**Supplemental Methods:**

Statistical analysis in individual cohorts

The covariates smoking status, pack years, height, height squared, age, age squared, and sex were adjusted to account for variability in the pulmonary function outcomes in order to investigate other associations that are not mediated through these factors, following common practice([1](#_ENREF_1), [2](#_ENREF_2)). The season variable is a potential confounding factor given that serum 25(OH)D varies with seasonality([3](#_ENREF_3)) and that pulmonary function may be influenced by season as well([4](#_ENREF_4)). In each cohort, a preliminary model with all the covariates, excluding the serum 25(OH)D term, was conducted to identify residual outliers, for each pulmonary function test (PFT) outcome. Given this, the sample size used in the subsequent primary analyses of 25(OH)D on PFT and secondary analyses that included 25(OH)D × smoking interaction may vary across the outcomes. The cutoff value for the studentized residual outliers was set at either 3 or 4, decided by each cohort separately.

Meta-analysis

Each cohort provided a results file that included: coefficient and standard error of the association of serum 25(OH)D with each PFT outcome in the primary models, and similarly the coefficients and standard errors of the serum 25(OH)D term [a], the 25(OH)D × current smoker term [b], the 25(OH)D × former smoker term [c], and the covariance between [a] and [b] and between [a] and [c] in the interaction models.

Besides the primary meta-analysis of serum 25(OH)D on PFTs, meta-analysis of the interaction terms of serum vitamin D and smoking status (current smokers and former smokers) was conducted, with never smokers as the reference. Significant meta-analyzed coefficients of the interaction terms were further explored by a meta-analysis of the serum 25(OH)D–PFT associations within each smoking status. The association of serum 25(OH)D with each PFT outcome among people with different smoking status in each cohort was computed from the requested parameter coefficients, standard errors, and covariance values, with example equations shown below.

β25(OH)D among current smokers = β25(OH)D among never smokers/reference group + βinteraction of 25(OH)D and current smokers

Var25(OH)D among current smokers = Var[1]25(OH)D among never smokers + Var[2]interaction of 25(OH)D and current smokers + 2 × Cov([1], [2])

Fixed-effects models were used for all the meta-analysis. Random-effects models were also tested and findings were similar to the findings generated by the fixed-effects models due to little heterogeneity (data not shown). For findings with moderate heterogeneity, meta-regression was conducted to explore the potential causes of heterogeneity.

Sensitivity analysis was conducted to assess whether the family structure within the Offspring and Gen3 cohorts in the Framingham Heart Study (FHS) would affect the meta-analysis results.

**Supplemental Table 1. Flowchart of sample size dynamics in each cohort in the CHARGE Consortium, stratified by ancestry\***

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| European Ancestry Cohort | ARIC | CARDIA | CHS | HABC† | MESA‡ | AGES§ | FHS|| | RS¶ |
| Original sample size | 11,478 | 2,478 | 4,346 | 1,794 | 2,501 | 5,519 | 9,219 | 9,895 |
| *No PFT excluded (outcome of interest)* | -47 | -538 | -980 | -117 | -1,119 | -2,672 | -1,485 | -2,542 |
| *Unacceptable PFT excluded* | -9 | 0 | -415 | -22 | 0 | -16 | NA | -2,774 |
| *No height excluded* | 0 | -10 | -43 | 0 | 0 | 0 | -1 | -1 |
| *No sex excluded* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *No age excluded* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *No smoking status excluded* | -7 | 0 | -63 | -2 | -12 | -63 | -2 | -6 |
| *No pack-years excluded* | -130 | 0 | -71 | -27 | -51 | -27 | -178 | -172 |
| *No site excluded (if applicable)* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *No genetic data excluded*\*\* | -1,947 | 0 | -786†† | -124 | 0 | -1,056 | -695 | -590 |
| *No serum 25(OH)D excluded*  *(exposure of interest)* | -1,011 | -1,758‡‡ | -683 | -90 | -198 | 0 | -1609 | -218 |
| *Unacceptable 25(OH)D excluded* | 0 | 0 | 0 | -1 | 0 | 0 | 0 | 0 |
| *No season excluded* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | -8 |
| *No weight excluded*  *(for the FVC analysis only)* | -7 | 0 | 0 | -26 | 0 | 0 | 0 | 0 |
| Sample size for the FEV1 analysis§§ | ***8,301***|||| | ***172*** | ***1,297*** | ***1,409*** | ***1,110*** | ***1,685*** | ***5,239*** | ***3,574*** |
| Sample size for the FVCanalysis§§ | ***8,310*** | ***172*** | ***1,297*** | ***1,385*** | ***1,112*** | ***1,685*** | ***5,246*** | ***3,570*** |
| Sample size for the FEV1/FVC analysis§§ | ***8,273*** | ***172*** | ***1,297*** | ***1,379*** | ***1,107*** | ***1,685*** | ***5,234*** | ***3,581*** |
| African Ancestry Cohort | **ARIC** | **CARDIA** | **CHS** | **HABC†** | **MESA**‡ |  |  |  |
| Original sample size | 4,266 | 2,637 | 885 | 1,281 | 2,575 |  |  |  |
| *No PFT excluded (outcome of interest)* | -80 | -823 | -262 | -95 | -1,646 |  |  |  |
| *Unacceptable PFT excluded* | -3 | 0 | -122 | -59 | 0 |  |  |  |
| *No height excluded* | 0 | -7 | -3 | 0 | 0 |  |  |  |
| *No sex excluded* | 0 | 0 | 0 | 0 | 0 |  |  |  |
| *No age excluded* | 0 | 0 | 0 | 0 | 0 |  |  |  |
| *No smoking status excluded* | -8 | -1 | -5 | -2 | -17 |  |  |  |
| *No pack-years excluded* | -129 | 0 | -22 | -12 | -37 |  |  |  |
| *No site excluded (if applicable)* | 0 | 0 | 0 | 0 | 0 |  |  |  |
| *No genetic data excluded*\*\* | -1,280 | 0 | -49†† | -117 | 0 |  |  |  |
| *No serum 25(OH)D excluded*  *(exposure of interest)* | -427 | -1,649‡‡ | -248 | -132 | -104 |  |  |  |
| *Unacceptable 25(OH)D excluded* | 0 | 0 | 0 | -1 | 0 |  |  |  |
| *No season excluded* | 0 | 0 | 0 | 0 | 0 |  |  |  |
| *No weight excluded*  *(for the FVC analysis only)* | -2 | 0 | 0 | -42 | 0 |  |  |  |
| Sample size for the FEV1 analysis§§ | ***2,335*** | ***156*** | ***168*** | ***863*** | ***760*** |  |  |  |
| Sample size for the FVCanalysis§§ | ***2,334*** | ***156*** | ***168*** | ***821*** | ***760*** |  |  |  |
| Sample size for the FEV1/FVC analysis§§ | ***2,327*** | ***156*** | ***168*** | ***815*** | ***759*** |  |  |  |

Abbreviations: 25(OH)D, 25-Hydroxyvitamin D; AGES, Age, Gene, Environment, Susceptibility Study—Reykjavik, Iceland; ARIC, Atherosclerosis Risk in Communities Study; CARDIA, Coronary Artery Risk Development in Young Adults Study; CHS, Cardiovascular Health Study; FEV1, Forced Expiratory Volume in the First Second; FHS, Framingham Heart Study; FVC, Forced Vital Capacity; HABC, Health, Aging, and Body Composition Study; MESA, Multi-Ethnic Study of Atherosclerosis; PFT, Pulmonary Function Test; RS, Rotterdam (Netherlands) Study.

\* The final sample size of each cohort for each outcome variable is shown in the last three rows for each ancestry (*n* = 27,069 for the FEV1 outcome, *n* = 27,016 for the FVC outcome, and *n* = 26,953 for the FEV1/FVC outcome).

† Flowcharts of sample size in Health ABC vary slightly for different outcomes and the flowchart for FEV1 is presented in the table.

‡ In MESA, PFT was measured only in a random sample of the entire cohort (*n* = 3,893 out of 5076)([5](#_ENREF_5)). In addition, the final sample size for each outcome additionally excluded participants who were related genetically (*n* = 8 for EAs, *n* = 8 for AAs).

§ In AGES, spirometry was only conducted in 2002-2004 for the purpose of prioritizing the time-consuming protocol (N3,000)([6](#_ENREF_6), [7](#_ENREF_7)). And 3219 out of the original sample size (*n* = 5,519) had their genetic data available([8](#_ENREF_8)).

|| The flowchart of sample size in FHS has combined participants in the Offspring cohort and the Generation 3 cohort. In the Offspring cohort, only 1972 out of 5124 participants attended the 6th (1995-1998) or 7th exam (1998-2001) and had 25(OH)D measured([9](#_ENREF_9)), while 25(OH)D measure was planned in Exam 1 for the entire Generation 3 cohort. Given FHS only has participants with acceptable PFT measures, the exclusion of unacceptable PFT is not applicable here. Serum 25(OH)D measures that were concurrent or within 5 years of PFT measures were included.

¶ In RS, the spirometry was introduced to the cohort in 2002. At that time, the total number of participants visiting the research center was 9,895.

\*\* Participants who did not have genetic data were excluded for the purpose of consistency and comparison with future gene by serum vitamin D meta-analysis.

†† In CHS, only those who did not have cardiovascular diseases at baseline, had available DNA, and consented to genetic testing had genetic data available (*n* = 3,865 out of 5,231).

‡‡ In CARDIA, serum 25(OH)D was only measured in an ancillary study of bone mineral homeostasis (*n* = 402). These participants were aged 24-36 years old and in good health condition([10](#_ENREF_10)).

§§ For each outcome, participants whose studentized residual outlier absolute value was greater than 3 (or 4), depending on each cohort, were excluded.

|||| In ARIC, for the FEV1 analysis, the number of participant used for the primary analysis of serum 25(OH)D on PFT was 8,301 while the sample size for the secondary interaction analysis was 8,300. All other cohorts have consistent sample sizes for analysis of each outcome (e.g. *n* for primary analysis equals *n* for secondary interaction analysis).

**Supplemental Table 2. Individual cohort descriptions, including detailed description of spirometry and serum 25(OH)D measurements**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Cohort | Country | Study baseline | Spirometry | Serum 25(OH)D |
| AGES | Iceland | 2002 | Spirometry was conducted on participants in a sitting position with a disposable mouthpiece, using a Vitalograph Gold Standard Plus (Vitalograph Ltd., Buckingham, UK). The spirometer was calibrated with 1L syringe routinely. A technician explained the details before testing. The pulmonary function test was successful if there were at least two acceptable maneuvers, which was defined as no more than 300mL difference between the two attempts for at least 6 seconds in each blow. Spirometry testing was only conducted in the first 2 years, and pre-bronchodilation testing was collected([7](#_ENREF_7)). | Fasting blood samples were collected in September 2002 to January 2008. The serum was stored on-site at −70°C in the Clinical Biochemistry Laboratory Holtasmára at the Icelandic Heart Association([11](#_ENREF_11)). The serum 25(OH)D, including D2 and D3, was quantified by a direct, competitive chemiluminescence immunoassay by using the LIAISON 25(OH)D Total assay (DiaSorin, Inc., Stillwater, Minnesota). The interassay coefficient of variation (CV) was 6.5% if using a previous serum pool as a control sample, and 12.7% if using the Liaison quality controls([12](#_ENREF_12)). |
| ARIC | USA | 1987-9 | Spirometry was conducted using a Collins Survey II water-seal spirometer (Warren E. Collins Inc., Braintree, MA) at visit 1 and 2 while SensorMedics model 1022 dry rolling seal spirometers (OMI, Houston, TX) was used at visit 5. The spirometer was calibrated daily and there was one single pulmonary function reading center to standardize the spirometry testing across the four study sites in ARIC. The test was successful if there were three acceptable attempts([13](#_ENREF_13)). | Fasting blood samples were collected in visit 2 (1990-1992). The serum and plasma samples were stored at −80°C till 2012-2013 when the serum vitamin D was measured. The serum 25(OH)D, including D2 and D3, was quantified by liquid chromatography in tandem with high-sensitivity mass spectrometry (Waters Alliance e2795; Waters, Milford, MA). The CV was 10.9% using duplicate serum 25(OH)D samples at visit 2, which contained variation in both laboratory method and sample processing([14](#_ENREF_14)). |
| CARDIA | USA | 1985 | At year 0, 2, 5, and 10, the pulmonary function test was performed on participants by the Collins Survey 8-liter water sealed spirometer with the Eagle II microprocessor (Warren E. Collins Inc., Braintree, MA). At year 20, a dry rolling-seal SensorMedics model 1022 OMI spirometer (Viasys, Yorba Linda, CA). At year 0, 2, 5, the 1979 American Thoracic Society (ATS) guidelines was used([15](#_ENREF_15)); at year 10, the 1987 ATS guideline was used([16](#_ENREF_16)); while at year 20, the 2005 ATS/European Respiratory Society (ERS) criteria was used([17](#_ENREF_17)). Accuracy of the spirometers was confirmed by the Pulmonary Waveform Generator (MH Custom Design and Manufacturing, Midvale, UT). The change of spirometers resulted in very slight difference in measurement for FEV1 and FVC (6mL and 21mL, respectively). The change in spirometry guidelines resulted in 47mL and 110mL lower in FEV1 and FVC([18](#_ENREF_18)). | The serum 25(OH)D was quantified by a radioimmunoassay (RIA) at the Calciotropic Hormone Reference Laboratory in the University of California, San Francisco([10](#_ENREF_10)). |
| CHS | USA | 1987 | The pulmonary function test was conducted at year 2, 6, and 9 in CHS, using a water-sealed spirometer (Collins Survey, Collins Medical, Inc., Braintree, MA) with accuracy validated, according to contemporary ATS criteria([19](#_ENREF_19)). | The serum samples were stored at −70°C at the Laboratory for Clinical Biochemistry Research in the University of Vermont by using methods that have shown stability of serum biomarkers over a long period of time. The serum 25(OH)D, including D2 and D3, was quantified by high-performance liquid chromatography and tandem mass spectrometry on a Waters Quattro micro mass spectrometer (Waters, Milford, MA). The interassay CV was < 3.4%([20](#_ENREF_20)). |
| FHS (Offspring) | USA | 1971 | Pulmonary function test was conducted at each examination, adhering to the 1994 ATS criteria([21](#_ENREF_21)). For the 5th, 6th, and 7th examinations of the offspring cohort, pulmonary function was measured using a 6-L water-filled Collins survey spirometer (Warren E. Collins Inc., Braintree, MA), connected to an S&M Instruments software (Doylestown, PA)([22](#_ENREF_22)). Spirometer was calibrated daily([22](#_ENREF_22)). | Fasting blood samples of the Offspring cohort were collected in 1997-2001 (Exam 5, 6, and 7)([23](#_ENREF_23)). The plasma/serum samples of the Offspring cohort were stored at −70°C till analysis([24](#_ENREF_24)). The serum 25(OH)D was quantified by a radioimmunoassay (RIA, DiaSorin Inc., Stillwater, MN)([23](#_ENREF_23), [25](#_ENREF_25)). The serum vitamin D was log transformed in the analyses. The CV was 8.5% for a 25(OH)D control of 36nmol/L and 13.2% for a 25(OH) control of 137nmol/L([23](#_ENREF_23)) in the Offspring cohort([26](#_ENREF_26)). The blood samples were analyzed after 1998 for serum 25(OH)D. |
| FHS (Gen3) | USA | 2002 | Pulmonary function test was conducted at each examination, adhering to the 1994 ATS criteria([21](#_ENREF_21)). For the 1st and 2nd examinations of the Generation 3 cohort, pulmonary function was measured by a dry rolling-seal spirometer, connect to the CPL System (Warren E. Collins Inc., Braintree, MA)([22](#_ENREF_22)). Spirometer was calibrated daily([22](#_ENREF_22)). | Fasting blood samples of the Generation 3 cohort were collected in 2001-2005 (Exam 1 and 2)([25](#_ENREF_25), [26](#_ENREF_26)). The storage temperature for the 3rd Generation cohort was −80°C([24](#_ENREF_24)). The serum 25(OH)D was quantified by a radioimmunoassay (RIA, DiaSorin Inc., Stillwater, MN)([23](#_ENREF_23), [25](#_ENREF_25)). The serum vitamin D was log transformed in the analyses. The CV was 12.5% in the 3rd Generation cohort([26](#_ENREF_26)). The blood samples were analyzed after 1998 for serum 25(OH)D. There might be small assay performance drift in FHS but the change should have been relatively small (the difference of mean 25(OH)D in 2003-2004 and 2005-2006 U.S. National Health and Nutrition Examination Survey was 2.5-5nmol/L([27](#_ENREF_27))). |
| HABC | USA | 1997 | Pulmonary function testing was conducted using a horizontal dry rolling seal spirometer (SensorMedics Corporation, Yorba Linda, CA) at baseline, year 4, year 7 and year 9. The spirometers were adjusted at the National Institute of Occupational Safety and Health (Morgantown, WV), and connected to a software used in the 3rd National Health and Nutrition Examination Survey. The spirometers were calibrated daily by trained technicians, using a 3-L syringe. Starting at year 8, the EasyOne Model 2001 diagnostic spirometer (ndd Medizintechnik AG, Zurich, Switzerland) was used in home visits. These two types of spirometers were compared and both produced very similar results. Participants were asked to give at least 3 maneuvers to at most 5 maneuvers. For participants with bronchodilator medication, their post-bronchodilator tracings were collected. All results have been reviewed centrally. A five-point quality score was created for each FVC, FEV1, and PEF (peak expiratory flow) of each individual([28](#_ENREF_28)). The reproducibility and acceptability of the pulmonary measure were based on the ATS criteria([21](#_ENREF_21)). Acceptable PFT in this paper needs to have a score of 1 or greater to reduce selection bias of healthy participants. | Fasting blood samples were collected and stored at −80°C in Year 2. The serum 25(OH)D was quantified by a 2-step radioimmunoassay method (25-hydroxyvitaminD 125I RIA kit; DiaSorin, Inc., Stillwater, MN). The lab has met the quality criteria established by the Vitamin D External Quality Assessment Scheme, whose purpose is to ensure the analytical reliability of serum 25(OH)D assays. The interassay CV was 6.8%([29](#_ENREF_29)). |
| MESA | USA | 2000 | Pulmonary function test was conducted using a dry rolling seal spirometer, connected to an automated quality control software (Occupational Marketing, Inc., Houston, TX), in accordance with the 2005 ATS/ERS criteria([17](#_ENREF_17)). Each participant had to have at least 3 acceptable maneuvers. A 5-point quality score was created based on a version of the National Lung Health Education Program. A quality score lower than C was viewed as low. All results have been reviewed centrally([30](#_ENREF_30)). | The fasting blood samples were collected and stored at −80°C at baseline in 2000-2002. In 2011-2012, the samples were shipped to University of Washington for serum 25(OH)D measurement([31](#_ENREF_31)). The serum 25(OH)D level was stable during the long-term storage with a temperature of −80°C([32](#_ENREF_32)). The serum 25(OH)D, including D2 and D3, was quantified by high-performance liquid chromatography in tandem with mass spectrometry, and calibrated by National Institute of Standards and Technology’s standard reference material (SRM) 972([33](#_ENREF_33)). The interassay CV for 25(OH)D3 was 4.4% at 10.4ng/mL with a minimum detection of 2.0ng/mL, and the interassay CV for 25(OH)D2 was 4.4% at 9.4ng/mL with a minimum detection of 0.5ng/mL([31](#_ENREF_31)). |
| RS | Netherlands | 1990 | Spirometry was conducted in 2002-2009 using a SpiroPro® portable spirometer (Erich Jaeger GmbH, Hoechberg, Germany), connected to a Jaeger Master Screen PFT Pro (Care Fusion, the Netherlands), since 2009. The test was done by trained technician, in accordance with the ATS/ERS criteria([34](#_ENREF_34)), and pre-bronchodilator results were collected. All measures were centrally assessed and validated by researchers([35](#_ENREF_35)). | Non-fasting blood samples were collected in 1,428 participants at the first visit and in 3,799 participants at the third visit of the RSI cohort. Among these samples, 1,323 were overlapped. Fasting blood samples were collected in 2,464 participants at the first visit of the RSII cohort (RSII-1) and in 3,420 participants at the first visit of the RSIII cohort (RSIII-1). In RSI-3, RSII-1, and RSIII-1, the serum 25(OH)D was quantified by an electrochemi-luminescense-based assay (Elecsys Vitamin D Total, Roche Diagnostics, Mannheim, Germany), with a detectable range of 7.5-175nmol/L, a sensitivity of 10nmol/L, a within-run precision of < 6.5%, and a total precision of < 11.5%([36](#_ENREF_36)). |

Abbreviations: 25(OH)D, 25-Hydroxyvitamin D; AGES, Age, Gene, Environment, Susceptibility Study—Reykjavik, Iceland; ARIC, Atherosclerosis Risk in Communities Study; ATS, American Thoracic Society; CARDIA, Coronary Artery Risk Development in Young Adults Study; CHS, Cardiovascular Health Study; CV, Coefficient of Variation; ERS, European Respiratory Society; FEV1, Forced Expiratory Volume in the First 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; RS, Rotterdam (Netherlands) Study.

**Supplemental Table 3. Cohort-specific data in the CHARGE Consortium on the time of measurement (year or exam number) for primary study variables**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Serum 25(OH)D  collection time | PFTs | Smoking Status | Pack-years | Height | Weight | Age |
| AGES | 2002-2004 | 2002-2004 | All the covariates are concurrent with PFT. | | | | |
| ARIC | 1990-1992 (Visit 2) | 1987 (Baseline) | All the covariates are concurrent with PFT. | | | | |
| CARDIA | 1992 (Year 7) | 1995  (Year 10) | All the covariates are concurrent with PFT. | | | | |
| CHS\* | 1992-1993 (Year 5) | 1993-1994  (Year 6) | 1992-  1993  (Year 5)† | 1992-  1993  (Year 5)†‡ | 1992-1993 (Year 5)† | 1992-1993 (Year 5)† | 1992-1993 (Year 5)† |
| FHS  (Offspring)§ | 1995-2001  (Between Exam 6 & Exam 7) | 1991-1995 (Exam 5)/  1995-1998 (Exam 6)/  1998-2001 (Exam 7) | All the covariates are concurrent with PFT. | | | | |
| FHS  (Gen 3)|| | 2002-2005 (Exam 1) | 2002-2005 (Exam 1)/  2008-2011 (Exam 2)¶ | All the covariates are concurrent with PFT. | | | | |
| HABC | 1998-1999 (Year 2) | 1997-1998 (Baseline) | All the covariates are concurrent with PFT. | | | | |
| MESA | 2000-2002 (Exam 1) | 2004-2006 (Exam 4) | All the covariates are concurrent with PFT. | | | | |
| RS |  |  |  |  |  |  |  |
| - RSI | 1997-1999 (Exam 3) | 2002-2004 (Exam 4) | All the covariates are concurrent with PFT. | | | | |
| * RSII | 2000-2001 (Exam 1) | 2004-2005 (Exam 2) | All the covariates are concurrent with PFT. | | | | |
| * RSIII | 2006- 2008 (Exam 1) | 2006-2008 (Exam 1) | All the covariates are concurrent with PFT. | | | | |

Abbreviations: 25(OH)D, 25-Hydroxyvitamin D; AGES, Age, Gene, Environment, Susceptibility Study—Reykjavik, Iceland; ARIC, Atherosclerosis Risk in Communities Study; CARDIA, Coronary Artery Risk Development in Young Adults Study; CHS, Cardiovascular Health Study; FHS (Offspring), Framingham Heart Study—Offspring Cohort; FHS (Gen3), Framingham Heart Study—Generation 3 Cohort; HABC, Health, Aging, and Body Composition Study; MESA, Multi-Ethnic Study of Atherosclerosis; PFT, Pulmonary Function Test; RS, Rotterdam (Netherlands) Study.

\* In CHS, covariates concurrent with vitamin D blood sample were used, but results were essentially the same using covariates measured in either year 5 or year 6.

† In CHS, height was only measured in year 5, not in year 6. The other covariates were used if they were concurrent with 25(OH)D. The results of the 25(OH)D–PFT association were similar using either covariates in year 5 (concurrent with 25(OH)D) or in year 6 (concurrent with PFT).

‡ In CHS, the original cohort (both European and African ancestry) was enrolled in 1989 and 1990 and the additional 2nd cohort (only African ancestry) was recruited in 1992 and 1993. For the 1st cohort, pack-years in year 5 was extrapolated from year 2; for the 2nd cohort, pack-years was measured in year 5. The extrapolation of pack-years for the 1st cohort is similar to the actual measure in year 2.

§ Serum 25(OH)D for the Offspring cohort in FHS was measured between exam 6 and exam 7. The PFT measure and other covariates were taken from the nearest exam, within 5 years.

|| Serum 25(OH)D of the Generation 3 cohort in FHS was measured in exam 1. The PFT measure and other covariates were taken from the nearest exam, within 5 years.

¶ 5 out of 3610 participants of the Generation 3 cohort in FHS used PFT measured in Exam 2; while the rest of participants had PFT measured in Exam 1.

**Supplemental Table 4. Cohort-specific model results for the interaction of vitamin D and smoking status on pulmonary function measures in the European ancestry cohorts** **in the CHARGE Consortium\***

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Cohort** | **Smoking**  **status** | **FEV1** | | | | **FVC** | | | | **FEV1/FVC (in percent)** | | | |
|  |  | **β†** | **SE** | **P-value** | **Sample Size** | **β†** | **SE** | **P-value** | **Sample Size** | **β†** | **SE** | **P-value** | **Sample Size** |
| **AGES** | Current | -0.7485 | 1.6840 | 0.6567 | 1685 | -0.6614 | 1.9780 | 0.7381 | 1685 | 0.0072 | 0.0310 | 0.8169 | 1685 |
|  | Former | 0.4603 | 0.9715 | 0.6357 | 1685 | 0.4408 | 1.1450 | 0.7003 | 1685 | 0.0277 | 0.0179 | 0.1213 | 1685 |
| **ARIC** | Current | -0.3190 | 0.5793 | 0.5819 | 8301 | -0.0226 | 0.6615 | 0.9727 | 8310 | 0.0039 | 0.0081 | 0.6324 | 8273 |
|  | Former | -0.4406 | 0.5394 | 0.4141 | 8301 | -0.0293 | 0.6154 | 0.9620 | 8310 | 0.0010 | 0.0075 | 0.8982 | 8273 |
| **CARDIA** | Current | -0.8417 | 3.6792 | 0.8193 | 172 | -2.8260 | 4.4428 | 0.5257 | 172 | 0.0305 | 0.0505 | 0.5465 | 172 |
|  | Former | 3.7482 | 2.3157 | 0.1075 | 172 | 2.8457 | 2.7920 | 0.3097 | 172 | 0.0202 | 0.0318 | 0.5272 | 172 |
| **CHS** | Current | 1.3387 | 1.3591 | 0.3248 | 1297 | 2.1117 | 1.5962 | 0.1862 | 1297 | -0.0140 | 0.0270 | 0.6216 | 1297 |
|  | Former | 1.9700 | 0.9228 | **0.0330** | 1297 | 3.1044 | 1.0839 | **0.0043** | 1297 | -0.0080 | 0.0190 | 0.6532 | 1297 |
| **FHS -**  **Offspring** | Current | -0.8214 | 1.6750 | 0.6238 | 1638 | 1.1250 | 1.9030 | 0.5545 | 1639 | -0.0234 | 0.0258 | 0.3641 | 1630 |
|  | Former | 0.3424 | 1.2530 | 0.7847 | 1638 | -0.3669 | 1.4250 | 0.7968 | 1639 | 0.0171 | 0.0192 | 0.3728 | 1630 |
| **FHS -**  **Gen3** | Current | 0.5584 | 0.5387 | 0.3000 | 3601 | 0.4636 | 0.6275 | 0.4601 | 3607 | 0.0011 | 0.0073 | 0.8830 | 3604 |
|  | Former | 0.2937 | 0.4291 | 0.4937 | 3601 | 0.6049 | 0.4996 | 0.2260 | 3607 | -0.0023 | 0.0058 | 0.6965 | 3604 |
| **HABC** | Current | 4.0180 | 1.8399 | **0.0291** | 1409 | 4.2278 | 2.0488 | **0.0392** | 1385 | 0.0662 | 0.0282 | **0.0190** | 1379 |
|  | Former | 0.5378 | 0.9930 | 0.5882 | 1409 | 1.2954 | 1.1003 | 0.2393 | 1385 | -0.0260 | 0.0151 | 0.0858 | 1379 |
| **MESA** | Current | -1.2897 | 1.7845 | 0.4700 | 1110 | 1.2085 | 2.0719 | 0.5598 | 1112 | -0.0337 | 0.0310 | 0.2763 | 1107 |
|  | Former | -1.3959 | 0.9830 | 0.1559 | 1110 | 0.2943 | 1.1453 | 0.7972 | 1112 | -0.0376 | 0.0171 | **0.0281** | 1107 |
| **RS** | Current | 2.3328 | 0.9272 | **0.0119** | 3574 | 2.4990 | 1.1069 | **0.0240** | 3570 | 0.0230 | 0.0137 | 0.0930 | 3581 |
|  | Former | 1.5620 | 0.7182 | **0.0297** | 3574 | 1.8851 | 0.8592 | **0.0283** | 3570 | 0.0056 | 0.0106 | 0.5994 | 3581 |

Abbreviations: AGES, Age, Gene, Environment, Susceptibility Study—Reykjavik, Iceland; ARIC, Atherosclerosis Risk in Communities Study; CARDIA, Coronary Artery Risk Development in Young Adults Study; CHS, Cardiovascular Health Study; FEV1, Forced Expiratory Volume in the First Second; FHS (Offspring), Framingham Heart Study – the Offspring Cohort; FHS (Gen3), Framingham Heart Study – the Generation 3 Cohort; FVC, Forced Vital Capacity; HABC, Health, Aging, and Body Composition Study; MESA, Multi-Ethnic Study of Atherosclerosis; RS, Rotterdam (Netherlands) Study.

\* Smoking status includes never smokers, former smokers, and current smokers. Never smoker was set as the reference group. Therefore, the two interaction terms are serum vitamin D × current smokers, and serum vitamin D × former smokers.

† β(mL) for FEV1 and FVC outcomes and β(%) for the FEV1/FVC ratio outcome are the coefficients of the interaction term. P-values that are ≤0.05 are bolded.

**Supplemental Table 5. Cohort-specific model results for the interaction of vitamin D and smoking status on pulmonary function measures in the African ancestry cohorts** **in the CHARGE Consortium\***

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Cohort** | **Smoking**  **status** | **FEV1** | | | | **FVC** | | | | **FEV1/FVC (in percent)** | | | |
|  |  | **β†** | **SE** | **P-value** | **Sample Size** | **β†** | **SE** | **P-value** | **Sample Size** | **β†** | **SE** | **P-value** | **Sample Size** |
| **ARIC** | Current | -0.4562 | 1.1974 | 0.7032 | 2335 | -0.7351 | 1.4158 | 0.6036 | 2334 | 0.0219 | 0.0193 | 0.2564 | 2327 |
|  | Former | -0.6694 | 1.2747 | 0.5995 | 2335 | 0.8071 | 1.5048 | 0.5918 | 2334 | -0.0242 | 0.0206 | 0.2396 | 2327 |
| **CARDIA** | Current | -2.4238 | 2.8172 | 0.3911 | 156 | -2.6302 | 3.0172 | 0.3849 | 156 | 0.0033 | 0.0415 | 0.9361 | 156 |
|  | Former | -2.3553 | 3.8314 | 0.5397 | 156 | -1.3659 | 4.1121 | 0.7403 | 156 | -0.0078 | 0.0564 | 0.8903 | 156 |
| **CHS** | Current | 1.3974 | 6.4750 | 0.8294 | 168 | 2.5597 | 7.8200 | 0.7438 | 168 | -0.0004 | 0.1360 | 0.9974 | 168 |
|  | Former | 3.3138 | 2.9512 | 0.2631 | 168 | 2.8647 | 3.5549 | 0.4215 | 168 | 0.0380 | 0.0620 | 0.5418 | 168 |
| **HABC** | Current | 1.6845 | 1.9362 | 0.3845 | 863 | 1.6975 | 2.1895 | 0.4384 | 821 | 0.0204 | 0.0342 | 0.5509 | 815 |
|  | Former | 0.4540 | 1.4883 | 0.7604 | 863 | 0.7175 | 1.6947 | 0.6721 | 821 | 0.0212 | 0.0265 | 0.4242 | 815 |
| **MESA** | Current | -0.8285 | 2.1932 | 0.7057 | 760 | -0.2406 | 2.6210 | 0.9269 | 760 | -0.0076 | 0.0410 | 0.8540 | 759 |
|  | Former | -0.8572 | 1.5037 | 0.5688 | 760 | 0.1427 | 1.7966 | 0.9367 | 760 | -0.0500 | 0.0278 | 0.0725 | 759 |

Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; CARDIA, Coronary Artery Risk Development in Young Adults Study; CHS, Cardiovascular Health Study; FEV1, Forced Expiratory Volume in the FirstSecond; FVC, Forced Vital Capacity; HABC, Health, Aging, and Body Composition Study; MESA, Multi-Ethnic Study of Atherosclerosis.

\* Smoking status includes never smokers, former smokers, and current smokers. Never smoker was set as the reference group. Therefore, the two interaction terms are serum vitamin D × current smokers, and serum vitamin D × former smokers.

† β(mL) for FEV1 and FVC outcomes and β(%) for the FEV1/FVC ratio outcome are the coefficients of the interaction term.

**Supplemental Table 6. The meta-analysis of the interaction of serum vitamin D and smoking status on pulmonary function measures, stratified by ancestry,** **in the CHARGE Consortium\***

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | FEV1 | | | | | FVC | | | | FEV1/FVC (in percent) | | | |
|  | **β** | | **SE** | | **P-value** | **β** | **SE** | | **P-value** | **β** | **SE** | | **P-value** |
| European ancestry†: |  |  | |  |  |  |  |  |  |  |  |  |  |
| Current vs. Never Smokers | 0.4805 | | 0.3241 | | 0.1382 | 0.7452 | 0.3756 | | **0.0473**‡ | 0.0047 | 0.0047 | | 0.3162 |
| Former vs. Never Smokers | 0.3725 | | 0.2507 | | 0.1373 | 0.7913 | 0.2908 | | **0.0065**‡ | -0.0015 | 0.0037 | | 0.6794 |
| African ancestry§: |  |  | |  |  |  |  |  |  |  |  |  |  |
| Current vs. Never Smokers | -0.2369 | | 0.8698 | | 0.7853 | -0.301 | 1.0105 | | 0.7658 | 0.0155 | 0.0145 | | 0.2851 |
| Former vs. Never Smokers | -0.2163 | | 0.7688 | | 0.7784 | 0.6433 | 0.8988 | | 0.4741 | -0.0149 | 0.0133 | | 0.2621 |

Abbreviations: FEV1, Forced Expiratory Volume in the First Second; FVC, Forced Vital Capacity.

\* Fixed effect models were used. β(mL) for FEV1 and FVC outcomes and β(%) for the FEV1/FVC ratio outcome are the coefficients of the interaction terms only (the interaction of current smoking status and serum vitamin D, and the interaction of former smoking status and serum vitamin D) with the reference group of never smokers.

† *n* = 22,787 for the FEV1 outcome, *n* = 22,777 for the FVC outcome, and *n* = 22,728 for the FEV1/FVC outcome in European ancestry cohorts.

‡ P-values that are ≤0.05 are bolded.

§ *n* = 4,282 for the FEV1 outcome, *n* = 4,239 for the FVC outcome, and *n* = 4,225 for the FEV1/FVC outcome in African ancestry cohorts.

**Supplemental Table 7. Cohort-specific model results for the primary analysis of vitamin D on pulmonary function measures** **in the CHARGE Consortium, stratified by ancestry**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Cohort** | **Ancestry** | **FEV1** | | | | | **FVC** | | | | | **FEV1/FVC (in percent)** | | | | | |
|  |  | **β\*** | | **SE** | **P-value** | **Sample Size** | **β\*** | **SE** | | **P-value** | **Sample Size** | **β\*** | **SE** | **P-value** | | **Sample Size** | |
| **AGES** | EA | 1.0350 | | 0.4696 | **0.0276** | 1685 | 0.8992 | 0.5570 | | 0.1067 | 1685 | 0.0059 | 0.0087 | 0.4982 | | 1685 | |
| **ARIC** | EA | 1.5158 | | 0.2422 | **<.0001** | 8301 | 1.8670 | 0.2816 | | **<.0001** | 8310 | -0.0090 | 0.0034 | **0.0077** | | 8273 | |
| **CARDIA** | EA | 0.6361 | | 1.0020 | 0.5265 | 172 | 0.0223 | 1.2104 | | 0.9853 | 172 | 0.0057 | 0.0137 | 0.6770 | | 172 | |
| **CHS** | EA | 0.9901 | | 0.4476 | **0.0270** | 1297 | 1.4899 | 0.5355 | | **0.0054** | 1297 | -0.0150 | 0.0090 | 0.1079 | | 1297 | |
| **FHS** | EA –  Offspring | 1.6300 | | 0.6022 | **0.0068** | 1638 | 1.5414 | 0.6994 | | **0.0275** | 1639 | -0.0105 | 0.0093 | 0.2563 | | 1630 | |
|  | EA –  Gen3 | 0.4989 | | 0.2018 | **0.0134** | 3601 | 0.7410 | 0.2395 | | **0.0020** | 3607 | -0.0071 | 0.0027 | **0.0090** | | 3604 | |
| **HABC** | EA | 1.0385 | | 0.4847 | **0.0323** | 1409 | 1.0349 | 0.5452 | | 0.0579 | 1385 | -0.0006 | 0.0074 | 0.9340 | | 1379 | |
| **MESA** | EA | 1.9165 | | 0.4884 | **<.0001** | 1110 | 1.3521 | 0.5783 | | **0.0196** | 1112 | 0.0030 | 0.0085 | 0.7270 | | 1107 | |
| **RS** | EA | 1.6213 | | 0.3212 | **<.0001** | 3574 | 1.8748 | 0.3912 | | **<.0001** | 3570 | 0.0010 | 0.0048 | 0.8400 | | 3581 | |
|  |  |  |  |  |  |  |  |  |  |  |  |  | |  |  |  |  |
| **ARIC** | AA | 1.5913 | | 0.5431 | **0.0034** | 2335 | 1.4779 | 0.6438 | | **0.0218** | 2334 | -0.0025 | 0.0088 | 0.7780 | | 2327 | |
| **CARDIA** | AA | 0.5740 | | 1.3184 | 0.6639 | 156 | 1.1119 | 1.4219 | | 0.4355 | 156 | -0.0056 | 0.0194 | 0.7745 | | 156 | |
| **CHS** | AA | 1.9361 | | 1.4718 | 0.1884 | 168 | 0.1999 | 1.7871 | | 0.9109 | 168 | 0.0470 | 0.0310 | 0.1236 | | 168 | |
| **HABC** | AA | 2.0883 | | 0.6766 | **0.0021** | 863 | 1.6116 | 0.7768 | | **0.0383** | 821 | 0.0219 | 0.0120 | 0.0689 | | 815 | |
| **MESA** | AA | 2.1447 | | 0.7209 | **0.0030** | 760 | 2.0604 | 0.8732 | | **0.0186** | 760 | -0.0091 | 0.0134 | 0.4960 | | 759 | |

Abbreviations: 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; CHS, Cardiovascular Health Study; EA, European Ancestry; FEV1, Forced Expiratory Volume in the First Second; FHS (Offspring), Framingham Heart Study – the Offspring Cohort; FHS (Gen3), Framingham Heart Study – the Generation 3 Cohort; FVC, Forced Vital Capacity; HABC, Health, Aging, and Body Composition Study; MESA, Multi-Ethnic Study of Atherosclerosis; RS, Rotterdam (Netherlands) Study.

\* The beta coefficient corresponds to the association of serum vitamin D on the specific pulmonary function outcome (β(mL) for FEV1 and FVC and β(%) for the FEV1/FVC ratio). P-values that are ≤0.05 are bolded.

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**Supplemental Figure 1. Serum vitamin D distribution in each cohort in the CHARGE Consortium, stratified by ancestry (*n* = 22,838 for EAs, *n* = 4,290 for AAs)**. The middle bar is the median of serum vitamin D level; the lower and upper bars of the box represent the 25 and 75 percentile values of serum vitamin D; the minimum and maximum of the whisker were computed as mean - SD, and mean + SD, respectively, given that the vitamin D distribution was approximately normal in each cohort.

Abbreviations: 25(OH)D, 25-Hydroxyvitamin D; AGES, Age, Gene, Environment, Susceptibility Study—Reykjavik, Iceland; ARIC, Atherosclerosis Risk in Communities Study; CARDIA, Coronary Artery Risk Development in Young Adults Study; CHS, Cardiovascular Health Study; FHS\_Os, Framingham Heart Study – the Offspring Cohort; FHS\_Gen3, Framingham Heart Study – the Generation 3 Cohort; HABC, Health, Aging, and Body Composition Study; MESA, Multi-Ethnic Study of Atherosclerosis; RS, Rotterdam (Netherlands) Study.

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**B**

**A**

**Supplemental Figure 2. Forest plots of the meta-analysis of serum 25(OH)D on FEV1/FVC** **across cohorts in the CHARGE Consortium, stratified by participant ancestry**. Associations are presented for serum 25(OH)D on (A) FEV1/FVC in European ancestry cohorts (*n* = 22,728) and (B) FEV1/FVC in African ancestry cohorts (*n* = 4,225). β (in percent) denotes the coefficient of the serum vitamin D–FEV1/FVC association, with its 95% confidence interval; The cohort name and sample size of each cohort are specified in subpart A and subpart B; a positive association is greater than 0 while a negative association is less than 0, and fixed effect meta-analysis was used.Cohorts listed in the forest plots were ordered from the least to the most precise, and heterogeneity is presented (I2).

Abbreviation: 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; CHS, Cardiovascular Health Study; CI, Confidence Interval; EA, European Ancestry; FE, Fixed-Effects; FEV1, Forced Expiratory Volume in the First 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; RS, Rotterdam (Netherlands) Study.

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**E**

**F**

**D**

**B**

**C**

**A**

****

**J**

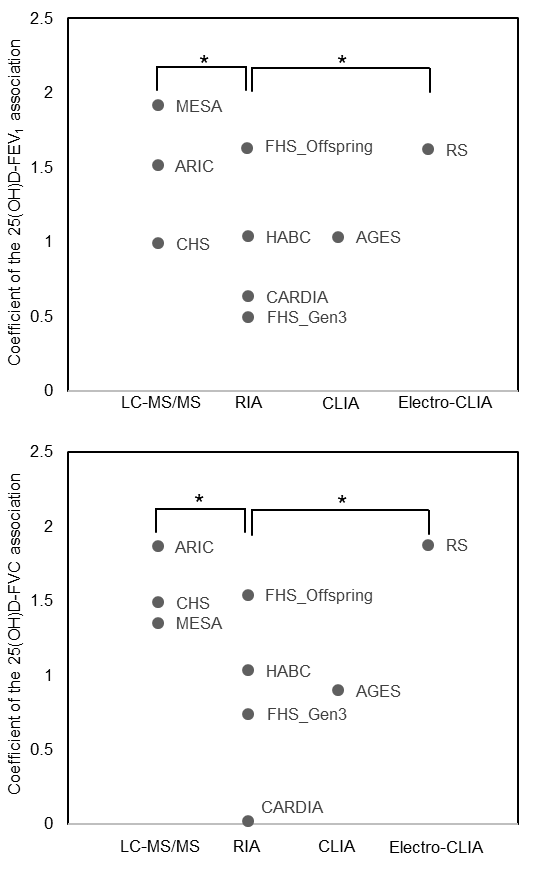
**I**

**H**

**G**

**Supplemental Figure 3. Meta-regression plots of individual modifiers** **against FEV1 and FVC, in nine European ancestry cohorts in the CHARGE Consortium.** The modifiers include proportion of ever smokers, proportion of current smokers, proportion of former smokers, time from 25(OH)D to PFT (days), and mean age (years) of each nine cohorts, to check for between-study heterogeneity explained by each modifier. The y axis is the association coefficient (β) of 25(OH)D (per nmol/L) with PFT (FEV1 or FVC, mL). (A) Plot of proportion of ever smokers against 25(OH)D–FEV1 association (P = 0.0002); (B) plot of proportion of ever smokers against 25(OH)D–FVC association (P = 0.001); (C) plot of proportion of current smokers against 25(OH)D–FEV1 association (P = 0.314); (D) plot of proportion of current smokers against 25(OH)D–FVC association (P = 0.053); (E) plot of proportion of former smokers against 25(OH)D–FEV1 association (P = 0.002); (F) plot of proportion of former smokers against 25(OH)D–FVC association (P = 0.037); (G) plot of measurement time interval against 25(OH)D–FEV1 association (P = 0.727); (H) plot of measurement time interval against 25(OH)D–FVC association (P = 0.405); (I) plot of cohort mean age against 25(OH)D–FEV1 association (P = 0.009); (J) plot of cohort mean age against 25(OH)D–FVC association (P = 0.083). The linear regression line is present in each scatter plot with a continuous modifier.

Abbreviation: 25(OH)D, 25-Hydroxyvitamin D; AGES, Age, Gene, Environment, Susceptibility Study—Reykjavik, Iceland; ARIC, Atherosclerosis Risk in Communities Study; CARDIA, Coronary Artery Risk Development in Young Adults Study; CHS, Cardiovascular Health Study; FEV1, Forced Expiratory Volume in the First 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; RS, Rotterdam (Netherlands) Study.

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**Supplemental Figure 4. Meta-regression of methods of 25(OH)D measure against the association estimates of 25(OH)D with PFT in nine European ancestry cohorts in the CHARGE Consortium.** The modifier is method of 25(OH)D measure in each of the nine cohorts. The method of 25(OH)D measure is a categorical variable with 4 categories (LC-MS/MS, RIA, CLIA, electro-CLIA). Pairwise comparisons of the 4 methods in the meta-regression model showed significant differences in the 25(OH)D–PFT associations between cohorts using RIA and cohorts using LC/MS/MS (p < 0.005), and also between cohorts using RIA and one cohort using electro-CLIA (p < 0.02).

Abbreviation: 25(OH)D, 25-Hydroxyvitamin D; AGES, Age, Gene, Environment, Susceptibility Study—Reykjavik, Iceland; ARIC, Atherosclerosis Risk in Communities Study; CARDIA, Coronary Artery Risk Development in Young Adults Study; CHS, Cardiovascular Health Study; CLIA, Chemiluminescence Immunoassay; FEV1, Forced Expiratory Volume in the First 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; LC-MS/MS, Liquid Chromatography in Tandem with Mass Spectrometry; MESA, Multi-Ethnic Study of Atherosclerosis; PFT, Pulmonary Function Test; RIA, Radioimmunoassay; RS, Rotterdam (Netherlands) Study.

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