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Meta-analysis across Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium provides evidence for an association of serum vitamin D with pulmonary function

Jiayi Xu[1], Traci M. Bartz[2,3]†, Geetha Chittoor[4,5]†, Gudny Eiriksdottir[6]†, Ani W. Manichaikul[7]†, Fangui Sun[8]†, Natalie Terzikhan[9,10]†, Xia Zhou[11]†, Sarah L. Booth[12], Guy G. Brusselle[9,10,13], Ian H. de Boer[14], Myriam Fornage[15,16], Alexis C. Frazier-Wood[17], Mariaelisa Graff[5], Vilmundur Gudnason[6,18], Tamara B. Harris[19], Albert Hofman[10,20,21], Ruixue Hou[22], Denise K. Houston[23], David R. Jacobs Jr[11], Stephen B. Kritchevsky[23,24,25], Jeanne Latourelle[26,27], Rozenn N. Lemaitre[3,14], Pamela L. Lutsey[11], George O'Connor[26], Elizabeth C. Oelsner[28], James S. Pankow[11], Bruce M. Psaty[3,14,29,30,31], Rebecca R. Rohde[5], Stephen S. Rich[7], Jerome I. Rotter[32], Lewis J. Smith[33], Bruno H. Stricker[10,20], V. Saroja Voruganti[22], Thomas J. Wang[34], M. Carola Zillikens[20,35], R. Graham Barr[28]‡, Josée Dupuis[8]‡, Sina A. Gharib[14,36]‡, Lies Lahousse[9,10,37]‡, Stephanie J. London[38]‡, Kari E. North[5]‡, Albert V. Smith[6,18]‡, Lyn M. Steffen[11]‡, Dana B. Hancock[39] and Patricia A. Cassano[1,40]*

[1]*Division of Nutritional Sciences, Cornell University, Ithaca, NY 14853, USA*
[2]*Department of Biostatistics, University of Washington, Seattle, WA 98195, USA*
[3]*Cardiovascular Health Research Unit, University of Washington, Seattle, WA 98101, USA*
[4]*Department of Biomedical and Translational Informatics, Geisinger, Danville, PA 17822, USA*
[5]*Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA*
[6]*Icelandic Heart Association, Holtasmari 1, 201 Kópavogur, Iceland*
[7]*Center for Public Health Genomics, University of Virginia School of Medicine, Charlottesville, VA 22903, USA*
[8]*Department of Biostatistics, Boston University School of Public Health, Boston, MA 02118, USA*
[9]*Department of Respiratory Medicine, Ghent University Hospital, 9000 Ghent, Belgium*
[10]*Department of Epidemiology, Erasmus Medical Center, 3000 CA Rotterdam, the Netherlands*
[11]*Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN 55454, USA*
[12]*Jean Mayer-US Department of Agriculture Human Nutrition Research Center on Aging, Tufts University, Boston, MA 02111, USA*
[13]*Department of Respiratory Medicine, Erasmus Medical Center, 3015 CE Rotterdam, The Netherlands*
[14]*Department of Medicine, University of Washington, Seattle, WA 98195, USA*
[15]*Institute of Molecular Medicine, University of Texas Health Science Center at Houston, Houston, TX 77030, USA*
[16]*Human Genetics Center, School of Public Health, University of Texas Health Science Center at Houston, Houston, TX 77030, USA*
[17]*Children's Nutrition Research Center, Baylor College of Medicine, Houston, TX 77030, USA*
[18]*University of Iceland, Saemundargata 2, 101 Reykjavik, Iceland*
[19]*Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, National Institutes of Health, Department of Health and Human Services, Bethesda, MD 20892, USA*
[20]*Netherlands Genomics Initiative (NGI)-sponsored Netherlands Consortium for Healthy Aging, 2333 ZC Leiden, The Netherlands*
[21]*Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA 02115, USA*
[22]*Department of Nutrition and Nutrition Research Institute, University of North Carolina at Chapel Hill, Kannapolis, NC 28081, USA*
[23]*Sticht Center on Aging, Wake Forest School of Medicine, Winston-Salem, NC 27157, USA*

Abbreviations: 1,25-$(OH)_2$D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; AA, African ancestry; AGES, Age, Gene, Environment, Susceptibility Study – Reykjavik, Iceland; ARIC, Atherosclerosis Risk in Communities Study; CARDIA, Coronary Artery Risk Development in Young Adults Study; CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology; CHS, Cardiovascular Health Study; COPD, chronic obstructive pulmonary disease; EA, European ancestry; FEV_1, forced expiratory volume in the 1st second; FHS (Offspring), Framingham Heart Study –Offspring Cohort; FHS (Gen3), Framingham Heart Study – Generation 3 Cohort; FVC, forced vital capacity; HABC, Health, Aging, and Body Composition Study; MESA, Multi-Ethnic Study of Atherosclerosis; PFT, pulmonary function test; RIA, radioimmunoassay.

* **Corresponding author:** P. A. Cassano, fax +1 607 255 2691, email pac6@cornell.edu

† These authors contributed equally to this work as analysts.

‡ These authors contributed equally to this work as principal investigators.

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[24]Section on Gerontology and Geriatric Medicine, Wake Forest School of Medicine, Winston-Salem, NC 27157, USA
[25]Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC 27157, USA
[26]The Pulmonary Center, Department of Medicine, Boston University, Boston, MA 02118, USA
[27]Department of Neurology, Boston University, Boston, MA 02118, USA
[28]Department of Medicine, Columbia University, New York, NY 10032, USA
[29]Department of Epidemiology, University of Washington, Seattle, WA 98195, USA
[30]Department of Health Services, University of Washington, Seattle, WA 98195, USA
[31]Kaiser Permanente Washington Health Research Institute, Seattle, WA 98101, USA
[32]Institute for Translational Genomics and Population Sciences, Los Angeles Biomedical Research Institute and Department of Pediatrics at Harbor-UCLA Medical Center, Torrance, CA 90502, USA
[33]Division of Pulmonary and Critical Care, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611, USA
[34]Division of Cardiovascular Medicine, Department of Medicine, Vanderbilt University, Nashville, TN 37232, USA
[35]Department of Internal Medicine, Erasmus Medical Center, 3000 CA Rotterdam, The Netherlands
[36]Center for Lung Biology, University of Washington, Seattle, WA 98109, USA
[37]Department of Bioanalysis, Ghent University, 9000 Ghent, Belgium
[38]Division of Intramural Research, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, NC 27709, USA
[39]Center for Omics Discovery and Epidemiology, Behavioral Health Research Division, RTI International, Research Triangle Park, NC 27709, USA
[40]Department of Healthcare Policy and Research, Division of Biostatistics and Epidemiology, Weill Cornell Medical College, New York, NY 10065, USA

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Abstract

The role that vitamin D plays in pulmonary function remains uncertain. Epidemiological studies reported mixed findings for serum 25-hydroxyvitamin D (25(OH)D)–pulmonary function association. We conducted the largest cross-sectional meta-analysis of the 25(OH)D–pulmonary function association to date, based on nine European ancestry (EA) cohorts (n 22 838) and five African ancestry (AA) cohorts (n 4290) in the Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium. Data were analysed using linear models by cohort and ancestry. Effect modification by smoking status (current/former/never) was tested. Results were combined using fixed-effects meta-analysis. Mean serum 25(OH)D was 68 (SD 29) nmol/l for EA and 49 (SD 21) nmol/l for AA. For each 1 nmol/l higher 25(OH)D, forced expiratory volume in the 1st second (FEV_1) was higher by 1·1 ml in EA (95 % CI 0·9, 1·3; $P < 0·0001$) and 1·8 ml (95 % CI 1·1, 2·5; $P < 0·0001$) in AA ($P_{\text{race difference}} = 0·06$), and forced vital capacity (FVC) was higher by 1·3 ml in EA (95 % CI 1·0, 1·6; $P < 0·0001$) and 1·5 ml (95 % CI 0·8, 2·3; $P = 0·0001$) in AA ($P_{\text{race difference}} = 0·56$). Among EA, the 25(OH)D–FVC association was stronger in smokers: per 1 nmol/l higher 25(OH)D, FVC was higher by 1·7 ml (95 % CI 1·1, 2·3) for current smokers and 1·7 ml (95 % CI 1·2, 2·1) for former smokers, compared with 0·8 ml (95 % CI 0·4, 1·2) for never smokers. In summary, the 25(OH)D associations with FEV_1 and FVC were positive in both ancestries. In EA, a stronger association was observed for smokers compared with never smokers, which supports the importance of vitamin D in vulnerable populations.

Key words: Vitamin D: Forced expiratory volume: Vital capacity: Respiratory function tests: Smoking: Whites: African Americans

Chronic obstructive pulmonary disease (COPD), the third leading cause of mortality in the USA[1] and among the top ten leading causes of total years of life lost in the world[2], is characterised by progressive airway obstruction. Pulmonary function tests (PFT), as performed by spirometry, are used to quantify pulmonary function parameters including forced expiratory volume in the 1st second (FEV_1) and forced vital capacity (FVC). Pulmonary function increases throughout childhood, plateaus in the 20s, and thereafter adults experience an age-related decline[3]. The majority of COPD cases (85 %) are related to smoking[4], which alters the trajectory in pulmonary function, by hindering growth, reducing peak function and accelerating age-related decline[5].

Vitamin D is proposed to have protective effects in the lungs via gene regulation[6]. *In vitro* studies found that 1,25-dihydroxyvitamin D (1,25-$(OH)_2$D), the active vitamin D metabolite, induced antimicrobial peptides for host defence in the lung and modulated airway remodelling[7]. In humans, 25-hydroxyvitamin D (25(OH)D) is the major vitamin D metabolite in serum, most of which forms a complex with vitamin D binding protein (DBP) (approximately 85–90 % is DBP-bound)[8], and then is metabolised to 1,25-$(OH)_2$D, the active steroid hormone form[8,9]. Total 25(OH)D is the commonly used biomarker of vitamin D status, and it is preferred to other vitamin D metabolites, such as non-DBP-bound 25(OH)D and 1,25-$(OH)_2$D, given that it is a comprehensive indicator for vitamin D stores, has a longer half-life (approximately 3 weeks) and is less affected by Ca[10,11]. On average, African ancestry (AA) populations have lower serum 25(OH)D concentrations,

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due to multiple factors including genetics and skin pigmentation[7], but evidence exists that AA populations have higher 1,25-$(OH)_2$D levels and greater bone mineral density compared with European ancestry (EA) populations[12].

Previous observational cross-sectional studies of the vitamin D–pulmonary function association in the general population reported mixed findings. Most of these studies reported a positive association between 25(OH)D and pulmonary function[13–19], although some reported a null or inverse association[20–22], and two others reported a positive association under certain conditions, such as only in male current smokers[23] or only in overweight and obese males[24]. The largest previous cross-sectional study, which included two Danish cohorts (total 18 507), reported positive associations of 25(OH)D with pulmonary function[16]. Only one prior cross-sectional study investigated serum 25(OH)D and pulmonary function in an ancestry group other than European, and it confirmed similar positive associations in the 3957 AA participants studied[13].

The current study investigated the hypothesis that serum 25(OH)D level is positively associated with pulmonary function. We leveraged the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium to include population-based data on serum 25(OH)D and pulmonary function in a harmonised analysis. In addition, we compared the association of serum 25(OH)D and pulmonary function across EA and AA groups and investigated effect modification by cigarette smoking.

Methods

Cohorts and participants

Nine prospective cohorts in the CHARGE Consortium were included (Table 1). All cohorts had EA participants, and five of the cohorts had AA participants. Only one cohort (Multi-Ethnic Study of Atherosclerosis (MESA)) has participants with other ancestries, and these other ancestries were not included in this study. Among the nine cohorts, the Framingham Heart Study (FHS) had two sub-cohorts analysed separately: the Offspring and the Third-Generation (Gen3) cohorts. Our analysis pipeline harmonised the outcome and exposure definitions, the units on all variables and the statistical modelling. The same exclusion criteria were applied to each cohort: missing PFT, unacceptable PFT using the American Thoracic Society and European Respiratory Society criteria for acceptability, missing serum 25(OH)D, serum 25(OH)D >374·4 nmol/l (or 150 ng/ml, leading to removal of a single outlier)[25] or missing on other covariates (online Supplementary Table S1).

Outcome and exposure assessment

Pre-bronchodilator pulmonary function outcomes (FEV_1, FVC and FEV_1/FVC), which have similar accuracy as post-bronchodilator measures for long-term outcomes[26], were measured in each cohort using standardised methods defined by the American Thoracic Society/European Respiratory Society criteria (online Supplementary Table S2). The methods used to measure 25(OH)D varied by cohort (online Supplementary Table S2). Three cohorts, including MESA, the Atherosclerosis Risk In Communities (ARIC) study, and the Cardiovascular Health Study (CHS), used the current reference method, liquid chromatography in tandem with mass spectrometry (LC-MS/MS); three cohorts, including FHS, the Coronary Artery Risk Development in Young Adults (CARDIA) study, and the Health, Aging, and Body Composition (HABC) study, used radioimmunoassay (RIA); one cohort, the Age, Gene, Environment, Susceptibility Study – Reykjavik, Iceland (AGES), used chemiluminescence immunoassay (CLIA); and one cohort (the Rotterdam Study (RS)) used electro-CLIA. Only MESA calibrated the serum 25(OH)D measurement against the standard reference material 972[27], which reflects the calendar time of the measurements in the cohorts, most of which occurred before the availability of the standard reference material (online Supplementary Table S3). Measurements of the outcome and exposure variables were planned for either the full cohort (ARIC, CHS, FHS, HABC and RS) or a subset of the cohort if the outcome or the exposure was only measured in an ancillary study (AGES, CARDIA and MESA)[28–31] (online Supplementary Table S1). Continuous variables were used for serum 25(OH)D and pulmonary function to capture the association of 25(OH)D on PFT across the broad distribution of ranges in the cohorts.

As shown in Table 1, among nine cohorts, four (AGES, CHS, FHS-Offspring and FHS-Gen3) had a mean time difference of <1 year in the PFT measurements and the preceding 25(OH)D measurement, and the greatest mean time difference between 25(OH)D and PFT measurement was <5 years (MESA). Participants in ARIC and HABC had blood drawn for serum 25(OH)D after their PFT measure, but within 3 years.

Other covariates, including smoking status, pack-years (number of packs of cigarettes smoked per d times the number of years smoked), height, weight and age, were measured concurrently with pulmonary function, except for CHS, which assessed covariates concurrent with the serum 25(OH)D measure, but within 1 year of the PFT measurement (online Supplementary Table S3). All data collection and analysis was approved by the Institutional Review Board at each cohort's respective institution. Spirometry measures are available on the database of Genotypes and Phenotypes via accession numbers as follows: ARIC (phs000280), CARDIA (phs000285), CHS (phs000287), FHS (phs000007) and MESA (phs000209). Serum vitamin D measures are also available at the same accession numbers for CHS, FHS and MESA.

Statistical analysis in individual cohorts

All analyses were first conducted independently in each cohort, stratified by ancestry, given the lower mean serum 25(OH)D level in AA participants[7]. For FEV_1 and FEV_1/FVC, models were adjusted for smoking status, pack-years, height, height squared, age, age squared, sex, season of blood draw and study centre (if applicable); for FVC, the model was further adjusted for weight. Residual outliers, identified using the studentised residuals of the linear models (online Supplementary methods for more details), were excluded from all models (about 0·3 % of the total sample size). The model was extended to test the

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interaction between 25(OH)D and smoking status (never (reference group), former and current smokers).

Meta-analysis

We tested the association of serum 25(OH)D on each PFT outcome among individuals in each ancestry group and each cohort, separately, and then combined the effect estimates (also referred to as two-stage meta-analysis[32]), using inverse variance weighting and assuming fixed-effects, with heterogeneity assessed via the I^2 statistic[33]. Random-effects meta-analysis was performed as a sensitivity analysis if there was potential heterogeneity ($I^2 > 30\%$). The comparison of meta-analysed coefficients of the 25(OH)D–PFT associations for the two ancestry groups was conducted using a Z test[34]. Meta-analysis of the interaction terms of 25(OH)D with smoking status was also performed (online Supplementary methods for more details, online Supplementary Tables S4 and S5 for cohort-specific findings and online Supplementary Table S6 for meta-analysed results).

Meta-regression was conducted to explore the potential causes of moderate heterogeneity in the meta-analysis of 25(OH)D on FEV_1 and FVC in the EA cohorts. Modifiers were tested individually in the meta-regression models to investigate heterogeneity; modifiers included factors that could vary between cohorts, such as proportion of ever, current and former smokers, mean 25(OH)D level, assay method for serum 25(OH)D, time between 25(OH)D and PFT measures, and mean age of participants in each cohort. The two-sided type I error was examined at 0·05 for all analyses. Meta-analysis and meta-regression were conducted using the metafor package (version 1.9-8) in R (version 3.2.3.; R Foundation for Statistical Computing).

Regression coefficients (β) with their standard errors calculated within each cohort per 1 nmol/l 25(OH)D are presented in the figures. In addition, to put the magnitude of the 25(OH)D–PFT associations in terms relevant to public health, the meta-analysed regression coefficients were multiplied by 10 nmol/l 25(OH)D, which is about half of the standard deviation of the 25(OH)D distribution.

Results

We studied 22 838 EA and 4290 AA participants. EA participants had higher FEV_1, FVC and serum 25(OH)D than AA participants in each cohort, whereas FEV_1/FVC was similar across ancestry groups (Table 1 and online Supplementary Fig. S1). CARDIA and FHS-Gen3 were younger than the seven other cohorts, with consequently lower pack-years smoked in ever smokers. Across all cohorts, among EA participants, 17 % were current smokers and 40 % were former smokers; among AA participants, 22 % were current smokers and 30 % were former smokers. The mean serum 25(OH)D level was highest among never smokers (70 (SD 30) nmol/l), followed by former smokers (67 (SD 29) nmol/l) and current smokers (64 (29) nmol/l) in EAs, whereas the trend was less obvious in AA (49 (SD 21) nmol/l in current smokers, 50 (SD 21) nmol/l in former smokers and 48 (SD 21) nmol/l in never smokers). The mean of serum 25(OH)D for EA participants across nine cohorts was 68 (SD 29) nmol/l and for AA participants across five cohorts the mean was 49 (SD 21) nmol/l.

Fixed-effects meta-analysis (Fig. 1) revealed a consistently positive association of serum 25(OH)D with the PFT outcomes, FEV_1 and FVC, in both ancestry groups. To put these findings into context, a 10 nmol/l (approximately 0·5 SD) higher 25(OH)D was associated with 11·1 ml higher FEV_1 in EA ($P < 0{\cdot}0001$) and 17·9 ml higher FEV_1 in AA ($P < 0{\cdot}0001$). Similarly, for a 10 nmol/l higher 25(OH)D, FVC was higher by 12·9 ml in EA ($P < 0{\cdot}0001$) and by 15·4 ml in AA ($P = 0{\cdot}0001$). The magnitudes of the 25(OH)D–PFT associations did not differ significantly between the two ancestry groups ($P = 0{\cdot}06$ and $P = 0{\cdot}56$ for FEV_1 and FVC, respectively). The association of serum 25(OH)D with FEV_1/FVC reached statistical significance only in EA ($P = 0{\cdot}0013$), and the magnitude was negligible; a 10 nmol/l higher 25(OH)D was associated with a ratio being lower by 0·055 % (online Supplementary Table S7 and Supplementary Fig. S2 for ancestry- and cohort-specific findings).

In the main-effect meta-analysis of serum 25(OH)D on pulmonary function, EA cohorts had low to moderate heterogeneity, whereas AA cohorts had low heterogeneity (Fig. 1, online Supplementary Fig. S2). We did a sensitivity analysis using random-effects meta-analysis among EA cohorts for the FEV_1 and FVC outcomes, and no substantial change was found in the meta-analysed effect estimates and corresponding SE (coefficient of 1 nmol/l 25(OH)D on the FEV_1 outcome was 1·11 (SE 0·12) ml in the fixed-effects model and 1·21 (SE 0·19) ml in the random-effects model; coefficient on the FVC outcome was 1·29 (SE 0·14) ml in the fixed-effects model and 1·31 (SE 0·20) ml in the random-effects model). Meta-regression was also performed in the EA cohorts and we found that among these cohorts, cohorts with lower mean 25(OH)D concentration had stronger 25(OH)D–PFT associations (Fig. 2). The proportion of ever smokers and of former smokers had significant linear associations with the 25(OH)D–PFT coefficients (online Supplementary Fig. S3), and these two variables were both highly correlated with mean 25(OH)D levels (Pearson's $r < -0{\cdot}75$ for all pairwise correlations). The 25(OH)D–PFT association in EA cohorts varied by 25(OH)D assay method (meta-regression $P = 0{\cdot}0059$); the association was attenuated in cohorts using RIA compared with cohorts using liquid chromatography in tandem with MS (pairwise $P < 0{\cdot}005$, online Supplementary Fig. S4). Mean age of each cohort was a significant positive modifier of the 25(OH)D–FEV_1 association, while time difference between 25(OH)D and spirometry measures did not affect the 25(OH)D–PFT association (online Supplementary Fig. S3).

To examine the potential impact of family relatedness between the FHS-Gen3 and the FHS-Offspring cohorts on the meta-analysis, sensitivity analysis confirmed that the findings were unchanged when either cohort was excluded (results not shown). In addition, the meta-analysis findings were not sensitive to exclusion of residual outliers.

In the EA cohorts, 25(OH)D had a greater positive association with FVC in current smokers than in never smokers ($\beta_{\text{current} \times 25(OH)D} =$ 7·5 ml for 10 nmol/l increment of 25(OH)D, $P = 0{\cdot}047$). Similarly, 25(OH)D had a greater positive association with FVC

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Table 1. Cross-sectional participant characteristics of each cohort in the Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium (*n* 27 128)*
(Mean values and standard deviations)

	ARIC		CARDIA		CHS†		HABC‡		MESA		AGES		FHS (Offspring)		FHS (Gen3)		RS	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
European ancestry cohorts																		
Number of participants	8327		172		1297		1411		1113		1685		1639		3610		3584	
Males (%)	46·0		58·7		30·2		53·3		49·2		40·8		48·1		47·3		44·6	
Current smoker (%)	23·4		11·6		9·4		6·5		8·4		9·8		14·3		15·3		16·0	
Former smoker (%)	34·9		16·3		44·9		49·8		47·2		42·4		50·5		28·0		52·9	
Pack-years§	28·0	20·9	6·2	7·2	28·1	25·3	36·4	32·0	30·1	29·6	24·6	21·9	26·5	22·8	12·4	13·4‖	22·9	21·6
Age (years)	54·2	5·7	34·8	3·1	73·7	4·4	73·7	2·8	66·3	9·9	76·2	5·6	59·4	9·3	40·2	8·7	64·4	9·7
Height (m)	1·69	0·09	1·73	0·09	1·63	0·09	1·67	0·09	1·69	0·10	1·67	0·09	1·68	0·09	1·71	0·09	1·69	0·09
Weight (kg)¶	76·8	16·2	76·9	17·0	70·6	14·2	74·5	14·5	79·7	17·3	75·4	14·7	79·4	17·2	78·6	18·4	79·5	14·6
FEV_1 (ml)	2946	767	3881	743	2010	611	2324	649	2556	768	2142	670	2724	757	3592	787	2848	866
FVC (ml)	3987	973	4967	999	2881	829	3118	810	3492	995	2877	837	3711	950	4621	999	3692	1063
FEV_1/FVC	0·739	0·077	0·785	0·060	0·700	0·095	0·745	0·078	0·734	0·087	0·744	0·087	0·733	0·078	0·779	0·063	0·771	0·082
Serum 25(OH)D (nmol/l)**	64·7	21·8	95·0	35·3	68·0	27·9	72·2	25·6	75·6	28·2	52·4	23·5	49·2	18·9	92·8	36·0	61·0	27·4
Never smoker	64·3	21·0	95·4	34·4	67·1	25·1	73·7	25·9	76·5	27·7	54·1	22·8	49·6	18·6	93·2	35·4††	59·7	25·9
Former smoker	67·1	21·5	94·5	43·0	69·4	29·4	71·7	24·8	76·2	28·5	52·3	24·1	49·8	18·6	93·5	37·0	62·3	27·7
Current smoker	61·8	23·1	92·7	29·5	65·4	33·2	65·0	28·1	66·9	28·2	44·5	22·7	45·9	20·6	89·9	36·3	59·5	29·4
Method of 25(OH)D measurement	LC-MS/MS		RIA		LC-MS/MS		RIA		LC-MS/MS		CLIA		RIA		RIA		Electro-CLIA	
Time from 25(OH)D to PFT (d)‡‡	−1073	67	1122	89	363	29	−382	39	1765	112	1	5	133	377	2	61	846	808
Season of 25(OH)D measurement (%)§§																		
Spring	31·2		8·1		20·5		30·5		29·0		22·4		29·2		26·8		29·6	
Summer	26·1		36·1		30·1		18·1		22·2		12·4		11·0		29·6		18·9	
Autumn	23·3		34·3		29·6		22·8		24·9		33·8		29·1		24·1		30·0	
Winter	19·5		21·5		19·8		28·6		23·9		31·4		30·7		19·4		21·5	
African ancestry cohort																		
Number of participants	2339		157		168		863		763									
Males (%)	35·3		51·6		25·6		44·5		47·4									
Current smoker (%)	27·5		26·1		10·7		15·8		15·7									
Former smoker (%)	23·9		9·6		42·9		39·3		38·3									
Pack-years§	21·4	20·7	5·3	4·6	21·9	18·3	29·4	23·4	23·6	21·8								
Age (years)	53·3	5·7	33·9	3·2	71·9	4·5	73·4	2·9	65·6	9·7								
Height (m)	1·68	0·09	1·71	0·10	1·63	0·08	1·66	0·09	1·68	0·10								
Weight (kg)¶	83·5	17·1	82·2	16·9	75·7	13·3	78·2	15·1	84·3	16·8								
FEV_1 (ml)	2495	638	3237	709	1801	508	1958	566	2200	667								
FVC (ml)	3255	806	4077	920	2507	706	2594	712	2933	869								

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Table 1. *Continued*

	ARIC		CARDIA		CHS†		HABC‡		MESA		AGES		FHS (Offspring)		FHS (Gen3)		RS	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
FEV_1/FVC	0·768	0·077	0·799	0·070	0·723	0·076	0·757	0·090	0·755	0·093								
Serum 25(OH)D (nmol/l)**	47·4	17·5	69·4	31·2	44·6	21·1	51·8	22·4	47·9	22·3								
Never smoker	46·8	16·7	71·3	30·1	43·7	19·2	51·8	22·7	49·1	22·3								
Former smoker	48·5	18·0	69·2	35·6	47·2	24·2	52·3	21·8	49·3	22·6								
Current smoker	47·5	18·4	64·8	32·4	38·3	14·9	50·4	23·2	40·9	20·0								
Method of 25(OH)D measurement	LC-MS/MS		RIA		LC-MS/MS		RIA		LC-MS/MS									
Time from 25(OH)D to PFT (d)‡‡	−1054	114	1101	104	350	26	−390	53	1719	115								
Season of 25(OH)D measurement (%)§§																		
Spring	30·0		10·2		58·9		35·6		34·6									
Summer	30·7		56·0		7·1		16·2		23·5									
Autumn	20·7		23·6		8·9		24·9		19·7									
Winter	18·6		10·2		25·0		23·3		22·3									

ARIC, Atherosclerosis Risk in Communities Study; CARDIA, Coronary Artery Risk Development in Young Adults Study; CHS, Cardiovascular Health Study; HABC, Health, Aging, and Body Composition Study; MESA, Multi-Ethnic Study of Atherosclerosis; AGES, Age, Gene, Environment, Susceptibility Study – Reykjavik, Iceland; FHS (Offspring), Framingham Heart Study – Offspring Cohort; FHS (Gen3), Framingham Heart Study – Generation 3 Cohort; RS, Rotterdam Study (Netherlands); FEV_1, forced expiratory volume in the 1st second; FVC, forced vital capacity; 25(OH)D, 25-hydroxyvitamin D; LC-MS/MS, liquid chromatography in tandem with MS; CLIA, chemiluminescence immunoassay; RIA, radioimmunoassay.

* AGES, RS and FHS only have participants of European ancestry; *n* 22 838 for EA, *n* 4290 for AA, total *n* 27 128.

† The number of participants used to compute descriptive statistics in CHS excluded those who had residual outliers based on the preliminary models (*n* 8 for EA and *n* 6 for AA); whereas other cohorts used the number of participants before applying residual exclusion for the descriptive statistics.

‡ Numbers vary slightly for different outcomes in HABC (for the FVC outcome, *n* 1385 for EA and *n* 821 for AA; for the ratio outcome, *n* 1382 for EAs and *n* 817 for AAs). The numbers of participants for the FEV_1 outcome are used. However, the descriptive statistics is similar across different outcomes.

§ Pack-years is calculated only among current and former smokers in each cohort.

‖ We used 1554 ever smokers here, instead of a total of 1561 ever smokers in the Gen3 cohort, because the pack-years of seven ever smokers were so small that they were coded as 0. Therefore, these seven ever smokers do not contribute to the pack-years descriptive statistics here.

¶ The number of participants who have weight data is slightly different from the total number of participants in each cohort. However, the descriptive statistics of weight stays similar.

** Mean (SD) of serum 25(OH)D level for all the participants in each cohort, and mean (SD) of 25(OH)D level in participants with each smoking status are shown here, stratified by ancestry.

†† We used 2046 never smokers, rather than a total of 2049 never smokers in the Gen3 cohort, to compute the 25(OH)D level in never smokers.

‡‡ The time difference is the interval between the time when pulmonary function was measured and the time when serum vitamin D was measured. The difference is positive, if the serum vitamin D was measured before the pulmonary function test; whereas the value is negative, if the serum vitamin D was measured after the pulmonary function test.

§§ The proportion of participants in each season when their serum was measured was rounded (thus rounding errors mean sums may not be exactly 100 %).

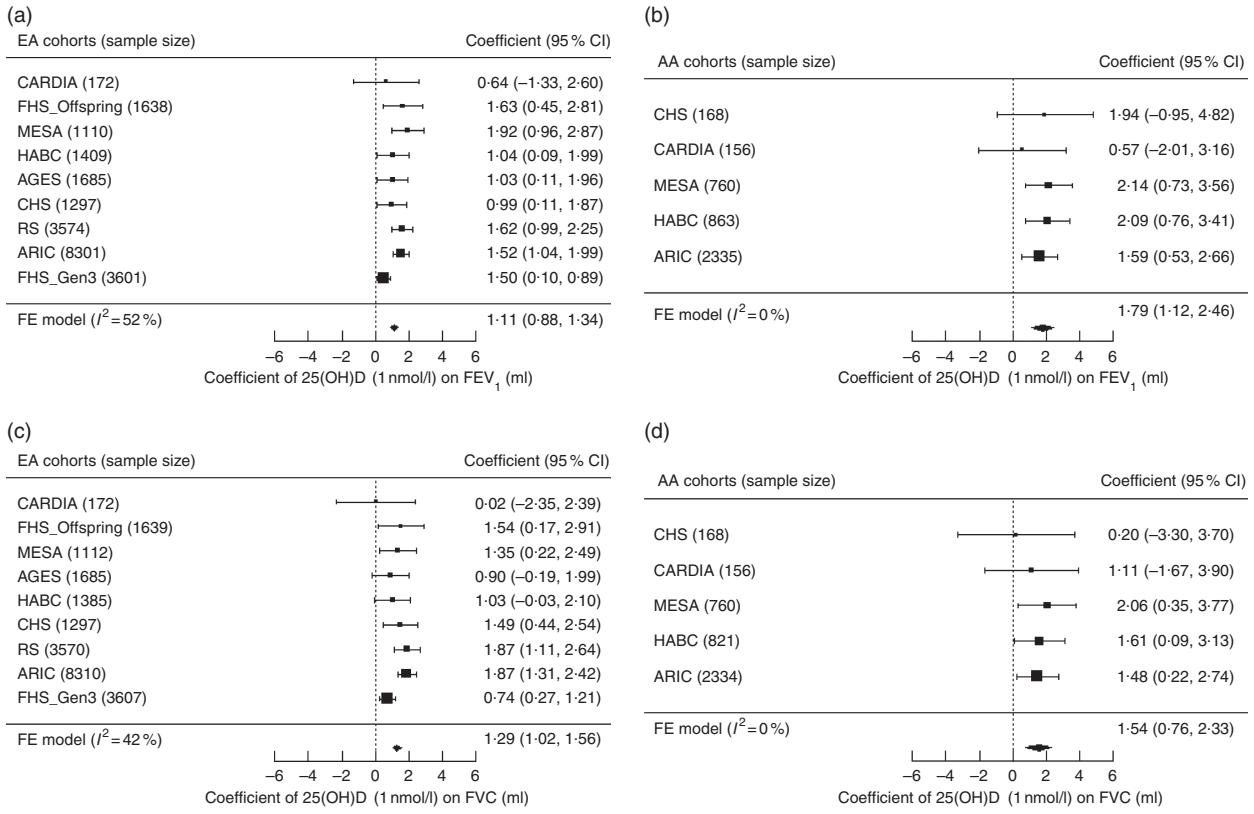

Fig. 1. Forest plots of the meta-analysis of serum 25-hydroxyvitamin D (25(OH)D) on forced expiratory volume in the 1st second (FEV_1) and forced vital capacity (FVC) across cohorts in the Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium, stratified by participant ancestry. Associations are presented for serum 25(OH)D on (a) FEV_1 in European ancestry cohorts (*n* 22 787). (b) FEV_1 in African ancestry cohorts (*n* 4282). (c) FVC in European ancestry cohorts (*n* 22 777). (d) FVC in African ancestry cohorts (*n* 4239). β (unit: ml) denotes the coefficient from the fixed-effects meta-analysis for serum 25(OH)D on the pulmonary function outcome per 1 nmol/l increment of 25(OH)D, with its 95 % CI. Cohorts findings were ordered from the least to the most precise, and heterogeneity is presented (I^2). EA, European ancestry; AA, African ancestry; CARDIA, Coronary Artery Risk Development in Young Adults Study; FHS (Offspring), Framingham Heart Study – Offspring Cohort; AGES, Age, Gene, Environment, Susceptibility Study – Reykjavik, Iceland; CHS, Cardiovascular Health Study; RS, Rotterdam Study (Netherlands); ARIC, Atherosclerosis Risk in Communities Study; FHS (Gen3), Framingham Heart Study – Generation 3 Cohort; FE, fixed-effects; HABC, Health, Aging, and Body Composition Study; MESA, Multi-Ethnic Study of Atherosclerosis.

in former smokers than in never smokers ($\beta_{\text{former} \times 25(OH)D} = 7{\cdot}9$ ml for 10 nmol/l increment of 25(OH)D, $P = 0{\cdot}0065$) (Fig. 3). For the FEV_1 outcome in the EA cohorts, the interaction coefficients for 25(OH)D and smoking status had the same positive direction as the coefficients for FVC, but were not statistically significant for either current ($P = 0{\cdot}14$) or former smokers ($P = 0{\cdot}14$). No statistical evidence of interaction of 25(OH)D and cigarette smoking was found in the AA cohorts for either outcome. To put the interaction finding into context, a 10 nmol/L higher serum 25(OH)D was associated with a 17·3 ml higher FVC in current smokers and a 16·6 ml higher FVC in former smokers, which was more than double the association magnitude in never smokers ($\beta = 7{\cdot}8$ ml). A similar trend was found for the FEV_1 outcome in the EA cohorts. For 10 nmol/l higher serum 25(OH)D, FEV_1 was higher by 14·0 ml in current smokers, 12·0 ml in former smokers and 8·0 ml in never smokers (Fig. 4).

Discussion

This study investigated the association of serum 25(OH)D with pulmonary function using multiple cohorts of different ancestries. We found a consistently positive association of serum 25(OH)D with FEV_1 and FVC across both EA and AA groups. In addition, in the EA group, a significantly stronger association was observed for current and former smokers, compared with never smokers.

A previous cross-sectional study in a EA population (two Copenhagen cohorts: *n* 10 116 and *n* 8391, respectively) similarly reported positive associations of 25(OH)D with FEV_1 percentage predicted and FVC percentage predicted, but not with FEV_1/FVC[16]. The magnitude of the association was about four times greater in the Copenhagen study, which may be due to the difference in the mean serum 25(OH)D (Danish median approximately 42 nmol/l *v.* CHARGE median of approximately 65 nmol/l) given our finding that the 25(OH)D–PFT association was stronger in cohorts with lower serum 25(OH)D. Our finding for the serum 25(OH)D–FEV_1 association was similar in magnitude to the association reported in a British cohort of 6789 participants with an average age of 45 years[17], but weaker than a previous report from the FHS cohort[15]. Given that the rate of decline in FEV_1 at age 45 years is increased by approximately 15 ml/year in current smokers[35], we estimate that a 10 nmol/l higher 25(OH)D is similar to approximately 1 year of current smoking-related decline in FEV_1 for both ancestries, but in the opposite direction. Several putative

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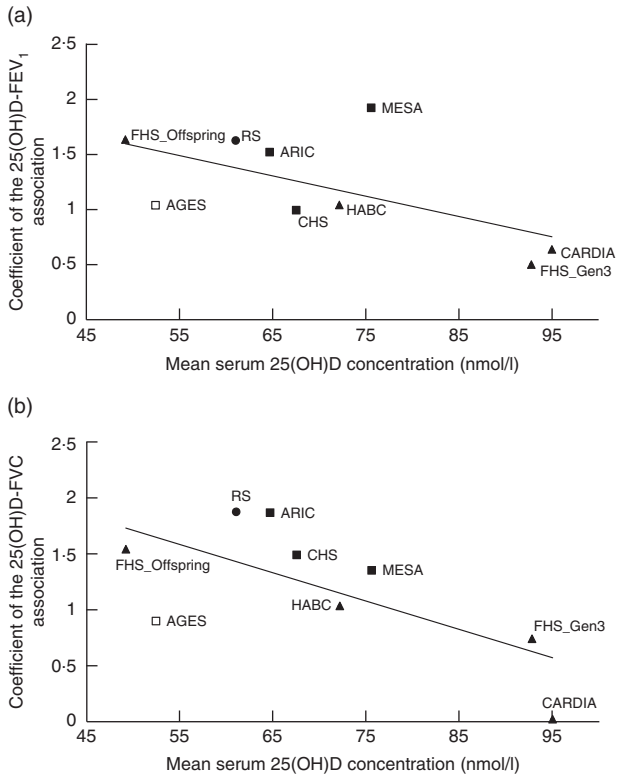

Fig. 2. Meta-regression of mean serum 25-hydroxyvitamin D (25(OH)D) levels against the association estimates of 25(OH)D with pulmonary function test in nine European ancestry cohorts in the Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium. (a) Forced expiratory volume in the 1st second (FEV_1) outcome (coefficient unit: ml per 1 nmol/l 25(OH)D), and (b) forced vital capacity (FVC) outcome (coefficient unit: ml per 1 nmol/l 25(OH)D). The modifier is mean serum 25(OH)D level of each nine cohorts. A linear regression line is present for each sub-figure, with a meta-regression *P* value of 0·0006 for the FEV_1 outcome, and 0·005 for the FVC outcome. The figure also shows the measurement method for the serum 25(OH)D assay (legend shows symbols for each of the four assay methods). ■, LC-MS/MS; ▲, RIA; □, CLIA; ●, Electro-CLIA. LC-MS/MS, liquid chromatography in tandem with mass spectrometry; RIA, radioimmunoassay; CLIA, chemiluminescence immunoassay; MESA, Multi-Ethnic Study of Atherosclerosis; FHS (Offspring), Framingham Heart Study – Offspring Cohort; RS, Rotterdam Study (Netherlands); ARIC, Atherosclerosis Risk in Communities Study; AGES, Age, Gene, Environment, Susceptibility Study – Reykjavik, Iceland; CHS, Cardiovascular Health Study; HABC, Health, Aging, and Body Composition Study; CARDIA, Coronary Artery Risk Development in Young Adults Study; FHS (Gen3), Framingham Heart Study – Generation 3 Cohort.

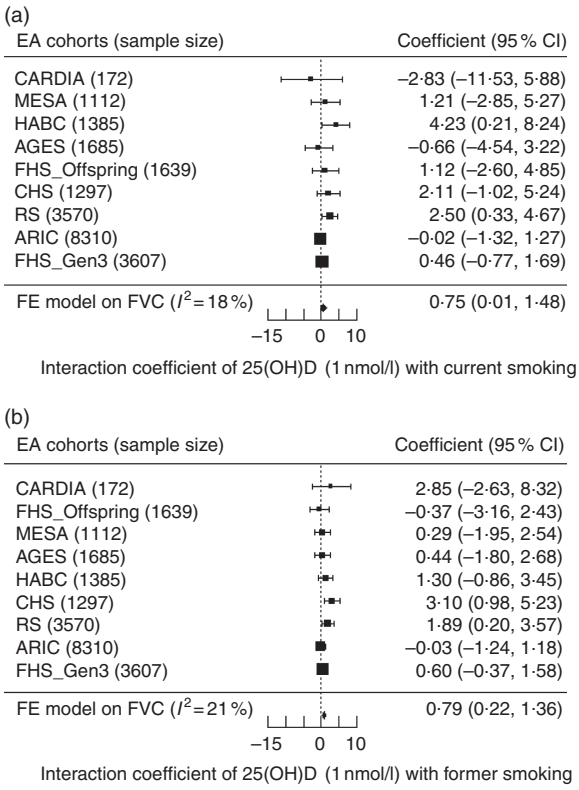

Fig. 3. Forest plots of the interaction meta-analysis of serum 25-hydroxyvitamin D (25(OH)D) and smoking status on forced vital capacity (FVC) in the European ancestry cohorts in the Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium (*n* 22 777). (a) Current smokers and (b) former smokers. β (unit: ml) denotes the interaction term coefficient of 25(OH)D and smoking status on FVC from the fixed effects meta-analysis, per 1 nmol/l increment of 25(OH)D, with its 95 % CI. Cohorts were ordered from the least to the most precise, and heterogeneity is presented (I^2). EA, European ancestry; CARDIA, Coronary Artery Risk Development in Young Adults Study; MESA, Multi-Ethnic Study of Atherosclerosis; HABC, Health, Aging, and Body Composition Study; AGES, Age, Gene, Environment, Susceptibility Study – Reykjavik, Iceland; FHS (Offspring), Framingham Heart Study – Offspring Cohort; CHS, Cardiovascular Health Study; RS, Rotterdam Study (Netherlands); ARIC, Atherosclerosis Risk in Communities Study; FHS (Gen3), Framingham Heart Study—Generation 3 Cohort; FE, fixed-effects.

biological mechanisms may support a causal association between low 25(OH)D levels and worse pulmonary function. First, lung tissue cells can locally convert 25(OH)D to 1,25-$(OH)_2D$[36], the active form of vitamin D, which could improve the immune and anti-inflammatory responses in lungs via gene regulation[36–38]. If there is not enough circulating 25(OH)D, it is likely that the resolution of inflammation in lungs would be slower, which could have a negative impact on pulmonary function. In addition, 1,25-$(OH)_2D$ in lungs, converted locally from 25(OH)D, can regulate the extracellular matrix homeostasis via the ERp60-mediated pathway[39], and this is important for maintenance of lung structure. Furthermore, low vitamin D status could decrease circulating Ca status, which in turn can adversely affect thoracic skeleton mobility and respiratory muscle performance[40,41].

Our findings show that the association of serum 25(OH)D with FEV_1 and FVC were stronger in magnitude in AA *v.* EA participants, although the difference by race did not reach statistical significance. The finding may reflect the lower serum 25(OH)D in AA participants, which is consistent with the meta-regression finding and with a previous study reporting attenuated associations at higher serum 25(OH)D[15]. Future studies that investigate genetic variation in EA and AA in the context of serum 25(OH)D may help explain the differences.

In EA participants, the positive interaction terms between serum 25(OH)D and smoking status supported a stronger magnitude of association of serum 25(OH)D with FVC in current and former smokers than in never smokers, with a consistent, but not statistically significant, difference for FEV_1. The interaction finding is consistent with a prior cross-sectional National Health and Nutrition Examination Survey (NHANES) study, which reported a stronger 25(OH)D–FEV_1 association in current and former smokers than in never smokers that was

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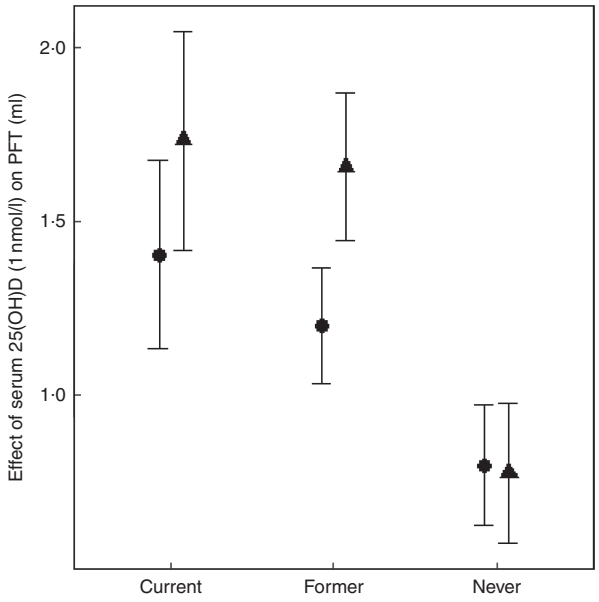

Fig. 4. Meta-analysis of the association of serum 25-hydroxyvitamin D (25(OH)D) – pulmonary function test outcomes among current, former and never smokers in the European ancestry cohorts in the Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium. Forced expiratory volume in the 1st second (FEV_1, ●) and forced vital capacity (FVC, ▲) are presented for each smoking status. β (unit: ml) denotes that 1 nmol/l higher serum 25(OH)D was associated with a β mL higher FEV_1 (or FVC), calculated from an analysis including the interaction of serum 25(OH)D and smoking status. The error bar represents ±1 standard error. We used 22 786 European ancestry (EA) participants for the FEV_1 outcome and 22 777 EA participants for the FVC outcome.

near statistical significance ($P = 0{\cdot}06$)[13]. Given smokers have a higher level of oxidative stress and lower pulmonary function than never smokers, partly due to chronic inflammation in lung tissue, the stronger protective association of 25(OH)D on pulmonary function in smokers suggests a benefit for smokers. To explore this interaction, estimates of the 25(OH)D–PFT association were computed within each smoking category. In EA participants, the 25(OH)D–FEV_1 (or FVC) associations were statistically significant in all strata. Generally, in ever smokers of EA, the coefficients for 25(OH)D were greater for FVC than for FEV_1.

Meta-regression provided additional evidence for effect modification by smoking. The proportion of ever smokers was a significant modifier of the association of serum 25(OH)D with FEV_1 and FVC. The higher the proportion of ever smokers, the greater the 25(OH)D–PFT association. More specifically, the proportion of former smokers explained the heterogeneity in the 25(OH)D–PFT association across cohorts more fully than the proportion of current smokers; this may be explained by a survival bias in older participants who were current smokers. The meta-regression, based on mean age of the cohorts, showed that cohorts with a higher mean age had a greater association magnitude of 25(OH)D with FEV_1. Given that meta-regression analysis uses cohort-level factors (e.g. mean age rather than age of each individual), ecological bias is possible[42]. Nevertheless, the age-related meta-regression finding was consistent with a prior NHANES study that showed the association of 25(OH)D and FEV_1 was stronger in people over age 60 compared with younger individuals[13].

Several methodological considerations should be taken into account in interpreting the findings of this study. First, the meta-regression showed stronger 25(OH)D–PFT associations in cohorts with lower mean serum 25(OH)D, indicating a non-linear 25(OH)D–PFT association. This finding is consistent with a prior study in the FHS cohort, which reported a non-linear association and a stronger 25(OH)D–FEV_1 association in participants at risk of vitamin D deficiency (<30 nmol/l)[15]. Second, serum 25(OH)D was measured by four different methods across the cohorts. For example, two cohorts with high mean 25(OH)D (>90 nmol/l) used RIA methods. These same cohorts had a lower magnitude estimate of the 25(OH)D–PFT association; if the higher mean represents the 'truth' (and is not caused by measurement error in the RIA assay), then the lower 25(OH)D–PFT association may be primarily driven by the vitamin D distribution and not by the RIA method. Whether the assay method itself directly influences the estimate of the 25(OH)D–PFT association requires further data. Third, in this cross-sectional meta-analysis, minor differences were found in the time separation between the measurement of serum 25(OH)D and pulmonary function, but the meta-regression test for heterogeneity confirmed that time separation between measurements did not affect the 25(OH)D–PFT associations. Indeed, past studies with longitudinal measurements of serum 25(OH)D reported a high correlation of 25(OH)D measurements over a long period of time, with a correlation coefficient of 0·7 for measurements separated by 1 year, 0·5 for measurements separated by 5 years[43], and 0·42–0·52 for measurements separated by 14 years[44], which supports the use of a single 25(OH)D measurement to represent usual level. Fourth, residual confounding was unlikely given the consistent results across multiple cohorts in various settings. Weight was adjusted for the FVC outcome, given that higher weight and adiposity negatively affects lung volume (i.e. FVC)[45]; weight was not adjusted in the FEV_1 models, given FEV_1 is a measure of airways obstruction and not physical restriction of lung volume. Physical activity was not adjusted because it is not a confounder in estimating the serum 25(OH)D–PFT association; while physical activity is known to contribute to O_2 utilisation in lungs[46], little evidence and no biological rationale exists for a causal association of physical activity with either FEV_1 or FVC[47], which are markers for airways obstruction and lung volume, respectively. Finally, even though three cohorts (AGES, CARDIA, MESA) had the outcome or the exposure only measured in an ancillary study (random subset of the entire cohort), we do not expect selection bias to affect the estimate of the serum vitamin D–PFT association in this meta-analysis; indeed, the association magnitude and direction was consistent across all cohorts, regardless of the proportion of the original cohort contributing to the analysis. Thus, selection bias is expected to be negligible and would likely lead to an underestimated association, given the participants retained in the cohorts are expected to be, on average, healthier than those who were lost to follow-up.

This study meta-analysed the serum 25(OH)D–PFT association across nine cohorts, according to a common pipeline that harmonised the variables and statistical analysis. The sample size comprised 17 569 EA participants from the USA;

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5269 EA participants from Iceland and the Netherlands; and 4290 AA participants from the USA, all of whom were 19–95 years old. The sample provided excellent representation of the US population, based on comparisons of demographic factors including sex, height, weight, smoking status and COPD prevalence (about 6·1 %) to national surveys[48–50], which strengthens the external validity of the study's findings.

In summary, using meta-analysis, we estimated a positive association of serum 25(OH)D with the pulmonary function parameters FEV_1 and FVC in both EA and AA participants. Associations varied by smoking status in the EA group, with stronger serum 25(OH)D–PFT associations seen in current and former smokers. The observational design means we cannot infer a causal association, and future studies, such as randomised controlled trials or Mendelian randomisation studies, are needed to further investigate the causality of 25(OH)D on pulmonary function.

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P. A. C., D. B. H. and J. X. conceived and designed the study. R. G. B., J. L., J. D., S. A. G., L. L., S. J. L., K. E. N., A. V. S., B. M. P. and L. M. S. provided the data and supervised the data analysis in each cohort. J. X., T. M. B., R. R. R., A. V. S., A. W. M., F. S., N. T. and X. Z. analysed data within each cohort. J. X., P. A. C. and D. B. H. meta-analysed and interpreted the data, co-wrote and edited the first draft of the manuscript and had primary responsibility for final content. All authors provided data, analytic support and/or study design suggestions at all stages, critically reviewed the manuscript and read and approved the final version.

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The study sponsors were not involved in study design, data collection, data analysis, data interpretation, report writing or decisions to submit the paper for publication. P. A. C. and D. B. H. had final responsibility for the decision to submit for publication.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114518002180

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