

# Relationship of vitamin D status to adult lung function and COPD

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## ABSTRACT

**Background** There is considerable interest in the possible role of vitamin D in respiratory disease, but only one population-based study has reported associations with lung function.

**Methods** The cross-sectional relationships of total dietary vitamin D intake, serum 25 hydroxy vitamin D (25(OH)D) concentrations and three vitamin D receptor (VDR) polymorphisms (Apa1, Fok1 and Cdx2) with lung function and spirometrically-defined chronic obstructive pulmonary disease (COPD) were investigated in men and women aged 59–73 years in the Hertfordshire Cohort Study, UK.

**Results** After controlling for confounders, total vitamin D intake was positively associated with forced expiratory volume in 1 s (FEV<sub>1</sub>; difference in FEV<sub>1</sub> between top and bottom quintiles of intake 0.079 l (95% CI 0.02 to 0.14), *p* trend=0.007, *n*=2942), ratio of FEV<sub>1</sub> to forced vital capacity (FEV<sub>1</sub>/FVC; *p* trend=0.008) and negatively associated with COPD (OR comparing top and bottom quintiles 0.57 (95% CI 0.38 to 0.87), *p* trend=0.02). In contrast, serum 25(OH)D concentrations were not related to FEV<sub>1</sub> (*p* trend=0.89, *n*=1197) but were positively associated with COPD (*p* trend=0.046). VDR genotypes were unrelated to lung function and did not modify the effects of dietary intake or 25(OH)D concentrations on lung function.

**Conclusions** The results of this study did not confirm a positive association between blood 25(OH)D concentrations and adult lung function. The apparent relationships with dietary vitamin D are likely to be explained by other highly correlated nutrients in the diet.

## INTRODUCTION

A reduced forced expiratory volume in 1 s (FEV<sub>1</sub>) is a powerful predictor of mortality, even in non-smokers.<sup>1–3</sup> Hence, aside from smoking cessation,<sup>4</sup> we need to identify other strategies to improve lung function in adults. A proportion of the British population is deficient in vitamin D,<sup>5,6</sup> and there is currently considerable interest in the hypothesis that improving suboptimal vitamin D status might be effective in the primary and secondary prevention of respiratory diseases<sup>7</sup> including asthma.<sup>8</sup> Vitamin D status is influenced largely by ultraviolet B (UVB) exposure and, to a lesser extent, by dietary intake, although the latter may be relatively more important during the winter in temperate countries when UVB exposure is limited. The gold standard measurement of total vitamin D exposure is the concentration of 25 hydroxy vitamin D (25(OH)D)

## Key messages

### What is the key question?

► Does vitamin D status influence adult lung function and COPD?

### What is the bottom line?

► While dietary intake of vitamin D was positively associated with lung function, serum concentration of 25 hydroxy vitamin D (the gold standard measure of vitamin D status) was not.

### Why read on?

► This study does not support findings from a previous population-based study of vitamin D and lung function, and we believe that the apparent dietary association in our study is likely to be confounded by other nutrients.

in serum.<sup>9</sup> A few studies have investigated the relationship of vitamin D to lung function in individuals with obstructive lung disease. Two small studies of adults and children with asthma have found positive associations between serum 25(OH)D concentrations and FEV<sub>1</sub>.<sup>10,11</sup> This was confirmed recently in a larger study of adult asthma from China,<sup>12</sup> but not in a larger study of childhood asthma after controlling for confounders.<sup>13</sup> While a recent study observed a positive association between 25(OH)D and FEV<sub>1</sub> in patients with chronic obstructive pulmonary disease (COPD),<sup>14</sup> another study of continuous smokers with COPD found no difference in baseline 25(OH)D concentrations between individuals who had a rapid decline in lung function and those with a slow decline.<sup>15</sup> However, only one study has examined the relation of serum 25(OH)D to lung function in the general population. In the Third National Health and Nutrition Survey (NHANES III), strong positive relations between serum 25(OH)D and FEV<sub>1</sub> and forced vital capacity (FVC) were reported.<sup>16</sup>

In an older adult UK population (the Hertfordshire Cohort Study) we have investigated the relationships of serum 25(OH)D and dietary vitamin D intake with lung function and spirometrically-defined COPD. In order to strengthen causal inference, we have also used a Mendelian randomisation approach<sup>17</sup> and examined associations between vitamin D receptor (VDR) gene polymorphisms and lung function, as well as exploring potential interactions between VDR genotypes and serum

25(OH)D concentrations and dietary intake of vitamin D on lung function.

## METHODS

### The Hertfordshire Cohort Study (HCS)

Details of the design of the HCS have been described previously.<sup>18</sup> Briefly, from 1911 to 1948, midwives recorded birth weight and other details of all infants born in the county of Hertfordshire, UK. In 1998, 7106 men and women born between 1931 and 1939 who were still alive and living in Hertfordshire were traced using the NHS central registry. General practitioners gave permission for us to write to 3126 men (82%) and 2973 women (91%). Of these, 1684 men (54%) and 1541 women (52%) agreed to a home interview; 1579 of the men (94%) and 1418 of the women (92%) subsequently attended a clinic for spirometry. Complete spirometry and dietary data were available for 1551 men and 1391 women. The study had ethical approval from the Bedfordshire and Hertfordshire local research ethics committee and the West Hertfordshire local research ethics committee. All participants gave written informed consent.

### Spirometry data

Lung function was measured using a Micro Spirometer (Care-Fusion UK, Basingstoke, Hants, UK) in the seated position without noseclips. After at least one practice blow, three FEV<sub>1</sub> and FVC readings were recorded. The highest FEV<sub>1</sub> and FVC values from satisfactory manoeuvres were used in the analyses (these did not necessarily come from the same blow). A bronchodilator was not given before spirometry was performed. For FEV<sub>1</sub>, 85.8% of the men and 92.2% of the women had a difference of  $\leq 0.15$  l between their two highest readings; for FVC the corresponding figures were 80.4% and 88.6%. However, we did not exclude those with differences of  $>0.15$  l.<sup>19</sup> The primary outcome of interest was FEV<sub>1</sub>. Secondary outcomes included FVC, FEV<sub>1</sub>/FVC and COPD (defined as FEV<sub>1</sub>/FVC below lower limit of normal, the latter calculated using separate equations for men and women).<sup>20</sup>

### Vitamin D assessments

Diet was assessed between 1998 and 2004 using a food frequency questionnaire (FFQ) based on the EPIC questionnaire.<sup>21, 22</sup> This was administered by a trained research nurse. The FFQ included 129 foods and food groups and was used to assess an average frequency of consumption of the listed foods over the 3-month period preceding the home interview. Prompt cards were used to show the foods included in each food group, to ensure standardised responses to the FFQ. Frequencies of other foods that were not listed on the FFQ were also recorded if consumed once per week or more. Standard portion sizes<sup>23</sup> were allocated to all foods except for milk and sugar, for which daily quantities consumed were recorded. Dietary vitamin D intake was calculated by multiplying the frequency of consumption of a portion of each food by its vitamin D content according to the UK national food composition database<sup>24</sup> or manufacturers' composition data. Information was also collected on supplement use in the previous 3 months. Vitamin D intakes from supplements were calculated using the frequency and dose of individual supplements reported by the participant and manufacturers' supplement composition data, enabling estimation of total intake from diet and supplements combined.

Blood samples were taken on the same day as spirometry was performed, and serum concentrations of 25(OH)D were measured using a DiaSorin Liaison automated chemiluminescent

assay with equal specificity for 25(OH)D<sub>2</sub> and 25(OH)D<sub>3</sub>. DNA was extracted from whole blood samples using standard salting-out procedures. Three single nucleotide polymorphisms (SNPs) in the VDR gene—rs10735810 (Apa1), rs11568820 (Fok1) and rs7975232 (Cdx2)—were typed by KBiosciences Ltd (Hoddesdon, Herts, UK; <http://www.kbioscience.co.uk>) using a competitive allele-specific PCR system (KASPar). These SNPs were chosen because previous studies have shown that they modulate the effects of vitamin D on various phenotypes. Genotyping success rate was  $>95\%$  and the error rate was  $<1\%$  for all SNPs tested.

### Statistical analysis

The statistical software package Stata Version 11 was used to analyse the data. Univariate and multiple linear regressions were used to analyse the relationships between total dietary vitamin D intakes and serum 25(OH)D concentrations and lung function outcomes. Lung function residuals adjusted for age and height were calculated for each sex and used throughout the unadjusted and adjusted analyses. In logistic regression analyses of COPD, age, sex and height were included in the models. We controlled for the following potential confounders: smoking status (never, ex, current), pack years smoked, whether exposed to tobacco smoke in the home, age left education (defined as  $\leq 14$  years or  $\geq 15$  years), home ownership status (owned/mortgaged, rented or other), number of rooms for household use, number of cars for household use, social class, body fat mass, activity score (0–100, derived from frequency of gardening, housework, climbing stairs and carrying loads in a typical week), energy intake, alcohol consumption, dietary supplement use, birth weight, father's social class at subject's birth, use of inhaled or oral steroids and use of paracetamol. In analyses of serum 25(OH)D we also controlled for season of clinic visit when blood samples were taken—that is, winter (December–February), spring (March–May), summer (June–August) and autumn (September–November)—but did not control for energy intake. Social class was identified on the basis of own current or most recent full-time occupation for men and never-married women, and on the basis of the husband's occupation for ever-married women.<sup>25</sup> Fat mass was calculated by multiplying body weight (in kg) by body fat percentage. Skinfold thickness was measured at the triceps, biceps, subscapular and suprailiac sites in triplicate. The triplicate values were averaged and then age- and gender-specific Durnin and Womersley equations were used to estimate body fat percentage.<sup>26</sup> Quintiles for total dietary vitamin D intake and serum 25(OH)D concentrations were defined using data from men and women combined. As there were no significant differences in the main results between men and women, we analysed the sexes together to optimise power.

Univariate gene main effects were evaluated using between genotype comparisons (variant homozygotes vs wild homozygotes and heterozygotes vs wild homozygotes) and also as continuous per minor allele effects. To explore effect modification of dietary and serum vitamin D effects, we stratified the confounder-adjusted effects of these exposures on lung function and COPD by VDR genotype.

## RESULTS

The characteristics of the study participants are given in table 1. The average age was 66 years and participants were almost exclusively white; 40% of individuals were taking vitamin D supplements and geometric mean total vitamin D intake (from diet plus supplements) was 4.4  $\mu\text{g}/\text{day}$  (3.15  $\mu\text{g}/\text{day}$  from diet alone and 3.45  $\mu\text{g}/\text{day}$  from supplements alone, among those taking supplements). The prevalence of spirometrically-defined

**Table 1** Characteristics of study participants

|                                                   | N       | Mean   | SD       |
|---------------------------------------------------|---------|--------|----------|
| Birth weight (kg)                                 | 2943    | 3.43   | 0.53     |
| Age (years)                                       | 2943    | 66.1   | 2.8      |
| Height (cm)                                       | 2940    | 167.9  | 9.1      |
| Physical activity score                           | 2943    | 60.1   | 15.5     |
| Fat mass (kg)*                                    | 2935    | 25.2   | 1.4      |
| Daily energy intake (cal)*                        | 2942    | 2077   | 1.3      |
| Daily total vitamin D intake ( $\mu\text{g}$ )* † | 2942    | 4.38   | 1.9      |
|                                                   | N       | Median | IQR      |
| Pack years smoked                                 | 2932    | 1      | 0.0–22.0 |
| Alcohol consumption (units per week)              | 2942    | 4      | 0.4–12.0 |
| Number of rooms for household use                 | 2934    | 6      | 5.0–6.0  |
|                                                   | Total N | N      | %        |
| Male                                              | 2943    | 1552   | 52.7     |
| Female                                            |         | 1391   | 47.3     |
| COPD                                              | 2937    | 521    | 17.7     |
| Smoker status                                     |         |        |          |
| Never                                             | 2942    | 1361   | 46.3     |
| Ex                                                |         | 1209   | 41.1     |
| Current                                           |         | 372    | 12.6     |
| Exposed to tobacco smoke in home                  |         | 366    | 12.8     |
| Social class                                      |         |        |          |
| I–IIINM                                           | 2895    | 1195   | 41.3     |
| IIIM–V                                            |         | 1700   | 58.7     |
| Father's social class at birth                    |         |        |          |
| I–IIINM                                           | 2760    | 446    | 16.2     |
| IIIM–V                                            |         | 2314   | 83.8     |
| Age left education                                |         |        |          |
| $\leq 14$                                         | 2943    | 543    | 18.5     |
| $\geq 15$                                         |         | 2400   | 81.5     |
| Home ownership status                             |         |        |          |
| Owned/mortgaged                                   | 2943    | 2350   | 79.9     |
| Rented                                            |         | 567    | 19.3     |
| Other                                             |         | 26     | 0.9      |
| No. of cars for household use                     |         |        |          |
| 0                                                 | 2942    | 330    | 11.2     |
| 1                                                 |         | 1623   | 55.2     |
| 2                                                 |         | 836    | 28.4     |
| 3+                                                |         | 153    | 5.2      |
| Dietary supplement use                            | 2942    | 1536   | 52.2     |
| Use of oral or inhaled steroids                   | 2943    | 234    | 8        |
| Paracetamol use                                   | 2943    | 283    | 9.6      |

\*Geometric mean and SD.

†Vitamin D intake from diet and supplements.

COPD was 18%, and 54% of individuals were ex- or current smokers. Supplements containing vitamin D were taken less commonly by those with COPD than by those without COPD (34% vs 41%,  $p=0.003$ ). When we compared the characteristics of those for whom serum 25(OH)D data were and were not available, we found that individuals with data were, on average, younger and shorter, with a higher physical activity score and calorie intake, lower alcohol intake and lower socioeconomic

**Table 2** Mean serum concentrations (nmol/l) of 25 hydroxy vitamin D and the prevalence of profound (<25 nmol/l) and moderate (<40 and <75 nmol/l) vitamin D deficiency, overall and by season of measurement

|                          | N              | Mean*    | SD       |
|--------------------------|----------------|----------|----------|
| Overall                  | 1197           | 41.8     | 1.6      |
| Winter                   | 307            | 35.6     | 1.6      |
| Spring                   | 375            | 35.7     | 1.6      |
| Summer                   | 189            | 55.0     | 1.5      |
| Autumn                   | 326            | 49.6     | 1.5      |
| <b>Overall</b>           | <b>Total N</b> | <b>N</b> | <b>%</b> |
| <25 nmol/l               |                | 195      | 16.3     |
| $\geq 25$ and <40 nmol/l | 1197           | 328      | 27.4     |
| $\geq 40$ and <75 nmol/l |                | 534      | 44.6     |
| $\geq 75$ nmol/l         |                | 140      | 11.7     |
| Winter and spring        |                |          |          |
| <25 nmol/l               |                | 172      | 25.2     |
| $\geq 25$ and <40 nmol/l | 682            | 218      | 32.0     |
| $\geq 40$ and <75 nmol/l |                | 251      | 36.8     |
| $\geq 75$ nmol/l         |                | 41       | 6.0      |
| Summer and autumn        |                |          |          |
| <25 nmol/l               |                | 23       | 4.5      |
| $\geq 25$ and <40 nmol/l | 515            | 110      | 21.4     |
| $\geq 40$ and <75 nmol/l |                | 283      | 55.0     |
| $\geq 75$ nmol/l         |                | 99       | 19.2     |

\*Geometric mean.

status and age at leaving education, but these differences were all very small (data not shown). Table 2 shows the mean serum concentrations of 25(OH)D and the prevalence of profound (<25 nmol/l) and moderate (<40 and <75 nmol/l) vitamin D deficiency, overall and by season of measurement. Concentrations were higher in summer and autumn, and prevalences of all levels of deficiency were higher in winter and spring. The correlation between total dietary intake and serum 25(OH)D concentrations, while weak overall (adjusted coefficient 0.14), was stronger in winter and spring (coefficients 0.25 and 0.17, respectively) than in summer and autumn (coefficients 0.04 and 0.09, respectively).

Table 3 shows the range of total vitamin D intake and serum 25(OH)D concentrations across quintiles and mean lung function by quintiles of these exposures. Mean FEV<sub>1</sub> and FVC tended to increase with increasing intake and serum concentrations of 25(OH)D. Dietary intake was also positively associated with FEV<sub>1</sub>/FVC and negatively with COPD prevalence. However, higher serum 25(OH)D concentrations were associated with a lower FEV<sub>1</sub>/FVC ratio and a higher prevalence of COPD.

Table 4 shows the associations between total dietary vitamin D intake and respiratory outcomes after controlling for energy intake and other confounders. Total vitamin D intake was positively associated with FEV<sub>1</sub> (difference in FEV<sub>1</sub> between top and bottom quintiles of intake 0.079 l (95% CI 0.02 to 0.14),  $p$  trend=0.007) and FEV<sub>1</sub>/FVC ( $p$  trend=0.008). The OR for COPD decreased with increasing intake of vitamin D (OR comparing top and bottom quintiles 0.57 (95% CI 0.38 to 0.87),  $p$  trend=0.02). There was no evidence of a 'plateau' in the effect across the range of exposure studied. When we restricted the dietary analyses to those subjects with serum 25(OH)D data, the effect estimates for FEV<sub>1</sub> and FVC became stronger than those seen for the whole cohort, and those for FEV<sub>1</sub>/FVC and COPD were similar.

After controlling for confounders, the serum 25(OH)D concentration was not associated with FEV<sub>1</sub> or FVC, but there was some evidence for a weak negative association with FEV<sub>1</sub>/FVC and higher serum concentrations were associated with

**Table 3** Mean lung function and prevalence of chronic obstructive pulmonary disease by fifths of total vitamin D intake and serum 25(OH)D concentrations

| Range of vitamin D ( $\mu\text{g}$ )   | FEV <sub>1</sub> (l) |      |      | FVC (l) |      |      | FEV <sub>1</sub> /FVC ratio |      |       | COPD    |     |     |      |
|----------------------------------------|----------------------|------|------|---------|------|------|-----------------------------|------|-------|---------|-----|-----|------|
|                                        | N                    | Mean | SD   | N       | Mean | SD   | N                           | Mean | SD    | Total N | N   | %   |      |
| Fifths of total vitamin D intake:      |                      |      |      |         |      |      |                             |      |       |         |     |     |      |
| 1 (lowest)                             | 0.54–2.59            | 589  | 2.35 | 0.69    | 588  | 3.33 | 0.93                        | 588  | 0.706 | 0.09    | 588 | 133 | 22.6 |
| 2                                      | 2.59–3.42            | 588  | 2.42 | 0.67    | 586  | 3.40 | 0.93                        | 586  | 0.713 | 0.09    | 586 | 104 | 17.7 |
| 3                                      | 3.42–5.21            | 589  | 2.47 | 0.68    | 589  | 3.46 | 0.93                        | 589  | 0.715 | 0.08    | 589 | 113 | 19.2 |
| 4                                      | 5.22–7.63            | 588  | 2.44 | 0.67    | 586  | 3.41 | 0.92                        | 586  | 0.719 | 0.09    | 586 | 98  | 16.7 |
| 5 (highest)                            | 7.64–59.5            | 588  | 2.50 | 0.65    | 587  | 3.45 | 0.90                        | 587  | 0.728 | 0.07    | 587 | 73  | 12.4 |
| Range of vitamin D (nmol/l)            | FEV <sub>1</sub> (l) |      |      | FVC (l) |      |      | FEV <sub>1</sub> /FVC ratio |      |       | COPD    |     |     |      |
|                                        | N                    | Mean | SD   | N       | Mean | SD   | N                           | Mean | SD    | Total N | N   | %   |      |
| Fifths of serum 25(OH)D concentration: |                      |      |      |         |      |      |                             |      |       |         |     |     |      |
| 1 (lowest)                             | 11.4–27.4            | 241  | 2.27 | 0.62    | 240  | 3.13 | 0.83                        | 240  | 0.726 | 0.09    | 240 | 41  | 17.1 |
| 2                                      | 27.5–38.2            | 239  | 2.36 | 0.65    | 239  | 3.26 | 0.87                        | 239  | 0.728 | 0.08    | 239 | 37  | 15.5 |
| 3                                      | 38.3–48.0            | 244  | 2.38 | 0.67    | 244  | 3.31 | 0.90                        | 244  | 0.721 | 0.09    | 244 | 41  | 16.8 |
| 4                                      | 48.1–62.8            | 234  | 2.46 | 0.71    | 233  | 3.43 | 0.96                        | 233  | 0.717 | 0.08    | 233 | 50  | 21.5 |
| 5 (highest)                            | 62.9–336.5           | 239  | 2.50 | 0.69    | 239  | 3.52 | 0.92                        | 239  | 0.712 | 0.09    | 239 | 49  | 20.5 |

FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; 25(OH)D, 25 hydroxy vitamin D.

a higher prevalence of COPD ( $p$  trend=0.046; table 5). The negative association with FEV<sub>1</sub>/FVC and the positive association with COPD were present (and stronger) among non-supplement users but not among supplement users. We also explored the relation between serum 25(OH)D concentration (as a continuous variable) and lung function separately in those with and without COPD. After controlling for confounders, this showed non-significant negative associations with FEV<sub>1</sub> and FVC in those with COPD ( $p=0.33$  and  $p=0.72$ , respectively) and non-significant positive associations in those without COPD ( $p=0.09$  and  $p=0.21$ , respectively).

Table 6 shows no clear associations between mean lung function and the three VDR genotypes. This was confirmed in regression analyses in which there was no evidence for significant trends (assuming linear effects per minor allele) (see tables

E1 and E2 in the online supplement). Tables E3–E5 in the online supplement show associations of dietary intake and 25(OH)D concentrations with lung function, stratified by VDR genotypes. On formal testing there was no evidence of significant interactions ( $p$  values not shown).

## DISCUSSION

In this population-based cross-sectional study we did not confirm a positive relation between serum concentrations of 25(OH)D and lung function after controlling for confounding factors, and found weak evidence to suggest that individuals with higher serum concentrations were more likely to have airflow obstruction. In contrast, we found that higher dietary intakes of vitamin D were associated with better lung function and a lower prevalence of COPD.

**Table 4** Relationship between total vitamin D intake and FEV<sub>1</sub> ( $n=2942$ ) and FVC, FEV<sub>1</sub>/FVC and COPD ( $n=2936$ )

| Fifths of vitamin D intake:                      | FEV <sub>1</sub>            |                   |         | FEV <sub>1</sub> /FVC   |                   |         |
|--------------------------------------------------|-----------------------------|-------------------|---------|-------------------------|-------------------|---------|
|                                                  | Regression coefficient (l)* | 95% CI            | p Value | Regression coefficient* | 95% CI            | p Value |
| 1 (lowest)                                       | —                           | —                 | —       | —                       | —                 | —       |
| 2                                                | −0.008                      | (−0.061 to 0.045) | 0.770   | 0.001                   | (−0.009 to 0.010) | 0.897   |
| 3                                                | 0.001                       | (−0.053 to 0.056) | 0.963   | 0.005                   | (−0.005 to 0.014) | 0.307   |
| 4                                                | 0.042                       | (−0.015 to 0.099) | 0.147   | 0.007                   | (−0.003 to 0.017) | 0.157   |
| 5 (highest)                                      | 0.079                       | (0.017 to 0.141)  | 0.012   | 0.014                   | (0.003 to 0.025)  | 0.010   |
| Effect per quintile increase in vitamin D intake | 0.020                       | (0.006 to 0.034)  | 0.007   | 0.003                   | (0.001 to 0.006)  | 0.008   |
| Fifths of vitamin D intake:                      | FVC                         |                   |         | COPD                    |                   |         |
|                                                  | Regression coefficient (l)* | 95% CI            | p Value | OR*                     | 95% CI            | p Value |
| 1 (lowest)                                       | —                           | —                 | —       | —                       | —                 | —       |
| 2                                                | −0.003                      | (−0.065 to 0.060) | 0.931   | 0.903                   | (0.644 to 1.266)  | 0.553   |
| 3                                                | −0.015                      | (−0.078 to 0.049) | 0.644   | 0.913                   | (0.650 to 1.281)  | 0.597   |
| 4                                                | 0.031                       | (−0.036 to 0.098) | 0.360   | 0.827                   | (0.572 to 1.197)  | 0.314   |
| 5 (highest)                                      | 0.056                       | (−0.016 to 0.128) | 0.128   | 0.570                   | (0.375 to 0.866)  | 0.008   |
| Effect per quintile increase in vitamin D intake | 0.014                       | (−0.003 to 0.031) | 0.109   | 0.894                   | (0.814 to 0.983)  | 0.020   |

\*Adjusted for energy intake, smoke in home, smoker status, pack years, age left education, home ownership status, no. of rooms, no. of cars, social class, fat mass, activity score, alcohol, dietary supplement use, birth weight, father's social class at birth, inhaled or oral steroids use and paracetamol use. Age, height and gender were also included in the COPD analyses. COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; 25(OH)D, 25 hydroxy vitamin D.

**Table 5** Relationship between serum 25(OH)D concentrations and FEV<sub>1</sub> (n=1197), FVC, FEV<sub>1</sub>/FVC and COPD (n=1195)

|                                         | FEV <sub>1</sub>            |                   |         | FEV <sub>1</sub> /FVC   |                   |         |
|-----------------------------------------|-----------------------------|-------------------|---------|-------------------------|-------------------|---------|
|                                         | Regression coefficient (I)* | 95% CI            | p Value | Regression coefficient* | 95% CI            | p Value |
| Fifths of 25(OH)D:                      |                             |                   |         |                         |                   |         |
| 1 (lowest)                              | —                           | —                 | —       | —                       | —                 | —       |
| 2                                       | 0.027                       | (-0.057 to 0.111) | 0.526   | 0.008                   | (-0.007 to 0.022) | 0.310   |
| 3                                       | -0.053                      | (-0.138 to 0.031) | 0.215   | -0.003                  | (-0.017 to 0.012) | 0.729   |
| 4                                       | -0.004                      | (-0.091 to 0.083) | 0.936   | -0.008                  | (-0.024 to 0.007) | 0.278   |
| 5 (highest)                             | 0.008                       | (-0.081 to 0.098) | 0.852   | -0.008                  | (-0.024 to 0.007) | 0.296   |
| Effect per quintile increase in 25(OH)D | -0.002                      | (-0.022 to 0.019) | 0.885   | -0.003                  | (-0.007 to 0.000) | 0.07    |
|                                         | FVC                         |                   |         | COPD                    |                   |         |
|                                         | Regression coefficient (I)* | 95% CI            | p Value | OR*                     | 95% CI            | p Value |
| Fifths of 25(OH)D:                      |                             |                   |         |                         |                   |         |
| 1 (lowest)                              | —                           | —                 | —       | —                       | —                 | —       |
| 2                                       | 0.010                       | (-0.084 to 0.104) | 0.831   | 0.992                   | (0.544 to 1.811)  | 0.980   |
| 3                                       | -0.058                      | (-0.152 to 0.037) | 0.229   | 1.230                   | (0.678 to 2.230)  | 0.496   |
| 4                                       | 0.023                       | (-0.074 to 0.121) | 0.640   | 1.728                   | (0.959 to 3.114)  | 0.069   |
| 5 (highest)                             | 0.049                       | (-0.051 to 0.149) | 0.336   | 1.524                   | (0.824 to 2.819)  | 0.179   |
| Effect per quintile increase in 25(OH)D | 0.011                       | (-0.012 to 0.034) | 0.342   | 1.151                   | (1.002 to 1.321)  | 0.046   |

\*Adjusted for smoke in home, smoker status, pack years, age left education, home ownership status, no. of rooms, no. of cars, social class, fat mass, activity score, alcohol, dietary supplement use, birth weight, father's social class at birth, inhaled or oral steroids use and paracetamol use, and season of clinic visit. Age, height and gender were also included in the COPD analyses.

COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; 25(OH)D, 25 hydroxy vitamin D.

There is a paucity of data on the relation between vitamin D status and lung function in the general population, and our findings are at odds with those from the large cross-sectional NHANES III study in the USA which reported a difference of over 100 ml between those in the top and bottom quintiles for serum 25(OH)D concentrations.<sup>16</sup> In keeping with NHANES, our population-based study will have included relatively few cases of severe COPD, in contrast to hospital-based studies of vitamin D and COPD. There are a number of possible explanations to consider for the discordant 25(OH)D results between our study and NHANES. First, ours was much smaller and therefore had less statistical power. However, the upper CI for the adjusted top versus bottom quintile difference in FEV<sub>1</sub> (98 ml) suggested that an effect as large as that reported in NHANES (106 ml) would be unlikely, although the estimate in NHANES for FVC (142 ml) was just within the upper confidence limit in our study (149 ml). Second, the mean concentration of serum 25(OH)D was considerably higher in NHANES than in our population, and it is possible that beneficial effects of vitamin D might be stronger at higher concentrations. Third,

we have no reason to believe that the measurements of 25(OH)D in our study were not robust. In our largely Caucasian UK population we observed slightly lower mean serum 25(OH)D concentrations than in two national adult surveys in Britain,<sup>5,6</sup> and the prevalence of profound vitamin D deficiency, defined by a cut-off of <25 nmol/l, was higher than that found in one of these surveys<sup>5</sup> but comparable to that found in the other.<sup>6</sup> Furthermore, the higher mean serum concentrations and lower prevalence of deficiency in summer and autumn compared with winter and spring were as expected,<sup>5</sup> as was the stronger correlation between dietary vitamin D intake and serum concentrations in the winter.<sup>6</sup>

While we had greater statistical power in the dietary analyses, the lack of a relation between 25(OH)D concentrations (the gold standard measure of vitamin D status) and FEV<sub>1</sub> would suggest that the observed association between dietary vitamin D intake and lung function is unlikely to be causal. Indeed, the value of analysing dietary vitamin D intake alone as a means of effectively establishing the influence of vitamin D on outcomes has been questioned, given its minor contribution to overall vitamin

**Table 6** Mean lung function and prevalence of COPD by vitamin D receptor genotype

| Genotype | Genotype | FEV <sub>1</sub> (l) |      |      | FVC (l) |      |      | FEV <sub>1</sub> /FVC ratio |       |      | COPD    |     |      |
|----------|----------|----------------------|------|------|---------|------|------|-----------------------------|-------|------|---------|-----|------|
|          |          | N                    | Mean | SD   | N       | Mean | SD   | N                           | Mean  | SD   | Total N | N   | %    |
| Apa1     | gg       | 1117                 | 2.46 | 0.68 | 1113    | 3.45 | 0.93 | 1113                        | 0.717 | 0.09 | 1113    | 193 | 17.3 |
|          | ga       | 1279                 | 2.41 | 0.68 | 1278    | 3.39 | 0.92 | 1278                        | 0.714 | 0.09 | 1278    | 238 | 18.6 |
|          | aa       | 373                  | 2.42 | 0.65 | 372     | 3.40 | 0.89 | 372                         | 0.717 | 0.09 | 372     | 68  | 18.3 |
| Fok1     | gg       | 1769                 | 2.43 | 0.68 | 1765    | 3.41 | 0.92 | 1765                        | 0.717 | 0.09 | 1765    | 305 | 17.3 |
|          | ga       | 871                  | 2.43 | 0.67 | 869     | 3.41 | 0.92 | 869                         | 0.715 | 0.09 | 869     | 163 | 18.8 |
|          | aa       | 98                   | 2.50 | 0.70 | 98      | 3.55 | 1.00 | 98                          | 0.709 | 0.07 | 98      | 20  | 20.4 |
| Cdx2     | aa       | 791                  | 2.42 | 0.66 | 789     | 3.40 | 0.93 | 789                         | 0.716 | 0.08 | 789     | 147 | 18.6 |
|          | ca       | 1349                 | 2.44 | 0.68 | 1346    | 3.41 | 0.89 | 1346                        | 0.716 | 0.09 | 1346    | 231 | 17.2 |
|          | cc       | 636                  | 2.45 | 0.68 | 635     | 3.44 | 0.94 | 635                         | 0.715 | 0.08 | 635     | 119 | 18.7 |

COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; 25(OH)D, 25 hydroxy vitamin D.

D status and the resulting misclassification of total exposure.<sup>9</sup> While we controlled extensively for lifestyle confounders, it seems likely that the apparent effect of dietary vitamin D on lung function may actually reflect the effects of other collinear nutrients in the diet. For example, in this population we have previously shown that a 'prudent' dietary pattern—characterised by a high consumption of fruit, vegetables, oily fish and wholemeal cereals—is associated with better lung function.<sup>27</sup> Higher prudent diet scores are associated with greater intakes of a range of micronutrients including vitamin D.<sup>28</sup> Our latest findings would suggest that the protective effect of the 'prudent' pattern, if causal, is unlikely to be attributable to a higher intake of vitamin D and is more likely to be explained by antioxidant nutrients in fruit, vegetables and whole grains or nutrients other than vitamin D in oily fish such as n3 fatty acids. A higher intake of fruit and whole grains, of various antioxidants including vitamins C and E, beta carotene and selenium, and of n3 fatty acids have all been linked to better lung function.<sup>29</sup>

One strength of our study was the availability of VDR genotype data. We used these in two ways. First, we analysed gene main effects on lung function in a Mendelian randomisation approach, given the crucial role of the VDR in mediating effects of vitamin D; any associations found would be unlikely to be explained by confounding or by 'reverse causation', despite the cross-sectional nature of our study.<sup>17</sup> As genetic data were available for the majority of the population, we had greater statistical power than we did for the analyses of serum 25(OH)D concentrations. Second, we explored potential modification of effects of serum 25(OH)D concentrations and vitamin D intake on lung function by VDR genotypes. If we had confirmed gene main effects or gene–vitamin D interactions, this would have supported a causal relation between vitamin D and lung function, but we did not. A limitation of our study is that we did not analyse the relation between polymorphisms in the vitamin D binding protein gene (GC) and lung function, as these have recently been shown to be a major determinant of circulating 25(OH)D concentrations<sup>30 31</sup> and to be linked to COPD risk.<sup>14 32</sup> Other limitations, as with the NHANES study, include its cross-sectional nature and the fact that serum 25(OH)D concentrations were measured on one occasion only, although we did control for seasonal variation in the analyses. Also, while we defined COPD spirometrically, which is the gold standard approach<sup>33</sup> and avoids potential problems of bias which might arise with self-reported disease, we did not measure post-bronchodilator lung function. This raises the possibility that a small minority of individuals classified as having COPD by our spirometric definition may have had asthma.

Just over half of those invited to take part agreed to home interviews and over 90% of those performed spirometry. Those who were interviewed were broadly similar in their characteristics to those participating in the nationally representative Health Survey for England,<sup>18</sup> and mortality from respiratory disease in men in the Hertfordshire Cohort is similar to that in England and Wales as a whole.<sup>34</sup> We therefore believe that our findings can be extrapolated to the wider English population. While we cannot rule out the possibility that non-response might have biased the associations between vitamin D and respiratory outcomes, weights at birth and at 1 year of age, which we have previously shown to be associated with lung function in late adult life and COPD mortality in another Hertfordshire cohort,<sup>35</sup> were similar for those who did and those who did not agree to home interview.<sup>18</sup>

In conclusion, and in contrast to a previous population-based study from the USA, our analyses of 25(OH)D concentrations

suggest that vitamin D is not an important determinant of adult lung function or COPD in the general UK population. The apparent relationships with dietary vitamin D are likely to be explained by other nutrients in the diet which are highly correlated with vitamin D.

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