of vitamin D relevant for respiratory health are complex, and there are several potential mechanisms that may be operating. Active vitamin D leads to a general reduction in inflammation[32], which together with direct anti-proliferative effects in human airway smooth muscle cells (through the inhibition of matrix metalloproteinases)[33] is believed to be instrumental for explaining the observed reductions in asthma risk[34]. $1,25(OH)_2D$ also influences barrier integrity, which could protect against the direct influence of harmful pathogens[35]. Furthermore, $1,25(OH)_2D$ reduces MHC II antigen expression on the cell membrane surface, and induces macrophages and epithelial cells to produce cathelicidin, a peptide involved in antimicrobial action[36]. However, adverse influences of high vitamin D intakes/status have been suggested. For example, the potential aggravation of allergic conditions has typically been explained by $1,25(OH)_2D$ influences on regulatory T-cell activity, the net result of which includes a shift in the balance between T-helper cell 1- and 2-type immunological responses towards T-helper cell 2 domination[37,38]. Evidence for both benefits and potentially harmful influences was also obtained from an animal experiment, where $1,25(OH)_2D$ administration reduced airway oeosinophilia (suggesting beneficial influences through a reduced inflammatory response), while allergen-induced T-cell proliferation was increased[39]. We have previously reported a strong J-shaped relationship between 25(OH)D and IgE concentrations in the 1958 British cohort[11]. However, as reported in the present study, the inverse association between 25(OH)D and lung function was little affected by adjustment for IgE concentration, nor was there any suggestion of reductions in lung function observed

British Journal of Nutrition

in individuals with high 25(OH)D concentrations. A systematic review of a RCT that used vitamin D compounds for the treatment and prevention of infectious diseases (including viral respiratory tract infections) found large heterogeneity in the baseline characteristics of the subjects and in the design of the trials[40]. Well-designed RCT are clearly needed to establish (1) whether by increasing intake of vitamin D it is possible to improve respiratory health, (2) what are the relevant mechanisms and (3) whether there are possible safety issues with supplementation at high dosages especially in individuals prone to allergic disease.

Several lifestyle factors had fairly strong associations with both 25(OH)D concentrations and lung function and/or respiratory infections, typically with the same categories associated with both vitamin D insufficiency and worse respiratory health. Smoking is a strong risk factor for lung function and respiratory infections, and could plausibly affect vitamin D status by the proposed reduction in parathyroid hormone production for smokers[41]. Correspondingly, individuals who are physically inactive and who spend more time indoors are likely to have both lower 25(OH)D concentrations and worse respiratory health. We observed an interaction between 25(OH)D and physical activity, the association with lung function being stronger for those who did not exercise compared with those who did, although the overall mean concentrations of 25(OH)D and FEV_1, FVC were higher in those who did engage in vigorous exercise. However, this might suggest that ensuring adequate vitamin D supplementation is especially beneficial for respiratory health in situations where there is limited activity or reflects lesser variations in vitamin D intake within the active group compared with others.

Methodological considerations

A strength of the present study is the rich data on 25(OH)D concentrations, measurements for lung function, respiratory infections/medications and several lifestyle and social factors potentially associated with vitamin D status and respiratory health. The large sample size is a further strength of the study. However, some limitations of the present study need to be considered. Despite extensive adjustments, we cannot discount possible residual confounding or reverse causality on the observed associations. The study was restricted to Caucasians (thereby reducing problems of population stratification), hence the present findings cannot be extrapolated to non-white ethnic groups. Furthermore, some sample attrition has occurred during the survey and although the present sample is broadly representative of the surviving cohort, some minority groups are under-represented[15]. Given the cross-sectional setting, it is not possible to demonstrate causality for the observed associations. Also, information on respiratory infections and medication was based on self-report rather than more objective forms of data acquisition.

Conclusion

RCT are warranted to investigate the role of vitamin D supplementation on respiratory health and to establish the underlying mechanisms. However, vitamin D deficiency is a known avoidable health hazard, and it is important to take action to reduce the prevalence even while waiting for further evidence to accumulate for any specific health outcome. Given the high global prevalence of hypovitaminosis D, the present findings suggest that ensuring adequate intakes of vitamin D throughout the year could have important population-level influences on respiratory health.

Acknowledgements

We thank Dr Ian Gibb and Steve Turner (Royal Victoria Infirmary, Newcastle-upon-Tyne) for carrying out the 25(OH)D assays; and Professor Gordon Lowe and Dr Ann Rumley (Department of Medicine, Glasgow Royal Infirmary University NHS Trust, Glasgow, UK) for processing measurements of CRP. Data were provided by the Centre for Longitudinal Studies, Institute of Education, University of London (original data producers). Data collection at the age of 44–46 years and statistical analyses were funded by the UK Medical Research Council (MRC grants G0601653 and G0000934) and the Child Health Research Appeal Trust Summer Vacation Studentship, and 25(OH)D assays were funded by the BUPA Foundation. E. H. is a Department of Health (UK) Public Health Career Scientist. The present study was undertaken at the Centre for Paediatric Epidemiology and Biostatistics, which benefits from funding support from the MRC in its capacity as the MRC Centre of Epidemiology for Child Health. Research at the University College London Institute of Child Health and Great Ormond Street Hospital for Children NHS Trust benefits from R&D funding received from the NHS Executive. The authors' contributions are as follows: D. J. B., K. H. and E. H. wrote the manuscript; D. J. B. and K. H. analysed the data. C. P. and E. H. participated in the data collection and obtained funding. E. H. developed the concepts and study objectives, and was responsible for the execution of the study. All authors contributed to the interpretation of the results, revision of the manuscript and approved the final version. None of the authors reported a conflict of interest.

References

1. Hypponen E & Power C (2007) Hypovitaminosis D in British adults at age 45 y: nationwide cohort study of dietary and lifestyle predictors. *Am J Clin Nutr* **85**, 860–868.
2. Hope-Simpson RE (1981) The role of season in the epidemiology of influenza. *J Hyg (Lond)* **86**, 35–47.
3. Cannell JJ, Vieth R, Umhau JC, *et al.* (2006) Epidemic influenza and vitamin D. *Epidemiol Infect* **134**, 1129–1140.
4. Hansdottir S, Monick MM, Hinde SL, *et al.* (2008) Respiratory epithelial cells convert inactive vitamin D to its active form: potential effects on host defense. *J Immunol* **181**, 7090–7099.
5. Camargo CA Jr, Rifas-Shiman SL, Litonjua AA, *et al.* (2007) Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. *Am J Clin Nutr* **85**, 788–795.
6. Devereux G, Litonjua AA, Turner SW, *et al.* (2007) Maternal vitamin D intake during pregnancy and early childhood wheezing. *Am J Clin Nutr* **85**, 853–859.

7. Gale CR, Robinson SM, Harvey NC, *et al.* (2008) Maternal vitamin D status during pregnancy and child outcomes. *Eur J Clin Nutr* **62**, 68–77.
8. Hypponen E, Sovio U, Wjst M, *et al.* (2004) Infant vitamin D supplementation and allergic conditions in adulthood: northern Finland birth cohort 1966. *Ann N Y Acad Sci* **1037**, 84–95.
9. Back O, Blomquist HK, Hernell O, *et al.* (2009) Does vitamin D intake during infancy promote the development of atopic allergy? *Acta Derm Venereol* **89**, 28–32.
10. Wjst M & Hyppönen E (2007) Vitamin D serum levels and allergic rhinitis. *Allergy* **62**, 4615–4622.
11. Hypponen E, Berry DJ, Wjst M, *et al.* (2009) Serum 25-hydroxyvitamin D and IgE – a significant but nonlinear relationship. *Allergy* **64**, 613–620.
12. Black PN & Scragg R (2005) Relationship between serum 25-hydroxyvitamin D and pulmonary function in the third national health and nutrition examination survey. *Chest* **128**, 3792–3798.
13. Ginde AA, Mansbach JM & Camargo CA Jr (2009) Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. *Arch Intern Med* **169**, 384–390.
14. Power C & Elliott J (2006) Cohort profile: 1958 British birth cohort (National Child Development Study). *Int J Epidemiol* **35**, 34–41.
15. Atherton K, Fuller E, Shepherd P, *et al.* (2008) Loss and representativeness in a biomedical survey at age 45 years: 1958 British birth cohort. *J Epidemiol Community Health* **62**, 216–223.
16. Hypponen E, Turner S, Cumberland P, *et al.* (2007) Serum 25-hydroxyvitamin D measurement in a large population survey with statistical harmonization of assay variation to an international standard. *J Clin Endocrinol Metab* **92**, 4615–4622.
17. Anonymous (1987) Statement of the American Thoracic Society. Standardization of spirometry – 1987 update. *Am Rev Respir Dis* **136**, 1285–1298.
18. Urashima M, Segawa T, Okazaki M, *et al.* (2010) Randomized trial of vitamin D supplementation to prevent seasonal influenza A in school children. *Am J Clin Nutr* **91**, 1255–1260.
19. Aloia JF & Li-Ng M (2007) Re: epidemic influenza and vitamin D. *Epidemiol Infect* **135**, 1095–1096.
20. Laaksi I, Ruohola JP, Mattila V, *et al.* (2010) Vitamin D supplementation for the prevention of acute respiratory tract infection: a randomized, double-blinded trial among young Finnish men. *J Infect Dis* **202**, 809–814.
21. Sabetta JR, DePetrillo P, Cipriani RJ, *et al.* (2010) Serum 25-hydroxyvitamin D and the incidence of acute viral respiratory tract infections in healthy adults. *PLoS One* **5**, e11088.
22. DeLuca HF (2004) Overview of general physiologic features and functions of vitamin D. *Am J Clin Nutr* **80**, 1689S–1696S.
23. Webb AR (2006) Who, what, where and when – influences on cutaneous vitamin D synthesis. *Prog Biophys Mol Biol* **92**, 17–25.
24. Sutherland ER, Goleva E, Jackson LP, *et al.* (2010) Vitamin D levels, lung function and steroid response in adult asthma. *Am J Respir Crit Care Med* **181**, 699–704.
25. Janssens W, Bouillon R, Claes B, *et al.* (2010) Vitamin D deficiency is highly prevalent in COPD and correlates with variants in the vitamin D-binding gene. *Thorax* **65**, 215–220.
26. Norman AW & Bouillon R (2010) Vitamin D nutritional policy needs a vision for the future. *Exp Biol Med (Maywood)* **235**, 1034–1045.
27. Heaney RP & Holick MF (2011) Why the IOM recommendations for vitamin D are deficient. *J Bone Miner Res* **26**, 455–457.
28. Institute of Medicine (2010) *Dietary Reference Intakes for Calcium and Vitamin D*. Washingon, DC: National Academy of Sciences.
29. Holick MF (2004) Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am J Clin Nutr* **80**, 1678S–1688S.
30. Wang TT, Tavera-Mendoza LE, Laperriere D, *et al.* (2005) Large-scale *in silico* and microarray-based identification of direct 1,25-dihydroxyvitamin D_3 target genes. *Mol Endocrinol* **19**, 2685–2695.
31. Holick MF (2007) Vitamin D deficiency. *N Engl J Med* **357**, 266–281.
32. Cohen-Lahav M, Douvdevani A, Chaimovitz C, *et al.* (2007) The anti-inflammatory activity of 1,25-dihydroxyvitamin D_3 in macrophages. *J Steroid Biochem Mol Biol* **103**, 558–562.
33. Song Y, Qi H & Wu C (2007) Effect of 1,25-$(OH)_2D_3$ (a vitamin D analogue) on passively sensitized human airway smooth muscle cells. *Respirology* **12**, 486–494.
34. Hughes DA & Norton R (2009) Vitamin D and respiratory health. *Clin Exp Immunol* **158**, 20–25.
35. Hewison M, Zehnder D, Chakraverty R, *et al.* (2004) Vitamin D and barrier function: a novel role for extra-renal 1 alpha-hydroxylase. *Mol Cell Endocrinol* **215**, 31–38.
36. Kamen DL & Tangpricha V (2010) Vitamin D and molecular actions on the immune system: modulation of innate and autoimmunity. *J Mol Med* **88**, 441–450.
37. Bikle DD (2008) Vitamin D and the immune system: role in protection against bacterial infection. *Curr Opin Nephrol Hypertens* **17**, 348–352.
38. Mora JR, Iwata M & von Andrian UH (2008) Vitamin effects on the immune system: vitamins A and D take centre stage. *Nat Rev Immunol* **8**, 685–698.
39. Matheu V, Back O, Mondoc E, *et al.* (2003) Dual effects of vitamin D-induced alteration of TH1/TH2 cytokine expression: enhancing IgE production and decreasing airway eosinophilia in murine allergic airway disease. *J Allergy Clin Immunol* **112**, 585–592.
40. Yamshchikov AV, Desai NS, Blumberg HM, *et al.* (2009) Vitamin D for treatment and prevention of infectious diseases: a systematic review of randomized controlled trials. *Endocr Pract* **15**, 438–449.
41. Gunnarsson O, Indridason OS, Franzson L, *et al.* (2009) Factors associated with elevated or blunted PTH response in vitamin D insufficient adults. *J Intern Med* **265**, 488–495.

British Journal of Nutrition