Omega-3 Fatty Acids and Genome-wide Interaction Analyses Reveal *DPP10*-Pulmonary Function Association

Jiayi Xu[1]; Nathan C. Gaddis[2]; Traci M. Bartz[3,4]; Ruixue Hou[5]; Ani W. Manichaikul[6]; Nathan Pankratz[7]; Albert V. Smith[8]; Fangui Sun[9]; Natalie Terzikhan[10,11]; Christina A. Markunas[12]; Bonnie K. Patchen[1]; Matthew Schu[13]; May A. Beydoun[14]; Guy G. Brusselle[10,11,15]; Gudny Eiriksdottir[16]; Xia Zhou[17]; Alexis C. Wood[18]; Mariaelisa Graff[19]; Tamara B. Harris[20]; M. Arfan Ikram[11]; David R. Jacobs, Jr.[17]; Lenore J. Launer[14]; Rozenn N. Lemaitre[4,21]; George O'Connor[22]; Elizabeth C. Oelsner[23]; Bruce M. Psaty[4,21,24,25,26]; Vasan S. Ramachandran[27]; Rebecca R. Rohde[19]; Stephen S. Rich[6]; Jerome I. Rotter[28]; Sudha Seshadri[29]; Lewis J. Smith[30]; Henning Tiemeier[11,31,32]; Michael Y. Tsai[7]; André G. Uitterlinden[11]; V. Saroja Voruganti[5]; Hanfei Xu[9]; Nuno R. Zilhão[16]; Myriam Fornage[33,34]; M. Carola Zillikens[35,36]; Stephanie J. London[37]; R. Graham Barr[23]; Josée Dupuis[9]; Sina A. Gharib[21,38]; Vilmundur Gudnason[16,39]; Lies Lahousse[11,40]; Kari E. North[19]; Lyn M. Steffen[17]; Patricia A. Cassano[1,41*]; Dana B. Hancock[12*]

*These authors contributed equally to this work.

1. Division of Nutritional Sciences, Cornell University, Ithaca, New York, United States;
2. Research Computing Division, RTI International, Research Triangle Park, North Carolina; United States;
3. Department of Biostatistics, University of Washington, Seattle, Washington, United States;
4. Cardiovascular Health Research Unit, University of Washington, Seattle, Washington, United States;
5. Department of Nutrition and Nutrition Research Institute, University of North Carolina at Chapel Hill, Kannapolis, North Carolina, United States;
6. Center for Public Health Genomics, University of Virginia, Charlottesville, Virginia, United States;
7. Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota, United States;
8. Department of Biostatistics, University of Michigan, Ann Arbor, Michigan, United States;
9. Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts, United States;

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10. Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium;

11. Department of Epidemiology, Erasmus Medical Center, Rotterdam, the Netherlands;

12. Center for Omics Discovery and Epidemiology, Behavioral Health Research Division, RTI International, Research Triangle Park, North Carolina, United States;

13. Genomics in Public Health and Medicine Center, Biostatistics and Epidemiology Division, RTI International, Research Triangle Park, North Carolina, United States;

14. Intramural Research Program, National Institute on Aging, National Institutes of Health, Bethesda, Maryland, United States;

15. Department of Respiratory Medicine, Erasmus Medical Center, Rotterdam, the Netherlands;

16. Icelandic Heart Association, Kopavogur, Iceland;

17. Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, Minnesota, United States;

18. USDA/ARS Children's Nutrition Research Center, Baylor College of Medicine, Houston, Texas, United States;

19. Gillings School of Global Public Health, Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States;

20. Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland, United States;

21. Department of Medicine, University of Washington, Seattle, Washington, United States;

22. The Pulmonary Center, Department of Medicine, Boston University, Boston, Massachusetts, United States;

23. Department of Medicine, Columbia University, New York, New York, United States;

24. Department of Epidemiology, University of Washington, Seattle, Washington, United States;

25. Department of Health Services, University of Washington, Seattle, Washington, United States;

26. Kaiser Permanente Washington Health Research Institute, Seattle, Washington, United States;

27. Division of Cardiology and Preventive Medicine, Department of Medicine, Boston University, Boston, Massachusetts, United States;

28. Institute for Translational Genomics and Population Sciences, Los Angeles Biomedical Research Institute and Department of Pediatrics at Harbor-UCLA Medical Center, Torrance, California, United States;

29. Department of Neurology, Boston University, Boston, Massachusetts, United States;

30. Division of Pulmonary and Critical Care, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, United States;

31. Department of Psychiatry, Erasmus Medical Center, Rotterdam, the Netherlands;

32. Department of Child and Adolescent Psychiatry, Erasmus Medical Center, Rotterdam, the Netherlands;

33. Institute of Molecular Medicine, University of Texas Health Science Center at Houston, Houston, Texas, United States;

34. Human Genetics Center, School of Public Health, University of Texas Health Science Center at Houston, Houston, Texas, United States;

35. Netherlands Genomics Initiative (NGI)-sponsored Netherlands Consortium for Healthy Aging, Leiden, the Netherlands;

36. Department of Internal Medicine, Erasmus Medical Center, Rotterdam, the Netherlands;

37. Division of Intramural Research, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, North Carolina, United States;

38. Center for Lung Biology, University of Washington, Seattle, Washington, United States;

39. University of Iceland, Reykjavik, Iceland;

40. Department of Bioanalysis, Faculty of Pharmaceutical Sciences, Ghent University, Ghent, Belgium.

41. Department of Healthcare Policy and Research, Division of Biostatistics and Epidemiology, Weill Cornell Medical College, New York, New York, United States.

Corresponding author:

Dana B. Hancock, PhD

Behavioral and Urban Health Program, RTI International

3040 East Cornwallis Road

Research Triangle Park, NC 27709

dhancock@rti.org

919 541 6701 (PH); 919 485 5555 (FAX)

CONTRIBUTORS

JX, PAC, and DBH conceived and designed the study. AWM, RGB, JD, BMP, SAG, RNL, MF, LL, KEN, AVS, VG, and LMS provided the data and supervised the data analysis in each cohort. JX, NCG, TMB, RH, RRR, AVS, AWM, NP, FS, NT, XZ, and CAM analyzed cohort-specific data and/or carried out meta-analyses. MS mirrored the meta-analysis and confirmed the results. JX, NCG, CAM, BKP, PAC and DBH interpreted the results. JX, CAM, BKP, PAC, and DBH co-wrote and edited the first draft of the manuscript. All authors provided

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AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Omega-3 poly-unsaturated fatty acids (n-3 PUFAs) have anti-inflammatory properties that may combat chronic inflammation and beneficially affect pulmonary function. However, few population-based studies have investigated the associations between n-3 PUFAs and pulmonary function, and although smokers have higher inflammation burden on average, no studies have examined whether smoking modifies these associations. Moreover, pulmonary function measures are heritable, with over 150 genetic loci identified through genome-wide association studies, yet no studies have assessed evidence for interactions between genetic variants and n-3 PUFAs or any other biomarker.

What This Study Adds to the Field

We investigated n-3 PUFA biomarker associations with pulmonary function tests (PFTs) in seven cohorts. After establishing the n-3 PUFA biomarker-PFT associations, we tested genome-wide interactions between genetic variants and the n-3 PUFA biomarkers on PFT measures and applied the joint 2 degree-of-freedom meta-analysis approach. In the model that included both docosahexaenoic acid and its interaction with genetic variants, we identified a novel *DPP10* association with forced vital capacity at genome-wide significance. This *DPP10* association was not found in standard genome-wide analyses, and was only discovered after incorporating the interaction into a model with the environmental variable, namely n-3 PUFA biomarker levels.

Note: This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org

ABSTRACT

Rationale: Omega-3 poly-unsaturated fatty acids (n-3 PUFAs) have anti-inflammatory properties that could benefit adults with comprised pulmonary health.

Objective: To investigate n-3 PUFA associations with spirometric measures of pulmonary function tests (PFTs) and determine underlying genetic susceptibility.

Methods: Associations of n-3 PUFA biomarkers (alpha-linolenic acid, eicosapentaenoic acid, docosapentaenoic acid [DPA], and docosahexaenoic acid [DHA]) were evaluated with PFTs (forced expiratory volume in the first second [FEV_1], forced vital capacity [FVC], and [FEV_1/FVC]) in meta-analyses across seven cohorts from the Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium (N=16,134 of European or African ancestry). PFT-associated n-3 PUFAs were carried forward to genome-wide interaction analyses in the four largest cohorts (N=11,962) and replicated in one cohort (N=1,687). Cohort-specific results were combined using joint 2 degree-of-freedom (2df) meta-analyses of single nucleotide polymorphism (SNP) associations and their interactions with n-3 PUFAs.

Results: DPA and DHA were positively associated with FEV_1 and FVC (P<0.025), with evidence for effect modification by smoking and by sex. Genome-wide analyses identified a novel association of rs11693320—an intronic *DPP10* SNP—with FVC when incorporating an interaction with DHA, and the finding was replicated ($P_{2df}=9.4\times10^{-9}$ across discovery and replication cohorts). The rs11693320-A allele (frequency~80%) was associated with lower FVC ($P_{SNP}=2.1\times10^{-9}$; $\beta_{SNP}=$ -161.0mL), and the association was attenuated by higher DHA levels ($P_{SNP\times DHA\ interaction}=2.1\times10^{-7}$; $\beta_{SNP\times DHA\ interaction}=36.2$mL).

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Conclusions: We corroborated beneficial effects of n-3 PUFAs on pulmonary function. By modeling genome-wide n-3 PUFA interactions, we identified a novel *DPP10* SNP association with FVC that was not detectable in much larger studies ignoring this interaction.

Keywords: forced expiratory volume; forced vital capacity; smoking; genome-wide association study; adult; n-3 PUFA; omega-3 fatty acids; docosahexaenoic acid; eicosapentaenoic acid; docosapentaenoic acid; alpha-linolenic acid

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INTRODUCTION

Pulmonary function tests (PFTs) provide indicators of lung health and mortality risk in the general population (1). Impaired pulmonary function increases the risk of chronic obstructive pulmonary disease (COPD) (2), which is one of the leading causes of death worldwide (3, 4). PFTs include measurement of forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC to diagnose COPD and follow its progression.

PFTs are heritable traits (~35%) (5), and genome-wide association studies (GWASs) have identified >150 PFT-associated loci (6-13). Environmental factors, including cigarette smoking that contributes to chronic inflammation (14), also influence PFTs. Omega-3 poly-unsaturated fatty acids (n-3 PUFAs) may mitigate the inflammatory response. N-3 PUFAs include alpha-linolenic acid (ALA), and its long-chain derivatives, eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA). ALA, the predominant n-3 PUFA in the western diet, is present in vegetable oils; EPA, DPA, and DHA are found mainly in fish. After absorption, some dietary ALA is converted through endogenous elongation and desaturation reactions (15) to the long-chain derivatives. However, dietary ALA may not adequately replace dietary EPA, DPA, and DHA given the limited conversion rate (16). We focused on these n-3 PUFAs based on prior evidence that they help combat inflammation in the lung by generating lipid-derived mediators, such as resolvins (17, 18).

Diets rich in n-3 PUFAs have been implicated in preventing chronic inflammatory diseases, including cardiovascular disease, rheumatoid arthritis, and dementia (19). Few studies have investigated the role of n-3 PUFAs in lung health. Two studies investigated dietary-reported n-3 PUFAs with PFTs; one found that higher n-3 PUFAs were associated with higher PFTs (20), while the other reported null associations (21). One study investigating serum n-3 PUFAs with

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PFTs found positive associations of DHA with FEV_1 and FVC (22). Another study, conducted only in ever smokers, found that higher plasma DHA was associated with lower odds of COPD (23).

Tests that jointly model environmental factors and gene-by-environment interactions can identify novel genetic associations (24-26). No prior GWAS of PFTs have investigated interactions with n-3 PUFAs or other nutrient biomarkers. Here, we tested the association of n-3 PUFA biomarkers with cross-sectional PFTs and then studied genome-wide interactions of single nucleotide polymorphisms (SNPs) and insertions/deletions (indels) with n-3 PUFAs on PFTs in the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium. We combined cohort-specific results to estimate the n-3 PUFA-PFT associations and to identify genetic associations with PFTs when accounting for n-3 PUFA interactions. Preliminary results of our study, reporting n-3 PUFA biomarker associations with PFTs, were previously published in the form of an abstract (27).

MATERIALS AND METHODS

Cohorts and Participants

Seven cohorts—AGES, ARIC, CARDIA, CHS, FHS, MESA, and RS—contributed to meta-analyses of n-3 PUFA-PFT associations. All cohorts included European ancestry (EA) participants; three cohorts also included African ancestry (AA) participants (**Table 1)**. Our genome-wide interaction analyses focused on the five largest cohorts (N>500). Additional cohort details are provided in the Supplement and **Tables E1–E3**. Institutional Review Boards at the respective institutions approved all data collection.

PFTs and N-3 PUFA Measurements

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PFTs, specifically FEV_1 (unit: mL), FVC (unit: mL), and FEV_1/FVC (unit: %), were measured by spirometry. N-3 PUFAs were measured in plasma phospholipids in all cohorts except FHS (Supplement, **Table E4** for measurement details and **Table E5** for measurement times**)**. N-3 PUFAs were measured in red blood cells in FHS, which are strongly correlated with plasma measures (16, 28). In each cohort, n-3 PUFAs were measured as a relative percent of total fatty acids. Both PFTs and n-3 PUFAs were continuous variables.

Statistical Analysis for n-3 PUFA Associations with PFTs

Linear regression models were run, separately by European or African ancestry in each cohort, to estimate n-3 PUFA associations with PFTs, as described in the Supplement. Models were extended to include interaction terms to assess effect modification by smoking status and sex. Fixed-effects meta-analysis was used to combine cohort- and ancestry-specific estimates of n-3 PUFA-PFT associations and n-3 PUFA interactions with smoking status and sex (29). Smoking-stratified meta-analyses were also performed, and heterogeneity at the cohort level was examined (Supplement).

Statistical Analysis for Genome-Wide Interaction with N-3 PUFAs on PFTs

Genome-wide interactions with n-3 PUFAs were studied using joint 2df meta-analyses (30) under a fixed-effects model, as done before in single ancestry (31) and cross-ancestry genome-wide meta-analyses (32). Robust standard error estimation and inverse variance weighting were applied (33), similar to the prior genome-wide variant×smoking study for PFTs in CHARGE (24). The same covariates were adjusted (Supplement) along with ancestral principal components. Cohort- and ancestry-specific coefficients of SNP/indel (henceforth, collectively referred to as SNP) additive dosage (β_{SNP}) and SNP×n-3 PUFA interaction term ($\beta_{SNP×n\text{-}3\ PUFA\ interaction}$) in the four discovery cohorts were combined using METAL with genomic

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control applied (N=11,962; 11,165 EA, 797 AA; **Table 1**). The standard *a priori* level of

genome-wide significance was used ($P<5\times10^{-8}$) for the discovery meta-analysis (34), as done in

our prior study (24). CARDIA was reserved for replication (N=1,687; 1,141 EA, 546 AA, **Table**

1). The threshold for declaring significance in the replication phase was 0.05 given that only one

SNP in one model was tested. To characterize top SNP findings, we pursued three additional

analyses across the discovery and replication cohorts: smoking-stratified and sex-stratified joint

2df meta-analyses to examine selected SNP×n-3 PUFA interactions; and standard 1df meta-

analyses to assess evidence of SNP associations without considering n-3 PUFA interaction.

Bioinformatics Analysis

Follow-up analyses were conducted to assess SNP regulatory potential and gene function.

In silico analyses used HaploReg v4.1 (35), Roadmap Epigenomics (36), Genotype-Tissue

Expression Project (GTEx, version 7) (37), and GeneMANIA (38) (Supplement).

RESULTS

Characteristics of cohort participants and their n-3 PUFA distributions are provided in

Table 1 (additional details in the Supplement**, Table E6**, and **Figure E1)**. There was little

correlation (|r|<0.2) between the n-3 PUFAs (ALA, EPA, DPA or DHA) with pack-years, and

average levels were similar across smoking strata, except for DHA, which showed a relatively

consistent pattern across cohorts with the highest levels in never smokers, followed by former

smokers, and then current smokers (**Table E7**).

Meta-Analysis of Associations of N-3 PUFAs and Interactions with Smoking and Sex on

PFTs

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For FEV_1 and FVC, cross-ancestry meta-analyses revealed positive associations of DHA and DPA at P<0.05 (**Figures 1**, **E2–E3** and **Table E8**). To convey the impact of differences in n-3 PUFA levels, we estimated that one standard deviation higher DHA (~1.3% of plasma total FAs) was associated with 18.6 mL higher FEV_1 (P=6.1×10^{-6}) and 10.9 mL higher FVC (P=0.02) and that one standard deviation higher DPA (~0.2% of plasma total FAs) was associated with 7.9 mL higher FEV_1 (P=0.0006) and 6.5 mL higher FVC (P=0.01) (sensitivity analysis in the Supplement). A positive association was also indicated between ALA and FVC: one standard deviation higher ALA (0.07% of plasma total FAs) being associated with 8.4 mL higher FVC (P=0.023). This ALA finding was mainly driven by AAs (**Table E8**).

Smoking status significantly modified the DHA-FEV_1 association ($P_{DHA×current\ smoking\ interaction}$=0.02; **Figure E4**) such that the magnitude of the association was larger in current smokers. To further interpret the DHA interaction with smoking status on FEV_1, β coefficients for current, former, and never smokers were estimated ($\beta_{DHA} + \beta_{DHA×smoking\ interaction}$). Across all cohorts, a 1% higher DHA was associated with a 39 mL higher FEV_1 (P=0.0001) in current smokers; this effect size was about three times the magnitude observed for former (13 mL; P=0.010) and never smokers (11 mL; P=0.012) (**Figure 2**).

For FEV_1/FVC, the cross-ancestry and EA-specific meta-analyses revealed associations with EPA and ALA (P<0.02) and with DHA among current smokers (P<0.0001) (**Figure E4**). However, because the effect sizes were small (<1% increase in FEV_1/FVC with 1 standard deviation higher n-3 PUFA; **Table E8–E9**), further analyses focused on FEV_1 and FVC. No significant interaction of smoking status with DPA was observed for any PFT outcome (P=0.06–0.35).

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Sex was an effect modifier in the DPA-FVC association ($P_{DPA \times sex\ interaction}$=0.035) such that the magnitude of the DPA association was larger in males (1 standard deviation [~0.2%] higher DPA had a greater association with FVC [by 10 mL] in males than in females). Sex modification, however, was not observed for DPA-FEV_1, DHA-FEV_1, or DHA-FVC associations ($P_{interaction}$=0.17–0.83).

Genome-Wide Interaction Analyses of N-3 PUFAs on PFTs

DHA and DPA were carried forward to genome-wide interaction analyses because each was associated at P<0.05 in both the EA-specific and the cross-ancestry meta-analyses. Since the ALA association was primarily driven by AA participants, which represented a small portion of the total sample size used for the n-3 PUFA-PFT analysis (~16%), ALA was not carried forward. Genome-wide joint 2df interaction analyses with n-3 PUFAs captured 7.2 million genotyped and 1000 Genomes-imputed SNPs with minor allele frequency >5% across 11,165 EAs and 797 AAs (**Table 1**). There was no indication of genomic inflation bias (λ_{gc}=1.02–1.03, **Figures E5–E8**).

Two novel loci were identified at cross-ancestry meta-analysis P_{2df}<5×10^{-8} (**Figures E6–E7**). For FEV_1, rs79992631, a downstream *C8orf4* SNP on chromosome 8p11, was identified when accounting for DPA interaction. However, because the signal was driven by a single cohort with sub-optimal imputation quality at this SNP (Rsq=0.65) and was not supported by other cohorts in the discovery meta-analysis with better imputation quality at this SNP, rs79992631 was not tested further as it is likely a false-positive. For FVC, rs11693320, a dipeptidyl peptidase like 10 (*DPP10*) intronic SNP on chromosome 2q14 (**Figure 3**), was identified when accounting for DHA interaction. Meta-analysis across all discovery cohorts revealed that rs11693320 was associated with FVC at P_{2df}=4.5×10^{-8} (**Table 2**). The rs11693320-FVC association was tested for replication in CARDIA (1,141 EAs, 546 AAs; **Table 1**) and found to be associated at P_{2df}=0.045

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with consistent directions of association (**Table 2**), and an overall $P_{2df}=9.4\times10^{-9}$ across all cohorts, which passed a stringent Bonferroni-corrected cutoff of 1.25×10^{-8} that takes into account all four genome-wide interaction models (DHA and DPA with FEV_1 and FVC). The rs11693320-A allele, which has a similar frequency across ancestries (81% in EAs, 79% in AAs), was associated with reduced FVC ($\beta_{SNP}=-161.0$ mL, $P_{SNP}=2.1\times10^{-9}$); this association was attenuated by higher DHA levels ($\beta_{SNP\times DHA\ interaction}=+36.2$ mL per 1% DHA of total FAs, $P_{SNP\times DHA\ interaction}=2.1\times10^{-7}$). In the discovery cohorts, the rs11693320 and rs11693320×DHA interaction effect sizes were larger in AAs ($\beta_{SNP}=-186.4$ and $\beta_{SNP\times DHA\ interaction}=39.7$ in the single AA cohort compared to $\beta_{SNP}=-155.8$ and $\beta_{SNP\times DHA\ interaction}=34.0$ in the EA-specific meta-analysis, **Table 2**). The same pattern was observed between AAs and EAs in the replication cohort (**Table 2**). Although not passing genome-wide significance, consistent directions were observed for the association of rs11693320 and its interaction with DHA on FEV_1 (meta-analysis β_{SNP} [SE]=-95.2 [23.9], $\beta_{SNP\times DHA\ interaction}$ [SE]=19.9 [6.0], and $P_{2df}=2.1\times10^{-4}$).

We also used our genome-wide results to look-up previous GWAS-identified SNPs associated with n-3 PUFA phenotypes and PFTs. Results are shown in the Supplement and **Tables E10–E11**.

DPP10 SNP Interaction with n-3 PUFA Biomarkers by Smoking Status and Sex

The joint 2df meta-analyses accounting for rs11693320×DHA interaction on FVC was further explored in models stratified by smoking status, which suggested that the interaction was mainly driven by former smokers (N=5,373; $\beta_{SNP}=-218.5$mL, $P_{SNP}=8.3\times10^{-6}$; $\beta_{SNP\times DHA\ interaction}=+53.8$mL, $P_{SNP\times DHA\ interaction}=6.7\times10^{-6}$). The directions of association were consistent in current and never smokers, but with weaker statistical evidence (current smokers: N=3,944; $\beta_{SNP}=-130.4$mL, $P_{SNP}=0.15$; $\beta_{SNP\times DHA\ interaction}=+21.8$mL, $P_{SNP\times DHA\ interaction}=0.45$; and never

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smokers: N=4,332; β_{SNP}=-93.7mL, P_{SNP}=0.030; $\beta_{SNP\times DHA\ interaction}$=+16.4mL, $P_{SNP\times DHA\ interaction}$=0.13).

When stratified by sex, the rs11693320×DHA interaction finding on FVC was mainly driven by males (N=6,231; β_{SNP}=-223.0mL, P_{SNP}=2.5×10^{-5}; $\beta_{SNP\times DHA\ interaction}$=+55.8mL, $P_{SNP\times DHA\ interaction}$=6.1×10^{-5}). The directions of association were consistent in females, but with weaker statistical evidence (N=7,418; β_{SNP}=-60.3mL, P_{SNP}=0.09; $\beta_{SNP\times DHA\ interaction}$=+11.6mL, $P_{SNP\times DHA\ interaction}$=0.20).

Follow-up Bioinformatics Analysis

According to HaploReg v4.1 (35), three variants in high LD (r^2>0.8) with rs11693320 are located within putative enhancer elements in lung tissue. Functional annotations of rs11693320 and variants with r^2>0.8 (1000 Genomes EUR) are provided (**Table E12**). Rs11693320 is a putative eQTL for *DPP10* in GTEx lung tissue: its A allele being associated with lower expression (P=0.036, N=383) (37). To better characterize *DPP10* gene function, we used GeneMANIA to create a network of genes biologically related to *DPP10* (**Figures 4 and E9**). Within this network of 20 genes, 5 genes were co-expressed (P<0.05) with *DPP10* in GTEx lung tissue: *DPP4*, *FMN2*, *FABP4,* and *VAT1L* were positively associated with *DPP10* expression, while *ADAM20* was inversely associated.

DISCUSSION

Our study tested the associations of n-3 PUFA biomarkers with PFTs combining data across multiple cohorts, which showed positive associations of DHA and DPA with FEV_1 and FVC. The FEV_1 outcome had slightly larger magnitudes of association with n-3 PUFAs, consistent with the pattern observed in the only previous study that investigated plasma n-3

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PUFA associations with PFTs (22). Importantly, we found, for the first time, that the association of FEV_1 with DHA differed by smoking status ($P_{DHA \times smoking\ interaction}$=0.02), with the magnitude of the association for current smokers (β=39 mL per 1% [about one standard deviation] higher DHA) being about 3-fold larger than the association in never (β=11mL) and former (β=13 mL) smokers. We also found a significant interaction of DHA with current smoking on FEV_1/FVC, although the magnitude of the association was negligible (<1% increase per 1% higher DHA). In addition, we found a DPA×sex interaction such that the magnitude of the DPA association with FVC was larger in males than in females (larger by 10 mL per 1 standard deviation [0.2%] higher DPA).

In genome-wide interaction meta-analyses, we identified the *DPP10* SNP rs11693320-A allele for its novel association with FVC (β_{SNP}= -161.0 mL), which was attenuated by higher DHA levels ($\beta_{interaction}$=+36.2 mL) (**Table 2**). To put the magnitude of the *DPP10*-FVC association into context, rs11693320-A was associated with 88.6 mL lower FVC at DHA level=2% of total FAs (about 1 standard deviation below the average DHA level), whereas rs11693320-A was associated with 16.2 mL lower FVC at DHA level=4% of total FAs (slightly above the average DHA level). In comparison, one year of age-related FVC decline is about 30 mL in US adults from the general population (39). Our findings indicate that nutrient biomarker levels might influence genetic factors underlying pulmonary function.

The only prior study to directly investigate n-3 PUFA biomarkers and PFTs (N=593) reported suggestive positive associations of DHA with percent predicted FEV_1 and FVC, and a positive association of DPA with percent predicted FVC in men only (22). Our study included large numbers, tested smoking interactions for the first time, and found a larger magnitude of the DHA association with FEV_1 in current smokers compared to former and never smokers. The

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positive associations of DHA and DPA with PFTs are biologically plausible and may be mediated by metabolic derivatives such as resolvins and protectins, which regulate the resolution of inflammation via mechanisms including the inhibition of pro-inflammatory gene expression and the clearance of inflammatory cells by macrophages (17). DHA-derived Resolvin D1 was shown to have anti-inflammatory effects in mice and human cell lines with cigarette smoke exposure (40).

The rs11693320 association with FVC was evident only by considering interaction with DHA. Rs11693320 did not attain genome-wide significance in standard 1df meta-analysis without DHA interaction in the model (P=1.7×10^{-4}; **Table 2**). Similarly, rs11693320 was not identified in previous GWASs of PFTs (6-12, 41). Our top *DPP10* SNPs, some of which were available as HapMap-imputed SNPs in a previous GWAS of FVC with a larger sample size (N=52,253) (10), achieved only borderline nominal significance (P=0.06–0.1) (**Table E13**). Moreover, rs11693320 had no association with DHA in our study (P=0.57 across the five cohorts), and nearby HapMap-imputed *DPP10* SNPs also were not associated with the DHA phenotype in a CHARGE GWAS meta-analysis of plasma n-3 PUFAs (**Table E13**) (41).

DPP10 was previously identified as a candidate gene for asthma (42-45), and a single study of asthma candidate genes suggested that major alleles of *DPP10* SNPs were associated with both FEV$_1$ and FVC decline under a recessive mode of inheritance (46). Similarly, in our study, we found that the major allele of rs11693320 on *DPP10* was associated with lower FEV$_1$ and FVC, although only the finding for FVC reached genome-wide significance. Prior GWAS for FVC similarly identified loci that were not detected in GWAS of FEV$_1$, suggesting that these correlated, but clinically different, measures have both shared and unique genetic risk factors (47). Previous speculation about the biological mechanism through which *DPP10* affects asthma

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relates to conduction of electric signals in the nervous system, which could affect the activity of airway smooth muscle (e.g. contraction) via neural regulation (44). *DPP10* is highly expressed in brain neurons (48) and slightly expressed in lung tissues (49). It encodes one member of the S9B family of serine proteases, which could be released to the extracellular space (50). The *DPP10*-encoded protein can bind to the voltage-gated potassium (K^+) channel and facilitate the trafficking of K^+ channel protein to the cell membrane (48).

Using the public bioinformatics tools, GeneMANIA (38) and GTEx (37), we found five genes related to *DPP10* function and 4 of them positively co-expressed with *DPP10* in lung tissue. Based on previous evidence (50-54), only *FABP4* and *DPP4* play a role in pulmonary function and may potentially interact with DHA in this regard. The *FABP4* gene is a putative biomarker for systemic inflammation in COPD patients, and FABP4 circulating level was associated with lower PFTs in COPD patients (51) and non-diseased individuals (52). A small clinical trial (N=14) reported that DHA+EPA supplementation, which increased serum DHA, led to a concurrent decrease in FABP4 level (53). The other *DPP10*-related gene, *DPP4*, plays a role in asthma pathogenesis, as *DPP10* does, albeit through a different mechanism (i.e. immune-suppression) (50). A study in diabetic patients directly linked *DPP4* to the DHA biomarker; the efficacy of a *DPP4* inhibitor on glycemic control was positively correlated with DHA nutriture (*r*=0.73) (54). Thus, DHA may play a beneficial role in pulmonary function, potentially through influencing *DPP10*, *DPP4*, and *FABP4,* but further research is needed to investigate the interplay between these genes and DHA.

Given that n-3 PUFAs are postulated to mitigate inflammatory responses brought about by cigarette smoking, we carried out smoking-stratified analyses and found that the rs11693320 effect size was largest in former smokers, when considering its interaction with DHA, suggesting

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potential effect moderation by cigarette smoking. A study of human fetal lung tissue reported

that *in utero* smoking exposure was associated with methylation changes in *DPP10* (55). Our

findings suggest an inverse association of *DPP10* SNPs with PFTs that are mitigated by

circulating DHA levels, and the interplay among *DPP10*, DHA, and smoking status needs further

investigation. We posit that current smoking, as compared with former smoking, induces

additional perturbations to lipid homeostasis (e.g., lipid peroxidation of cell membranes of

vulnerable cells such as airway epithelial cells expressing *DPP10*) via oxidative stress and

epigenetic changes (including DNA methylation, histone modifications and/or micro-RNA

dysregulation), which might affect the beneficial effects of n-3 PUFAs and their attenuation of

genetic risk factors on FVC. Moreover, the association pattern among former smokers may also

underlie our observed sex-stratified results, whereby the largest effect sizes for rs11693320 and

its interaction with DHA occurred in men, who are more likely to have smoked, smoked more

heavily, and reported being more severely dependent to nicotine in their current and past

smoking histories as compared to women (56, 57).

Our findings are likely to have strong external validity, thus are expected to generalize

well to adult populations in the US and Europe. Overall, average FEV_1/FVC of the included

cohorts was in the expected 70–80% range for healthy US adults (**Table E6**), and the prevalence

of COPD is expected to be similar to the US prevalence (~6.1%) (58). Participant selection bias

is expected to be minimal given that all the measurements (spirometry, n-3 PUFA biomarkers,

and genetic data) were collected either in all cohort participants or in a random set of

participants. Finally, only 1,343 AAs contributed data for the genome-wide interaction analysis,

which led us to combine EAs and AAs in cross-ancestry meta-analyses (total N=13,649) to

increase power. Even though the rs11693320 and rs11693320×DHA interaction effect sizes were

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larger in AAs than EAs, which has been observed for other reported SNP associations with complex traits (e.g., *CHRNA5* SNP rs16969968 with cigarettes smoked per day (59)), drawing an inference of ancestral differences for this SNP was limited given fewer AAs (total N=1,343) than EAs (total N=12,306) available for study. While the cross-sectional design prohibits direct causal inferences, these findings are strengthened by the internal consistency of findings across cohorts with different contexts. Future studies that investigate longitudinal PFTs and the complex interplay of fatty acid components are needed to further strengthen the causal inference of associations observed in our study.

This study has several strengths. First, we used objectively measured n-3 PUFA biomarkers, instead of self-reported dietary intake, as the exposures. The n-3 PUFA biomarkers reflect intake as well as inter-individual differences in absorption and incorporation into phospholipids (for n-3 PUFAs from dietary sources) and metabolic efficiency (for n-3 PUFAs from endogenous biosynthesis). Therefore, it is a more reliable measure of n-3 PUFA nutrients that are available to tissues/organs, compared to self-reported dietary intake of n-3 PUFAs. Second, we conducted association analyses of n-3 PUFAs on PFTs across multiple cohorts that together had sufficient sample size to examine effect modification by smoking and by sex. Third, we investigated the genome-wide variant×nutrient interactions on PFTs via joint 2df meta-analyses and discovered a novel genetic association with pulmonary function, when considering the interaction with n-3 PUFAs, which was not identified previously using the standard GWAS approach with even larger sample sizes.

We found positive associations of DHA and DPA biomarkers with PFTs, specifically FEV_1 and FVC, and the magnitude of the DHA-FEV_1 association was ~3-fold larger in current smokers. This suggested a greater beneficial effect of n-3 PUFAs, especially DHA, on

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pulmonary function in current smokers. We also identified the *DPP10* locus, where the intronic rs11693320-A was inversely associated with FVC, and a higher DHA level attenuated this effect. Few genome-wide studies investigate how nutrient status and genetic predisposition can influence each other and affect PFTs, and the results of this study are important in contributing to the evidence base needed to provide targeted dietary advice for COPD prevention.

AUTHOR DISCLOSURE

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Table 1. Participant Characteristics in All Seven Cohorts (N = 16,134; 13,629 EA and 2,505 AA)[*]

Top banner spanning all cohort columns: **N-3 PUFA biomarkers and genome-wide interaction on PFT measures**

Sub-banners: **Discovery phase of genome-wide interaction analysis of n-3 PUFA biomarkers** (ARIC, FHS, MESA) — **Replication phase** (CARDIA)

Cohort/Sub-Cohort	AGES	RS	CHS[‡‡]	CHS[‡‡]	ARIC	FHS -Offspring	FHS -Gen3	MESA	MESA	CARDIA	CARDIA
Ancestry	EA	EA	AA	EA	EA	EA	EA	AA	EA	AA	EA
N for n-3 PUFA-PFT association[†]	424	141	243	1,690	3,254	2,169	3,052	801	1,140	1,461	1,759
N for genome-wide interaction[‡]	NA[§§]	NA[§§]	NA[§§]	1,684	3,143	5,198[‖‖‖]	(merged)	797	1,140	546[***]	1,141[***]
Males, %	45.0	48.9	30.9	39.1	48.5	45.0	47.2	47.7	49.6	39.3	46.5
Age, year	76.3 (5.5)	74.6 (5.7)	72.9 (5.2)	74.5 (4.8)	53.8 (5.6)	66.0 (8.9)	46.0 (8.8)	65.6 (9.7)	66.4 (9.9)	44.6 (3.8)	45.8 (3.4)
Height, m	1.67 (0.09)	1.68 (0.09)	1.64 (0.08)	1.64 (0.09)	1.69 (0.09)	1.67 (0.10)	1.70 (0.09)	1.68 (0.10)	1.69 (0.10)	1.70 (0.10)	1.72 (0.09)
Weight, kg[§]	76.4 (14.8)	77.9 (13.7)	77.4 (13.0)	71.3 (13.8)	77.9 (16.2)	79.3 (17.6)	81.1 (19.3)	84.8 (17.2)	79.8 (17.5)	90.5 (23.0)	81.8 (19.5)
Current smokers, %	11.1	14.2	12.3	8.4	22.8	8.0	9.8	15.5	8.7	24.1	14.3
Former smokers, %	40.1	57.5	42.0	48.5	39.5	53.0	32.2	38.6	47.1	13.5	24.4
Pack-Years[‖]	24.6 (17.5)	27.0 (23.5)	25.4 (26.0)	28.7 (25.2)	26.8 (19.7)	24.6 (21.7)	13.1 (14.3)	24.6 (23.5)	29.7 (29.1)	10.8 (9.2)	12.2 (12.5)
FEV_1, mL	2176 (664)	2387 (748)	1765 (482)	2036 (614)	3080 (780)	2630 (767)	3388 (773)	2189 (662)	2555 (761)	2704 (684)	3329 (753)
FVC, mL	2920 (815)	3238 (952)	2440 (694)	2936 (838)	4144 (984)	3651 (995)	4449 (993)	2920 (862)	3494 (983)	3409 (871)	4291 (979)
FEV_1/FVC (%)	74.4 (8.1)	73.7 (8.3)	73.0 (8.1)	69.6 (9.7)	74.3 (7.3)	72.0 (7.8)	76.3 (6.6)	75.4 (9.5)	73.3 (8.7)	79.7 (7.0)	77.9 (6.3)
ALA (% of total FAs)	0.23 (0.09)	0.17 (0.06)	0.14 (0.04)	0.15 (0.06)	0.14 (0.05)	0.18 (0.11)	0.17 (0.07)	0.16 (0.06)	0.18 (0.10)	0.17 (0.08)	0.19 (0.08)
EPA (% of total FAs)	2.87 (1.66)	0.85 (0.57)	0.61 (0.36)	0.60 (0.39)	0.56 (0.25)	0.74 (0.48)	0.67 (0.42)	0.91 (0.72)	0.93 (0.73)	0.68 (0.42)	0.84 (0.61)

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	N-3 PUFA biomarkers and genome-wide interaction on PFT measures										
				Discovery phase of genome-wide interaction analysis of n-3 PUFA biomarkers						Replication phase	
DPA (% of total FAs)	1.18 (0.21)	0.94 (0.17)	0.86 (0.20)	0.83 (0.17)	0.90 (0.17)	2.76 (0.46)	2.55 (0.45)	0.95 (0.23)	0.93 (0.22)	0.93 (0.21)	0.94 (0.21)
DHA (% of total FAs)	6.33 (1.52)	3.52 (0.93)	3.55 (0.98)	2.98 (0.95)	2.81 (0.86)	4.87 (1.37)	4.19 (1.22)	4.28 (1.37)	3.53 (1.33)	3.29 (0.99)	3.10 (1.12)
Total n-3 PUFAs (% of total FA)**	10.60 (3.08)	5.48 (1.38)	5.16 (1.31)	4.56 (1.27)	4.41 (1.04)	8.56 (2.00)	7.59 (1.78)	6.29 (2.07)	5.57 (2.02)	5.07 (1.32)	5.08 (1.65)
Time Difference between PFT and n-3 PUFAs, days††	1 (6)	1705 (178)	353 (27)	362 (29)	0 (0)	3 (77)	0 (0)	1724 (116)	1769 (110)	0 (0)	0 (0)

Abbreviations: AA = African ancestry; AGES = Age, Gene, Environment, Susceptibility Study—Reykjavik, Iceland; ALA = Alpha-linolenic acid; ARIC = Atherosclerosis Risk in Communities; CARDIA = Coronary Artery Risk Development in Young Adults; CHS = Cardiovascular Health Study; DHA = Docosahexaenoic acid; DPA = Docosapentaenoic acid; EA = European ancestry; EPA = Eicosapentaenoic acid; FA= Fatty acid; FEV_1 = 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; MESA = Multi-Ethnic Study of Atherosclerosis; NA = Not applicable; n-3 PUFA = Omega-3 poly-unsaturated fatty acid; PFT = Pulmonary function test; RS = Rotterdam (Netherlands) Study.

[*]Data are presented as mean (standard deviation) unless otherwise indicated. Seven cohorts are included in total. All the cohorts measured n-3 PUFAs in plasma, except FHS, which measured n-3 PUFAs in red blood cells in its two sub-cohorts (the Offspring Cohort and the Generation 3 Cohort). The descriptive statistics presented here are based on all participants in the main n-3 PUFA-PFT association analyses.

[†]The total sample size for the meta-analysis of omega-3 fatty acid biomarker associations with PFTs was 16,134, in which 13,629 were European ancestry participants, and 2,505 were African ancestry participants.

[‡]The total sample size for the genome-wide interaction analyses of omega-3 fatty acid biomarkers (84.6% of those included in the n-3 PUFA-PFT association analysis) was 13,649, in which 12,306 were European ancestry participants (90.3% of all EA participants), and 1,343 were African ancestry participants (53.6% of all AA participants). Any discrepancy in numbers of participants for the n-3 PUFA-PFT association and discovery-phase genome-wide analyses was due to participants whose genetic data did not pass quality control.

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§Number of participants with weight data was slightly different from the number of participants shown in this table for some cohorts. In CHS, 242 out of 243 AAs and 1,687 out of 1,690 EAs had weight data. In CARDIA, all 1,759 EAs and 1,456 out of 1,461 AAs had weight data.

||Descriptive statistics of pack-years was conducted among ever smokers.

**Total n-3 PUFA biomarkers is the sum of ALA, EPA, DPA, and DHA in plasma or red blood cells.

††The time difference refers to the interval between measurement of PFT and n-3 PUFA biomarkers. The difference is positive if the n-3 PUFA biomarkers were measured before the PFTs, while the value is negative if the n-3 PUFA biomarkers were measured after the PFTs. In MESA, 16 EA participants and 18 AA participants had missing data for the time difference variable.

‡‡In CHS, 6 EA participants and 6 AA participants were excluded as residual outliers (studentized residual >4 for EA participants, and >3 for AA participants), based on the main effect model without the n-3 PUFA term. All other cohorts have descriptive statistics on participants before applying the exclusion of residual outliers. In addition, in CHS, 1,684 EA participants and 242 AA participants were used for the descriptive statistics of weight and FVC.

§§Genome-wide interaction analysis was not performed in these cohorts/sub-cohorts due to their small sample sizes (N<500).

||||The genome-wide interaction analysis in FHS was performed using two sub-cohorts combined, with adjustment of family relatedness.

***CARDIA was used as a replication cohort to test novel associations from the genome-wide interaction analyses. The n-3 PUFAs-PFT association analysis did not exclude participants according to their availability of genetic data. Therefore, the sample size was smaller for the genetic analysis.

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Table 2. Cohort-Specific Results for the Association of *DPP10* rs11693320-A with FVC, with and without DHA Interaction Included in the Model[*]

Cohort and ancestry (sample size)	A allele frequency	Model without interaction with DHA (total N = 13,649)[†]		Model with interaction with DHA (total N = 13,649)[‡]				
		β (SE)	P	β_{SNP} (SE)	P_{SNP}	$\beta_{SNP \times DHA}$ interaction (SE)	$P_{SNP \times DHA}$ interaction	P_{2df}
Discovery Cohorts:								
ARIC EA (n = 3,143)	0.80	-65.9 (18.0)	2.4×10^{-4}	-145.6 (60.0)	0.015	28.3 (20.4)	0.17	4.4×10^{-4}
CHS EA (n = 1,684)	0.80	-72.6 (26.4)	0.0060	-15.0 (90.6)	0.87	-19.8 (29.1)	0.50	0.011
FHS EA (n = 5,198)	0.82	-8.6 (15.2)	0.57	-147.6 (56.9)	0.0095	34.7 (11.8)	0.0032	0.011
MESA EA (n = 1,137)	0.81	-15.8 (29.6)	0.30	-156.1 (84.9)	0.066	38.7 (22.2)	0.081	0.15
MESA AA (n = 797)	0.79	-16.0 (35.1)	0.20	-186.4 (116.6)	0.11	39.7 (25.1)	0.11	0.27
Discovery cohort meta-analysis (EA only)		-36.0 (10.0)	2.7×10^{-4}	-155.8 (28.7)	5.8×10^{-8}	34.0 (7.6)	7.4×10^{-6}	1.5×10^{-7}
Discovery cohort meta-analysis (EA and AA)		-34.9 (9.6)	2.9×10^{-4}	-157.1 (27.7)	**1.4×10^{-8}**	34.3 (7.2)	1.7×10^{-6}	**4.5×10^{-8}**
Replication Cohort:								
CARDIA EA (n = 1,141)	0.81	-49.6 (63.2)	0.43	-115.5 (160.1)	0.47	36.6 (47.3)	0.44	0.76
CARDIA AA (n = 546)	0.77	-32.4 (50.5)	0.52	-320.7 (153.1)	0.036	107.3 (43.1)	0.013	0.061
Replication cohort meta-analysis		-39.1 (39.4)	0.32	-222.6 (110.7)	**0.044**	75.2 (31.9)	**0.018**	**0.045**
Overall meta-analysis		-35.1 (9.3)	1.7×10^{-4}	-161.0 (26.9)	**2.1×10^{-9}**	36.2 (7.0)	2.1×10^{-7}	**9.4×10^{-9}**

Abbreviations: AA = African ancestry; ARIC = Atherosclerosis Risk in Communities; CARDIA = Coronary Artery Risk Development in Young Adults; CHS = Cardiovascular Health Study; DHA = Docosahexaenoic acid; EA = European ancestry; FHS =

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Framingham Heart Study; FVC = Forced vital capacity; MESA = Multi-Ethnic Study of Atherosclerosis; SE = Standard error; SNP = Single nucleotide polymorphism.

*Genome-wide significant ($P<5\times10^{-8}$) results are shown in bold. The imputation quality of rs11693320 ranged from 0.72–0.85 across discovery cohorts.

†Model included SNP/indel additive dosage as the predictor and age, age^2, sex, standing height, standing $height^2$, weight, study site (if applicable), current/former smoking (dummy variables, never smokers as the reference group), pack-years, and principal components (PCs) as covariates.

‡Model included DHA as the exposure, SNP/indel additive dosage and SNP/indel interaction term with DHA as predictors, and age, age^2, sex, standing height, standing $height^2$, weight, study site (if applicable), current/former smoking (dummy variables, never smokers as the reference group), pack-years, and PCs as covariates.

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Figure Legends

Figure 1. Forest Plots of the Meta-Analysis of Omega-3 Fatty Acid Biomarkers on FEV$_1$ and FVC. Associations are presented for (A) DHA-FEV$_1$, (B) DPA-FEV$_1$, (C) DHA-FVC, and (D) DPA-FVC. β (unit: mL) denotes the coefficient from the fixed-effects meta-analysis for each omega-3 fatty acid biomarker (DHA or DPA) on the pulmonary function outcome per 1% (of total fatty acids) increment, with its 95% confidence interval. The linear model in each cohort was adjusted for smoking status (never/former/current smokers), pack-years, sex, age, age^2, height, height^2, weight (FVC outcome only), and study center (if applicable). The vertical line in the center indicates no association of the omega-3 fatty acid biomarker with the pulmonary function outcome; β value to the right of the line indicates a positive effect, while β value to the left of the line denotes a negative or inverse effect. The size of black square for each cohort represents the variance of the β coefficient, so that cohorts with smaller variances have larger black squares. Cohorts listed in the forest plots are in alphabetical order, with sample size of each cohort shown in parenthesis. [*]FHS has omega-3 fatty acid biomarkers measured in red blood cells, rather than plasma. Abbreviations: AA = African ancestry; AGES = Age, Gene, Environment, Susceptibility Study—Reykjavik, Iceland; ARIC = Atherosclerosis Risk in Communities; CARDIA = Coronary Artery Risk Development in Young Adults; CHS = Cardiovascular Health Study; CI= Confidence interval; DHA = Docosahexaenoic acid; DPA = Docosapentaenoic acid; EA = European ancestry; FEV$_1$ = 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; MESA = Multi-Ethnic Study of Atherosclerosis; RS = Rotterdam (Netherlands) Study.

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Figure 2. Meta-Analysis of the Association of DHA Biomarker–FEV$_1$ Outcome, by Smoking Status. Smoking status categories were never smoker, former smoker, and current smoker. The y-axis shows the coefficient β (unit: mL), which denotes that a 1% (of total fatty acids) higher DHA level was associated with a β mL higher FEV$_1$, in participants stratified by smoking status. The error bar represents ± 1 standard error. A total of 16,106 participants was used for the FEV$_1$ outcome.

Abbreviations: DHA = Docosahexaenoic acid; FEV$_1$ = Forced expiratory volume in the first second.

Figure 3. Novel *DPP10* Locus Identified at Genome-Wide Significance (P$_{2df}$ < 5×10^{-8}) for FVC, Accounting for SNP/indel × DHA Interaction. SNP/indel associations are shown from the cross-ancestry joint 2df meta-analysis across *DPP10* and its 100kb flanking region (NCBI build 37 positions presented), using the LocusZoom tool. r^2 values between the top SNP rs11693320 and all other SNPs are shown in reference to the 1000 Genomes European (panel A) or African ancestry (panel B). Indels with missing r^2 values are indicated in grey.

Figure 4. GeneMANIA Network Built Around *DPP10*. 20 genes are included in this network. Network genes with a red star are the ones that were co-expressed with *DPP10* in GTEx v7 lung tissue (N = 383), after adjustment of sex, age and three genotyping principal components. The associations (coefficient estimate, standard error, and p-value) with *DPP10* expression in GTEx lung tissue are shown in the table portion of the figure (all P < 0.05).

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AGES_EA (N = 424)		13.5 [-16.5, 43.5]
ARIC_EA (N = 3244)		34.2 [15.2, 53.1]
CARDIA_AA (N = 1460)		38.9 [14.4, 63.5]
CARDIA_EA (N = 1754)		13.4 [-5.6, 32.4]
CHS_AA (N = 243)		-29.8 [-77.5, 17.8]
CHS_EA (N = 1690)		12.7 [-10.7, 36.1]
FHS_Gen3_EA* (N = 3047)		11.7 [-1.0, 24.5]
FHS_Offspring_EA* (N = 2169)		20.8 [6.6, 35.0]
MESA_AA (N = 797)		-9.5 [-32.4, 13.5]
MESA_EA (N = 1137)		-2.5 [-23.7, 18.8]
RS_EA (N = 141)		-23.3 [-121.5, 74.9]
Summarized Effect		14.3 [8.1, 20.5]

-160.0   -80.0   -20.0   40.0

Figure 1a. Forest Plots of the Meta-Analysis of Omega-3 Fatty Acid Biomarkers on FEV_1 and FVC. Associations are presented for (A) DHA-FEV_1, (B) DPA-FEV_1, (C) DHA-FVC, and (D) DPA-FVC. β (unit: mL) denotes the coefficient from the fixed-effects meta-analysis for each omega-3 fatty acid biomarker (DHA or DPA) on the pulmonary function outcome per 1% (of total fatty acids) increment, with its 95% confidence interval. The linear model in each cohort was adjusted for smoking status (never/former/current smokers), pack-years, sex, age, age^2, height, $height^2$, weight (FVC outcome only), and study center (if applicable). The vertical line in the center indicates no association of the omega-3 fatty acid biomarker with the pulmonary function outcome; β value to the right of the line indicates a positive effect, while β value to the left of the line denotes a negative or inverse effect. The size of black square for each cohort represents the variance of the β coefficient, so that cohorts with smaller variances have larger black squares. Cohorts listed in the forest plots are in alphabetical order, with sample size of each cohort shown in parenthesis. *FHS has omega-3 fatty acid biomarkers measured in red blood cells, rather than plasma. Abbreviations: AA = African ancestry; AGES = Age, Gene, Environment, Susceptibility Study—Reykjavik, Iceland; ARIC = Atherosclerosis Risk in Communities; CARDIA = Coronary Artery Risk Development in Young Adults; CHS = Cardiovascular Health Study; CI= Confidence interval; DHA = Docosahexaenoic acid; DPA = Docosapentaenoic acid; EA = European ancestry; FEV_1 = 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; MESA = Multi-Ethnic Study of Atherosclerosis; RS = Rotterdam (Netherlands) Study.

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Figure 1b. Forest Plots of the Meta-Analysis of Omega-3 Fatty Acid Biomarkers on FEV_1 and FVC. Associations are presented for (A) DHA-FEV_1, (B) DPA-FEV_1, (C) DHA-FVC, and (D) DPA-FVC. β (unit: mL) denotes the coefficient from the fixed-effects meta-analysis for each omega-3 fatty acid biomarker (DHA or DPA) on the pulmonary function outcome per 1% (of total fatty acids) increment, with its 95% confidence interval. The linear model in each cohort was adjusted for smoking status (never/former/current smokers), pack-years, sex, age, age^2, height, $height^2$, weight (FVC outcome only), and study center (if applicable). The vertical line in the center indicates no association of the omega-3 fatty acid biomarker with the pulmonary function outcome; β value to the right of the line indicates a positive effect, while β value to the left of the line denotes a negative or inverse effect. The size of black square for each cohort represents the variance of the β coefficient, so that cohorts with smaller variances have larger black squares. Cohorts listed in the forest plots are in alphabetical order, with sample size of each cohort shown in parenthesis. *FHS has omega-3 fatty acid biomarkers measured in red blood cells, rather than plasma. Abbreviations: AA = African ancestry; AGES = Age, Gene, Environment, Susceptibility Study—Reykjavik, Iceland; ARIC = Atherosclerosis Risk in Communities; CARDIA = Coronary Artery Risk Development in Young Adults; CHS = Cardiovascular Health Study; CI= Confidence interval; DHA = Docosahexaenoic acid; DPA = Docosapentaenoic acid; EA = European ancestry; FEV_1 = 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; MESA = Multi-Ethnic Study of Atherosclerosis; RS = Rotterdam (Netherlands) Study.

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AGES_EA (N = 424)	13.3 [-21.0, 47.6]
ARIC_EA (N = 3252)	22.8 [1.4, 44.2]
CARDIA_EA (N = 1758)	11.9 [-11.2, 34.9]
CARDIA_AA (N = 1454)	20.4 [-7.5, 48.3]
CHS_EA (N = 1687)	13.1 [-15.0, 41.2]
CHS_AA (N = 242)	-18.7 [-79.8, 42.5]
RS_EA (N = 140)	-46.3 [-155.9, 63.3]
MESA_EA (N = 1140)	-8.8 [-33.8, 16.1]
FHS_Offspring_EA* (N = 2167)	19.1 [2.7, 35.6]
FHS_Gen3_EA* (N = 3050)	0.8 [-14.0, 15.6]
MESA_AA (N = 797)	-13.0 [-40.3, 14.4]
Summarized Effect	8.4 [1.2, 15.7]

-160.0   -80.0   -20.0   40.0

Figure 1c. Forest Plots of the Meta-Analysis of Omega-3 Fatty Acid Biomarkers on FEV_1 and FVC. Associations are presented for (A) DHA-FEV_1, (B) DPA-FEV_1, (C) DHA-FVC, and (D) DPA-FVC. β (unit: mL) denotes the coefficient from the fixed-effects meta-analysis for each omega-3 fatty acid biomarker (DHA or DPA) on the pulmonary function outcome per 1% (of total fatty acids) increment, with its 95% confidence interval. The linear model in each cohort was adjusted for smoking status (never/former/current smokers), pack-years, sex, age, age^2, height, $height^2$, weight (FVC outcome only), and study center (if applicable). The vertical line in the center indicates no association of the omega-3 fatty acid biomarker with the pulmonary function outcome; β value to the right of the line indicates a positive effect, while β value to the left of the line denotes a negative or inverse effect. The size of black square for each cohort represents the variance of the β coefficient, so that cohorts with smaller variances have larger black squares. Cohorts listed in the forest plots are in alphabetical order, with sample size of each cohort shown in parenthesis. *FHS has omega-3 fatty acid biomarkers measured in red blood cells, rather than plasma. Abbreviations: AA = African ancestry; AGES = Age, Gene, Environment, Susceptibility Study—Reykjavik, Iceland; ARIC = Atherosclerosis Risk in Communities; CARDIA = Coronary Artery Risk Development in Young Adults; CHS = Cardiovascular Health Study; CI= Confidence interval; DHA = Docosahexaenoic acid; DPA = Docosapentaenoic acid; EA = European ancestry; FEV_1 = 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; MESA = Multi-Ethnic Study of Atherosclerosis; RS = Rotterdam (Netherlands) Study.
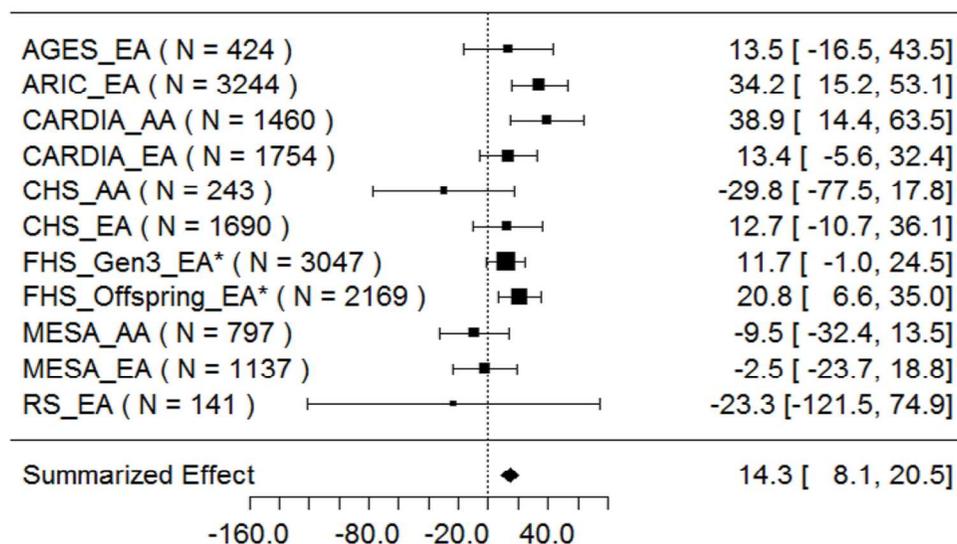
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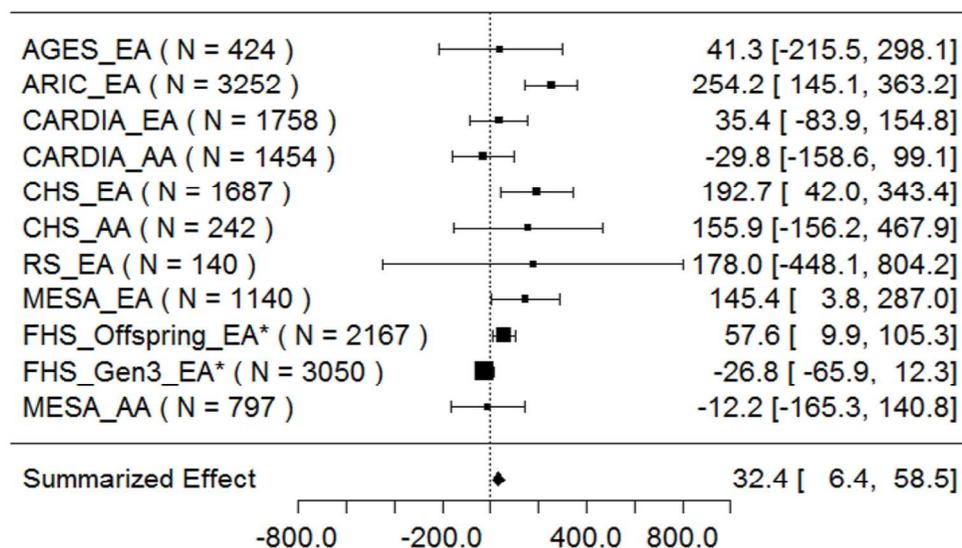
Figure 1d. Forest Plots of the Meta-Analysis of Omega-3 Fatty Acid Biomarkers on FEV_1 and FVC. Associations are presented for (A) DHA-FEV_1, (B) DPA-FEV_1, (C) DHA-FVC, and (D) DPA-FVC. β (unit: mL) denotes the coefficient from the fixed-effects meta-analysis for each omega-3 fatty acid biomarker (DHA or DPA) on the pulmonary function outcome per 1% (of total fatty acids) increment, with its 95% confidence interval. The linear model in each cohort was adjusted for smoking status (never/former/current smokers), pack-years, sex, age, age^2, height, $height^2$, weight (FVC outcome only), and study center (if applicable). The vertical line in the center indicates no association of the omega-3 fatty acid biomarker with the pulmonary function outcome; β value to the right of the line indicates a positive effect, while β value to the left of the line denotes a negative or inverse effect. The size of black square for each cohort represents the variance of the β coefficient, so that cohorts with smaller variances have larger black squares. Cohorts listed in the forest plots are in alphabetical order, with sample size of each cohort shown in parenthesis. *FHS has omega-3 fatty acid biomarkers measured in red blood cells, rather than plasma. Abbreviations: AA = African ancestry; AGES = Age, Gene, Environment, Susceptibility Study—Reykjavik, Iceland; ARIC = Atherosclerosis Risk in Communities; CARDIA = Coronary Artery Risk Development in Young Adults; CHS = Cardiovascular Health Study; CI= Confidence interval; DHA = Docosahexaenoic acid; DPA = Docosapentaenoic acid; EA = European ancestry; FEV_1 = 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; MESA = Multi-Ethnic Study of Atherosclerosis; RS = Rotterdam (Netherlands) Study.

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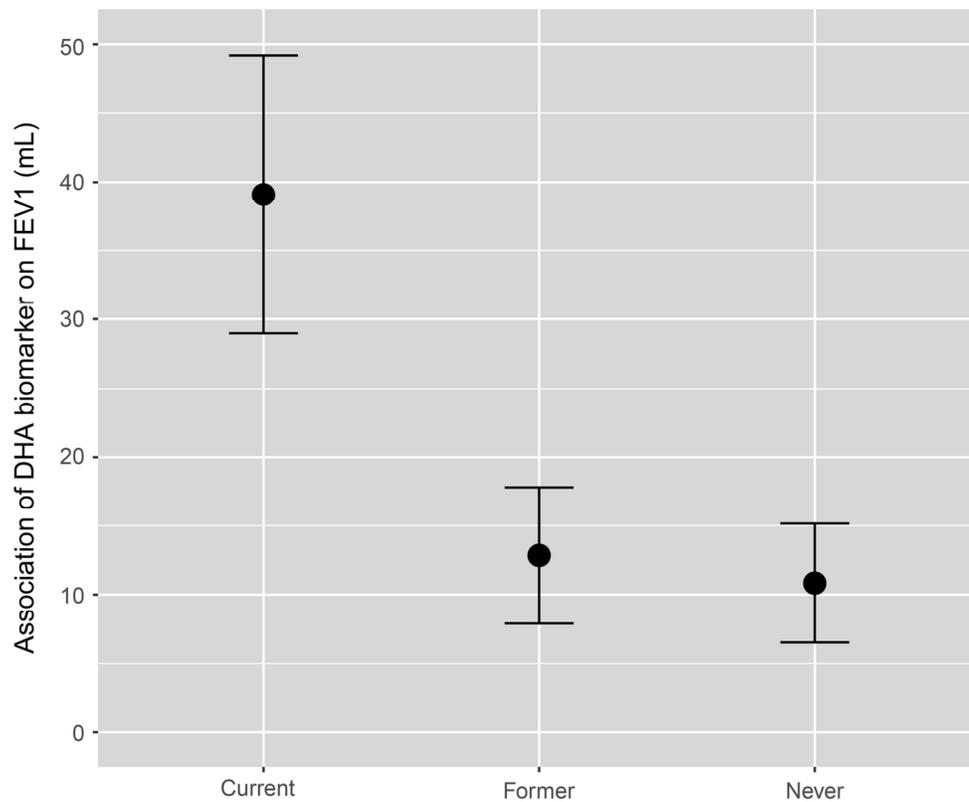
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Figure 2. Meta-Analysis of the Association of DHA Biomarker–FEV_1 Outcome, by Smoking Status. Smoking status categories were never smoker, former smoker, and current smoker. The y-axis shows the coefficient β (unit: mL), which denotes that a 1% (of total fatty acids) higher DHA level was associated with a β mL higher FEV_1, in participants stratified by smoking status. The error bar represents ± 1 standard error. A total of 16,106 participants was used for the FEV_1 outcome.
Abbreviations: DHA = Docosahexaenoic acid; FEV_1 = Forced expiratory volume in the first second.

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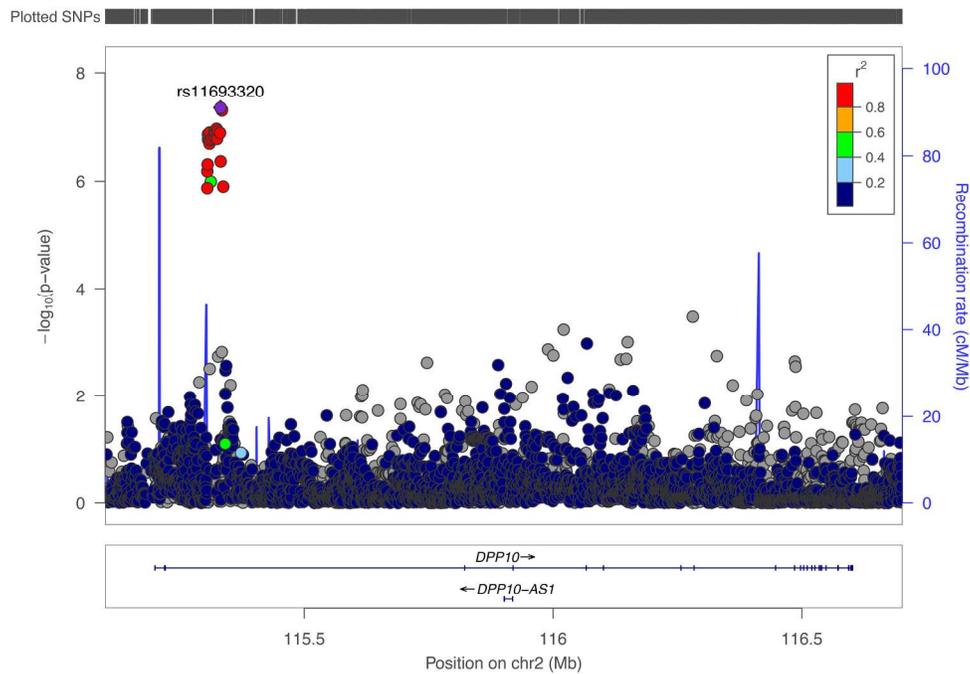
Figure 3a. Novel *DPP10* Locus Identified at Genome-Wide Significance ($P_{2df} < 5 \times 10^{-8}$) for FVC, Accounting for SNP/indel × DHA Interaction. SNP/indel associations are shown from the cross-ancestry joint 2_{df} meta-analysis across *DPP10* and its 100kb flanking region (NCBI build 37 positions presented), using the LocusZoom tool. r^2 values between the top SNP rs11693320 and all other SNPs are shown in reference to the 1000 Genomes European (panel A) or African ancestry (panel B). Indels with missing r^2 values are indicated in grey.

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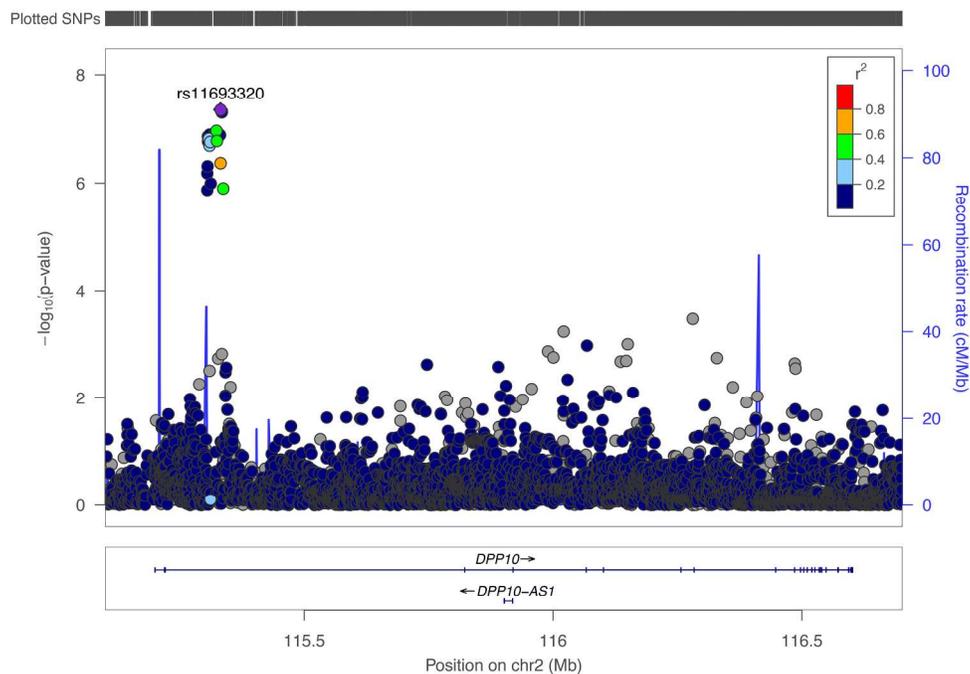
Figure 3b. Novel *DPP10* Locus Identified at Genome-Wide Significance ($P_{2df} < 5\times10^{-8}$) for FVC, Accounting for SNP/indel × DHA Interaction. SNP/indel associations are shown from the cross-ancestry joint 2_{df} meta-analysis across *DPP10* and its 100kb flanking region (NCBI build 37 positions presented), using the LocusZoom tool. r^2 values between the top SNP rs11693320 and all other SNPs are shown in reference to the 1000 Genomes European (panel A) or African ancestry (panel B). Indels with missing r^2 values are indicated in grey.

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Networks legend
- Co-expression
- Co-localization
- Genetic Interactions
- Pathway
- Physical interactions
- Predicted
- Shared protein domains

Gene Symbol	Coefficient Estimate	Standard Error	P-value
DP P4	0.25992	0.04937	2.4×10^{-7}
FMN2	0.15635	0.0504	0.0021
FAB P4	0.139496	0.050099	0.0056
ADAM20	-0.11103	0.05034	0.028
VATIL	0.10216	0.0509	0.046

Figure 4. GeneMANIA Network Built Around *DPP10*. 20 genes are included in this network. Network genes with a red star are the ones that were co-expressed with *DPP10* in GTEx v7 lung tissue (N = 383), after adjustment of sex, age and three genotyping principal components. The associations (coefficient estimate, standard error, and p-value) with *DPP10* expression in GTEx lung tissue are shown in the table portion of the figure (all P < 0.05).

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Online Data Supplement

Omega-3 Fatty Acids and Genome-wide Interaction Analyses Reveal *DPP10*-Pulmonary

Function Association

Supplemental Methods

Cohorts and Participants

Seven cohorts in the Cohorts for Heart and Aging Research in Genomic Epidemiology
(CHARGE) Consortium were used for the meta-analysis of omega-3 poly-unsaturated fatty acid
(n-3 PUFA) biomarkers on pulmonary function, with a total sample size of 16,134 participants.
Among these cohorts, the Framingham Heart Study (FHS) is sub-divided into the Offspring
cohort and the Generation 3 cohort (Gen3). One cohort [Multi-Ethnic Study of Atherosclerosis
(MESA)] includes Hispanic and Chinese participants, but these were not included in this meta-
analysis study given the limited sample size.

Our genome-wide interaction analyses focused on the five largest cohorts (N>500):
ARIC EAs, CHS EAs, FHS EAs, and MESA EAs and AAs for discovery, and CARDIA EAs
and AAs for replication. Besides having limited statistical power, small sample sizes can produce
inflated type-I error, especially when analyzing interactions (1, 2). We found genomic control λ
(λ_{gc}) values ranging from 1.14 to 1.33 for the smallest cohorts; λ_{gc}=1 is optimal, whereas λ_{gc}>1.1
is viewed as problematic in the conduct of genome-wide meta-analysis (3). All cohorts with
N>500 had λ_{gc} values ranging from 0.98 to 1.07. Other genome-wide interaction studies
conducted in the CHARGE consortium had similar minimum cohort-specific sample sizes (4-7).

An analysis pipeline was developed and distributed to each cohort, in which we

harmonized the definitions and units of outcomes, exposures, and other covariates, as well as the statistical models. The exclusion criteria for the analyses of n-3 PUFA biomarkers (**Table E1**) included missing data on pulmonary function, unacceptable pulmonary function data that failed to meet the criteria of American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (**Table E4** for more details about the ATS/ERS criteria used in each cohort), and missing data on n-3 PUFAs and/or other covariates.

Genotyping, quality control, and imputation

Participants were excluded from the genome-wide interaction analyses if they had poor call rate, unusually high heterozygosity, outlying ancestry, and/or relatedness (for population-based studies only) (see details in **Table E2**). Relatedness was not used as an exclusion criterion for FHS; instead, relatedness was taken into account in statistical analyses of this family-based study.

Different genotyping platforms were used across the cohorts. Genotyped single nucleotide polymorphisms (SNPs) were excluded if they had poor call rate, Hardy Weinberg disequilibrium, high duplicate discordance rates, and/or monomorphism (**Table E3**). Imputation was performed using 1000 Genomes reference panels (8) to harmonize SNPs and insertions/deletions (indels) for the meta-analysis (**Table E3**). Cohort-specific genomic data are available on the database of Genotypes and Phenotypes (dbGaP) via accession numbers: ARIC (phs000280), CARDIA (phs000285), CHS (phs000287), FHS (phs000007), and MESA (phs000209).

Pulmonary Function Test (PFT) Outcomes

Spirometry testing was planned for all the participants who remained in the cohorts at the time of measurement (**Table E4** for measurement details in each cohort), except MESA and

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AGES (Age, Gene, Environment, Susceptibility Study—Reykjavik, Iceland), in which

pulmonary function was measured in a random subset (~54% of the MESA population and ~78%

of the AGES population, respectively) (**Table E1**). Cohorts adhered to strict quality control and

American Thoracic Society/European Respiratory Society standardization guidelines once

released. Forced expiratory volume in the first second (FEV_1) and its ratio with forced vital

capacity (FVC) are commonly used parameters to assess airway obstruction, whereas FVC is an

indicator of restrictive lung disorders; across the PFT outcomes, lower values indicate worse

pulmonary function. Pre-bronchodilator pulmonary function data was used, and results would

likely have remained similar if post-bronchodilator data was used, given the expected small

percentage of participants with evidence of asthma (9).

N-3 PUFA Biomarkers

Measurement of n-3 PUFA biomarkers was planned for either all the participants with

blood samples available, or a random set of participants (**Table E1**). All cohorts have PFTs and

n-3 PUFA biomarkers measured concurrently or within 1 year on average, with the exception of

MESA and RS (Rotterdam Study), in which the PFTs were performed ~5 years after the n-3

PUFA biomarkers were measured (see **Table E5** for details of measurement time in each

cohort). The representativeness of single n-3 PUFA measurement with long-term n-3 PUFA

status is fairly strong, with correlations ranging from 0.5 to 0.8 for EPA, DPA, and DHA

between measurements separated by 6 years in a subset of CHS participants (10) and modest

correlations over a 15-year period (ranged from 0.2–0.5 for ALA, EPA, DPA, and DHA) (11).

Therefore, a single measurement of the n-3 PUFA biomarker and a corresponding PFT

measurement within 5 years is not likely to lead to severe bias in the estimated cross-sectional

association of n-3 PUFA biomarkers with pulmonary function. In addition, the n-3 PUFAs have

been reported to be stable for about 4 years in red blood cells (12), and over 10 years in plasma, if stored at -80℃ (13).

Statistical Analysis in Individual Cohorts

Using linear regression models, covariates measured concurrently with PFTs—smoking status (indicator variables for current and former smoking, with never smoking as the reference), pack-years (defined as number of packs of cigarettes smoked per day, multiplied by number of years the participant has smoked), sex, age (unit: year), age^2, standing height (unit: meter), standing $height^2$, weight (unit: kilogram, for FVC outcome only), and study center (if applicable for studies with more than one site)—were adjusted to reduce potential confounding. Age^2 and $height^2$ were included to more fully adjust for the non-linear relationship of age and height to PFTs (14), as done in prior GWAS (9, 15, 16). CHS used covariates measured concurrently with n-3 PUFA biomarkers, and they were within 1 year of the PFT measures (**Table E5**). The FHS models added a random effect to account for familial relatedness. Weight was included in the FVC analyses only because it could affect the expiratory reserve volume included in FVC, which is not relevant for FEV_1. In preliminary models without the n-3 PUFA predictor term included, participants who had studentized residuals greater than ±3 (or ±4), depending on each cohort, were excluded from further analyses. The number of participants excluded could vary across the three PFT outcomes (FEV_1, FVC, and FEV_1/FVC) (**Table E1**). After exclusion of outliers, ancestry-specific association testing of each n-3 PUFA with each PFT measure was conducted. Interactions of select n-3 PUFAs with smoking status and with sex on PFTs were also tested.

For the genome-wide testing of SNP/indel (henceforth, collectively referred to as SNP) and SNP × n-3 PUFA biomarker interaction, each cohort ran four genome-wide linear regression models that included FEV_1 or FVC as the outcome, DPA or DHA as the n-3 PUFA exposure,

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and SNP additive dosage and SNP × n-3 PUFA (DPA or DHA) interaction term as the predictors (linear regression model: FEV_1 or FVC ~ DHA [or DPA] + SNP + DHA [or DPA] × SNP + other covariates). The covariates are the same as the ones included for the associations of n-3 PUFA biomarkers on PFTs, with ancestral principal components (PCs) added to minimize confounding by population stratification. Models were run separately by cohort and ancestry using ProbAbel (17), R (18) or SUGEN (19) (**Table E3**). Genomic control (gc) was applied to results by correcting the p-values via a genomic inflation factor (λ_{gc}). λ_{gc} was defined as the ratio of observed median chi-square statistics with 2 degree-of-freedom (2df) over the expected median, to quantify the extent of inflation, which could lead to false positive findings.

Meta-Analysis of the Associations of N-3 PUFAs and Interactions with Smoking on PFTs

Both ancestry-specific and cross-ancestry meta-analyses were performed. The interaction term of the n-3 PUFA (ALA, EPA, DPA, DHA) and smoking status (current smokers and former smokers, with never smokers as the reference) was meta-analyzed. If the interaction term was significant, additional meta-analysis was conducted stratified by smoking status. The cohort-specific n-3 PUFA-PFT associations by smoking status were calculated from the requested coefficients, standard errors, and covariance, with equations shown below.

$$\beta_{\text{n-3 PUFA in current smokers}} = \beta_{\text{n-3 PUFA in never smokers/reference group}} + \beta_{\text{interaction of n-3 PUFA and current smokers}} \quad (1)$$

$$Var_{\text{n-3 PUFA in current smokers}} = Var_{\text{n-3 PUFA in never smokers}} [a] + Var_{\text{interaction of n-3 PUFA and current smokers}} [b]$$

$$+ 2 \times Cov([a],[b]) \quad (2)$$

Fixed-effects meta-analysis was used to evaluate the magnitude and significance of the association of each n-3 PUFA biomarker with each PFT measure, while random-effects meta-analysis was used to assess the between-study heterogeneity. The metafor package (version 1.9-

9) in R (version 3.3.1, R Foundation for Statistical Computing, Vienna, Austria) was used for the meta-analyses and follow-up meta-regression analyses of the n-3 PUFA-PFT associations, and the interaction meta-analyses of n-3 PUFA with smoking on PFT measures.

Joint 2df Meta-Analysis to Test Genome-Wide Interactions with N-3 PUFAs

Joint 2df testing is constrained on a joint null hypothesis for the variant main effect and interaction; the regression framework means that it can accommodate other covariates and is amenable to various coding schemes for predictors and outcomes. Joint 2df testing has been shown repeatedly in theoretical (1, 20-22) and empirical (4, 23, 24) studies to offer more statistical power over a range of variant main and interactive effects, as compared to 1df tests of variant main or interactive effects only. In this study, ancestry-specific coefficients of the SNP additive dosage (β_{SNP}) and the SNP × n-3 PUFA interaction term ($\beta_{interaction}$) in each cohort were combined via joint 2df meta-analysis using METAL (25), with genomic control applied for variants with minor allele frequency (MAF) > 5% and imputation quality > 0.3. Meta-analysis results are presented for SNP variants tested in two or more cohorts.

Bioinformatics Analysis

HaploReg v4.1 (26) and Roadmap Epigenomics data [chromHMM (for chromatin state discovery and characterization)] (27) were used to functionally characterize the novel locus and any variants in high linkage disequilibrium (LD) ($r^2 \geq 0.8$ in 1000 Genomes Phase 1 EUR reference panel), focusing on predicted functional elements in lung tissue. The predicted fetal lung chromatin state based on Roadmap Epigenomics chromatin immunoprecipitation sequencing data (27) was viewed in the UCSC Genome Browser using the GRCh37/hg19 human assembly. Presence of certain chromatin marks could indicate the presence of an enhancer element. If a variant of interest is located nearby a region with predicted enhancer activity, it may

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be more likely to influence the expression of nearby (or even distant) genes. The Genotype-Tissue Expression Project (GTEx, version 7) *cis*-expression quantitative trait locus (*cis*-eQTL) results were used to look up whether the novel intronic variant is an eQTL for its host gene in lung tissue (28). GeneMANIA, a gene function prediction tool, was used to construct a network of genes biologically related to the gene of interest (29). R v3.2.4 was used to run linear regression models to test for association between network genes identified from GeneMANIA and the gene of interest in lung tissue (linear regression model: normalized expression of gene of interest in GTEx ~ normalized expression of GeneMANIA network gene in GTEx + sex + age + genotyping principal components), using GTEx v7 RNA-Seq data (fully processed, filtered and normalized expression data, as previously described) (28). Nominal p-value of 0.05 was used as a significance threshold for co-expressions of genes in lung tissues.

Supplemental Results

N-3 PUFA Distributions

Of the n-3 PUFAs, DHA had the highest level (average of 3.7% of total FAs); ALA had the lowest level (average of 0.2% of total FAs; **Table E6**). ALA, EPA, and DHA levels were similar in plasma phospholipids and red blood cells. DPA measured in red blood cells was nearly three times more concentrated than in plasma (~2.6% vs ~0.9%, **Table E6**). Whether the differences between red blood cell and plasma measurements reflect true differences between cohorts or differences that derive mainly from compartment of measurement cannot be fully addressed by these data. Average n-3 PUFAs ranged from 4.4% of total FAs to 10.6% of total FAs across cohorts (**Figure E1**).

Meta-Analysis of N-3 PUFA Associations with PFTs

Cross-ancestry meta-analyses revealed positive associations of DHA and DPA with FEV_1 and FVC at P<0.05. These associations were largely driven by EA participants, which comprise most of the total sample size (**Table E8** for ancestry-specific results). To explore the linearity of the n-3 PUFA-PFT associations across cohorts, a meta-regression analysis tested whether the β coefficients varied by mean of each n-3 PUFA; the cohort-specific β and mean n-3 PUFA level had little to no association (results not shown), supporting a linear n-3 PUFA-PFT association across the range of each n-3 PUFA. Also, sensitivity analyses demonstrated that DHA and DPA were robustly associated with FEV_1 and FVC, when limited to cohorts with n-3 PUFAs measured in plasma only (**Figure E2)** or cohorts with n-3 PUFA measurements within one year of PFTs (**Figure E3**).

Targeted Look-up of Established N-3 PUFA and PFT-Related Variants

We used our 2df meta-analysis results to look-up previous GWAS-identified SNPs associated with n-3 PUFA phenotypes (**Table E10**). Using Bonferroni correction for 14 variants ($P<3.6\times10^{-3}$), one previously identified DPA-related SNP, rs174468 (upstream of *FADS3* on chromosome 11), was associated with FEV_1 when considering its interaction with DPA ($P_{2df}=1.8\times10^{-3}$).

Similarly, we used our 2df meta-analysis results to look-up SNPs identified in previous GWAS of PFTs (**Table E11**). Using Bonferroni correction for 199 variants ($P<2.5\times10^{-4}$), ten previously identified FEV_1-related SNPs were associated with FEV_1 in this study when considering interaction with either DHA or DPA. However, signals were primarily driven by main effects, not interactive effects with n-3 PUFAs ($P_{SNP\times\text{n-3 PUFA interaction}}=0.11-1.00$).

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Table E1. Flowchart of Sample Size Dynamics in Each Cohort for the Meta-Analysis of Omega-3 Fatty Acid Biomarker Associations with Pulmonary Function Tests, Stratified by Ancestry[*]

European Ancestry Cohort	CARDIA[§]	CHS[ǁ]	MESA[**]	AGES[††]	ARIC[§§]	FHS[ǁǁǁ]	RS[***]
Original sample size	2,478	4,346	2,501	5,519	11,478	6,158	9,895
Excluded for the following reasons:							
Missing PFT (outcome of interest)	-632	-980	-1,119	-2,672	-47	-354	-2,542
Unacceptable PFT (outcome of interest)	0	-415	0	-16	-9	NA	-2,774
Missing height	0	-43	0	0	0	0	-1
Missing gender	0	0	0	0	0	0	0
Missing age	0	0	0	0	0	0	0
Missing smoking status	-15	-63	-12	-63	-7	-123	-6
Missing pack-years	0	-71	-51	-27	-130	-116	-172
Missing site (if applicable)	0	0	0	0	0	0	0
Missing genetic data[†]	0[†††]	-786	0	-1,056	-1,947	-344	-590
Missing n-3 PUFA biomarkers data (exposure of interest)	-72	-292	-170	-1,261	-6,084	0	-3,669
Missing weight (for the FVC analysis only)	0	-3	0	0	0	0	0
Sample size for the FEV$_1$ analysis[‡]	*1,754*	*1,690*	*1,137*	*424*	*3,244*	*5,216*	*141*
Sample size for the FVC analysis[‡]	*1,758*	*1,687*	*1,140*	*424*	*3,252*	*5,217*	*140*
Sample size for the FEV$_1$/FVC analysis[‡]	*1,753*	*1,690*	*1,134*	*424[‡‡]*	*3,233*	*5,205*	*141*
African Ancestry Cohort	CARDIA[§]	CHS[ǁ]	MESA[**]				
Original sample size	2,637	885	2,575				
Excluded for the following reasons:							
Missing PFT (outcome of interest)	-1,053	-262	-1,646				
Unacceptable PFT (outcome of interest)	0	-122	0				
Missing height	-5	-3	0				
Missing gender	0	0	0				
Missing age	0	0	0				
Missing smoking status	-12	-5	-17				
Missing pack-years	0	-22	-37				
Missing site (if applicable)	0	0	0				
Missing genetic data[†]	0[†††]	-49	0				
Missing n-3 PUFA biomarkers data (exposure of interest)	-106	-173	-65				
Missing weight (for the FVC analysis only)	-5	-1	0				
Sample size for the FEV$_1$ analysis[‡]	*1,460*	*243*	*797*				
Sample size for the FVC analysis[‡]	*1,454*	*242*	*797*				
Sample size for the FEV$_1$/FVC analysis[‡]	*1,440*	*243*	*797*				

Abbreviations: AGES = Age, Gene, Environment, Susceptibility Study – Reykjavik; ARIC = Atherosclerosis Risk in Communities; CARDIA = Coronary Artery Risk Development in Young Adults; CHS = Cardiovascular Health Study; FEV_1 = Forced expiratory volume in the first second; FHS = Framingham Heart Study; FVC = Forced vital capacity; MESA = Multi-Ethnic Study of Atherosclerosis; n-3 PUFA = Omega-3 poly-unsaturated fatty acid; PFT = Pulmonary function test; RS = Rotterdam Study.

[*]The final sample size of each cohort for each outcome variable is shown in the last three rows, stratified by ancestry.

[†]Participants who did not have genetic data were excluded for consistency and comparison with the genome-wide analyses.

[‡]For each outcome, participants whose studentized residual absolute value is greater than 3 (or 4), depending on each cohort, were excluded.

[§]PFTs were measured in year 20, therefore some CARDIA participants might have dropped out at that time point.

[ǁ]In CHS, PFTs were measured in year 6, therefore some participants might have dropped out at that time point. In addition, 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 terms of n-3 PUFA biomarker data, they were measured in all available blood samples in year 5 (N= 3,941).

[**]PFTs were measured in 3,965 participants who were enrolled in the MESA Lung Study (30, 31). The MESA Lung Study enrolled 3,965 participants out of 4,484 selected who were randomly sampled among those who consented to genetic analyses, underwent baseline endothelial function measures, and attended an examination in the MESA-Lung recruitment period in 2004-2006 (99%, 89%, and 91% of the MESA cohort, respectively) (31). In addition, the final sample size for each outcome additionally excluded participants who were related genetically ($N_{European\ Ancestry}$=9, $N_{African\ Ancestry}$=9).

[††]In AGES, only a random set of participants had PFTs (N= 3,000 out of 5,519) (32), and n-3 PUFA biomarkers (N = 1,012 out of 5,519) measured (33). In addition, only 3,219 out of 5,519 participants had genetic data (34).

[‡‡]In AGES, for FEV_1/FVC, two participants had residuals around 4.3 but were not filtered out. We would not expect this to influence the results much given that this was such a small number, and the residual values were close to 4.

[§§]In ARIC, genotyping was planned for the whole cohort (34). N-3 PUFA biomarkers were measured only in the Minneapolis study center, out of the 4 study centers across U.S (N=4,009) (35).

[ǁǁ]The flowchart of sample size in FHS has combined participants in the Offspring cohort and the Generation 3 cohort. FHS only has participants with acceptable PFT measures, therefore the exclusion criteria of unacceptable PFTs are not applicable here. N-3 PUFA biomarkers were measured at Exam 8 of the Offspring cohort, and at Exam 2 of the 3rd Generation cohort. The starting sample size for Exam 8 of the Offspring cohort and Exam 2 of the 3rd Generation cohort was 6,158.

[***]In RS, spirometry was not carried out in the cohort until 2002. At that time point, the total sample size of participants who still visited the research center was 9,895. Plasma n-3 PUFAs were measured for a nested case-control study of depression in the RS-I cohort during Exam 3 and only the participants in the control group were included in this meta-analysis. They were randomly selected from the RS-I cohort among those who had negative results for the depression screening (N = 461) (36).

[†††]In CARDIA, which was used for replication of top findings from the genome-wide interaction analyses, the analysis of omega-3 fatty acid biomarkers with pulmonary function did not exclude participants according to the availability of genetic data.

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Table E2. Genotyping QC for Participants and Genetic Analysis Sample Size in Each Cohort[*]

Study (ancestry)	QC filters for excluding participants	N, genotyped participants passing QC	N, genotyped participants passing QC with PFT, n-3 FA biomarkers and complete covariate data
ARIC (EA)	call rate<95%, sex mismatch, discordances with prior genotyping, >8 SD for any of the first 10 principal components, outlying average identity-by-state estimates, or first-degree relatives	9,338	3,143
CHS (EA)	call rate<95%, non-European ancestry, sex mismatch, or discordance with prior genotyping	3,268	1,684
FHS – Offspring (EA)	call rate<97%, non-European ancestry heterozygosity>5 SD from the mean, or >1000 Mendelian errors	3,753	2,158
FHS – Gen3 (EA)	call rate<97%, non-European ancestry heterozygosity>5 SD from the mean, or >1000 Mendelian errors	3,893	3,040
MESA (EA)	call rate < 95%, unexpected first-degree relatives, or first three PCs of ancestry > 3.5 SD from the mean	2,685	1,137 for FEV_1 and 1,140 for FVC
MESA (AA)	call rate < 95%, unexpected first-degree relatives, or first three PCs of ancestry > 3.5 SD from the mean	2,588	797
CARDIA (EA)	call rate < 98%, non-European ancestry, sex mismatch, sample duplicates, or first- or second-degree relatives	1,663	1,141
CARDIA (AA)	call rate < 98%, low heterozygosity (inbreeding coefficient F < -0.15), sex mismatch, sample duplicates, or first- or second-degree relatives	955	546

Abbreviations: AA = African ancestry; ARIC = Atherosclerosis Risk in Communities; CARDIA = Coronary Artery Risk Development in Young Adults; CHS = Cardiovascular Health Study; EA = European ancestry; FHS (Offspring) = Framingham Heart Study—Offspring Cohort; FHS (Gen3) = Framingham Heart Study—Generation 3 Cohort; MESA = Multi-Ethnic Study of Atherosclerosis; n-3 FA = Omega-3 fatty acid; PFT = Pulmonary function test; QC = Quality control; SD = Standard deviation.

[*]ARIC, CHS, FHS, and MESA were used for discovery, and CARDIA was used for replication.

Table E3. Genotyping, QC, and Analysis Details for Genotyped SNPs*

Study (ancestry)	Genotyping platform	QC filters for excluding genotyped SNPs	N, genotyped autosomal SNPs passing QC	Imputation software	1000 Genomes imputation reference panel, using all available individuals	N, imputed autosomal SNPs used for analysis	Statistical analysis software
ARIC (EA)	Affymetrix 6.0 chip freeze 3	call rate < 95%, HWE P < 10^{-6}, MAF < 0.001, or no chromosomal location	719,415	Michigan Imputation Server, using minimac	phase 3 (version 5)	15,482,662	SUGEN (19)
CHS (EA)	Illumina 370CNV merged with ITMAT-Broad-CARe Illumina iSELECT	call rate < 97%, no heterozygotes, HWE P < 10^{-5}, > 2 duplicate errors or, Mendelian inconsistency (for HapMap CEU trios), or SNPs not found in HapMap	359,592	MaCH to pre-phase, minimac	phase 1 (version 3)	6,375,477 (for FEV$_1$) 6,375,546 (for FVC)	R (18)
FHS - Offspring (EA)[†] FHS – Gen3 (EA)[†]	Affymetrix 500K + 50K Human Gene Focused Panel	call rate < 96.9%, HWE P < 10^{-6}, MAF < 1%, Mendelian errors > 1000, not being on chromosomes 1–22 or X, duplicates	412,053	MACH/minimac (37)	phase 1 (version 3)	6,194,157	R (18)
MESA (EA) MESA (AA)	Affymetrix 6.0	call rate < 95%, heterozygosity > 53%, or monomorphic SNPs	897,981	Minimac3	phase 3 (version 5)	6,779,137 9,020,042	ProbAbel (17)
CARDIA (EA)	Affymetrix 6.0	call rate < 95%, HWE P < 10^{-5}, duplicates,	610,015	BEAGLE (38)	phase 1 (version 3)	NA[‡]	ProbAbel (17)

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		monomorphic SNPs					
CARDIA (AA)	Affymetrix 6.0	call rate < 95%, HWE P < 10^{-5}, duplicates, MAF < 1%	682,448	Minimac (39)	phase 1 (version 3)	NA‡	ProbAbel (17)

Abbreviations: AA = African ancestry; ARIC = Atherosclerosis Risk in Communities; CARDIA = Coronary Artery Risk Development in Young Adults; CHS = Cardiovascular Health Study; EA = European ancestry; FHS (Offspring) = Framingham Heart Study—Offspring Cohort; FHS (Gen3) = Framingham Heart Study—Generation 3 Cohort; HWE = Hardy Weinberg equilibrium; MAF = Minor allele frequency; MESA = Multi-Ethnic Study of Atherosclerosis; QC = Quality control; SNP = Single nucleotide polymorphism.

[*]ARIC, CHS, FHS, and MESA were used for discovery, and CARDIA was used for replication.

[†]To account for family relatedness, FHS used the linear regression models with a robust variance method via generalized estimating equations, in which each extended pedigree is one cluster and an independent working correlation structure is implemented.

[‡]Not applicable (NA) because although genome-wide imputed genotype data are available in CARDIA, this cohort was used for replication testing of the top finding in the current study.

Table E4. Details of Spirometry and Omega-3 Fatty Acid Biomarkers in Each Cohort

Cohort	Cohort description	Spirometry	Omega-3 fatty acids biomarkers
AGES	The Age, Gene/Environment Susceptibility – Reykjavik Study (AGES) came from the Reykjavik study, a cohort initiated in 1967 and included a random sample of 30,795 men and women who were born in 1907-1935 and lived in the greater Reykjavik area of Iceland in 1967, and they were divided into 6 groups (40). The AGES examinations started in 2002 and 11,549 participants in the Reykjavik Study were still alive at that time. Recruitment into the AGES study was randomly selected within the 6 groups of participants. The AGES exams ended in 2006 with a sample size of 5,764 survivors (32, 41).	A Vitalograph Gold Standard Plus (Vitalograph Ltd., Buckingham, UK) was used to carry out spirometry through a disposable mouthpiece on participants who were in a sitting position. The spirometer was routinely calibrated with 1L syringe. The spirometry procedure was detailed by a technician before testing. The pulmonary function testing was deemed successful if there were at least two acceptable maneuvers, defined as no more than 300mL difference between the two attempts for at least 6 seconds in each blow. Pre-bronchodilation spirometry testing was conducted in only the first 2 years (41).	Fasting blood was collected and plasma was stored at -80℃. Fatty acids (FAs) in the phospholipid fraction (PL) were measured, which reflects the short-term dietary intake of FAs (weeks to months) and the pool of FAs available to tissues. The analyses of FAs were conducted at the Fred Hutchinson Cancer Research Center (Seattle, WA). PLs was separated from other lipids using thin layer chromatography (TLC). Fatty acid methyl esters were generated by transesterification and isolated by Agilent 7890 gas chromatograph (GC) with a flame ionization detector and a Supelco-fused silica 100-m capillary column SP-2560. FAs were expressed as a weight percentage %. The coefficients of variation (CV) of pooled quality-control samples for EPA and DHA were 2.05% and 1.44% (33).
ARIC	The Atherosclerosis Risk in Communities (ARIC) Study is a	A Collins Survey II water-sealed spirometer (Warren E. Collins Inc., Braintree, MA) was used	Fasting blood was collected. Plasma was stored at -70℃. One technician analyzed fatty acid

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	population-based cohort of about 16,000 middle-aged men and women recruited from 4 communities in U.S. in 1987-1989. They went through a 3 to 4-hour examination in clinics at baseline. For this study, only participants from the suburban Minneapolis area were included given the n-3 PUFA biomarker measures were only conducted in this population (35, 42).	to carry out spirometry at visits 1 and 2. SensorMedics model 1022 dry rolling seal spirometers (OMI, Houston, TX) were used to carry out spirometry at visit 5. The spirometer was calibrated daily, and a single pulmonary function reading center was used to standardize the spirometry testing across the four study sites in ARIC. The test was deemed successful if there were three acceptable attempts (43).	composition about 2 years later. The cholesterol ester (CE) and PL were extracted with chloroform/methanol, and separated using TLC. The methyl esters of fatty acids in CE and PL were measured separately by a Model 5890 GC (Hewlett-Packard, Avondale, PA). A total of 28 fatty acids were identified using GC. The short-term (usually several weeks) reliability coefficients were 0.31 for EPA in phospholipids and 0.58 for DHA in phospholipids. The long-term (within 3 years) reliability coefficient was 0.51 for EPA in phospholipids. Overall the reliability coefficient for DHA was greater than the one for EPA (42). The concentration was expressed as % of total fatty acids. The correlations between plasma and dietary polyunsaturated fatty acids were 0.25 for PL and 0.31 for CE (44).
CARDIA	The Coronary Artery Risk Development in Young Adults (CARDIA) study is a longitudinal cohort that recruited participants from 4 U.S. metropolitan areas, including Birmingham, AL, Chicago, IL, Minneapolis, MN, and Oakland, CA. CARDIA began in 1985-1986 and comprised 5,115 white and black young adults aged 18-30 yrs (45).	A dry rolling-sealed SensorMedics model 1022 OMI spirometer (Viasys, Yorba Linda, CA) was used at year 20, and the 2005 American Thoracic Society (ATS)/ European Respiratory Society (ERS) criteria was followed (46). The Pulmonary Waveform Generator (MH Custom Design and Manufacturing, Midvale, UT) validated the accuracy of the spirometer. The OMI spirometers performed better than the ATS criteria for accuracy and precision (47).	Fasting plasma samples were collected at Year 20 and EDTA plasma was frozen at -70℃. Lipids were extracted from plasma through chloroform/methanol. CE, PL, triglyceride, and free FAs were separated using TLC. The fatty acid methyl esters were generated from transesterification from the PL fraction and were measured by GC with a flame ionization detector. 28 fatty acids were identified and were expressed as % of total fatty acids (48).
CHS	The Cardiovascular Health Study (CHS) comprised 5,201 men and women aged ≥ 65 yrs who were recruited from 4 U.S. communities, including Forsyth County, NC, Sacramento County, CA, Washington County, MD, and Allegheny County, Pittsburgh, PA, in 1989. An additional 687 African Americans were recruited in 1992 and later on. The participants recruited were a random sample from the eligibility lists of Medicare from the Health Care	A water-sealed spirometer (Collins Survey, Collins Medical, Inc., Braintree, MA) and software from S&M instruments (50) were used to carry out pulmonary function testing at years 2, 6, and 9, with accuracy validated, according to contemporary ATS criteria (51). Due to the timing of omega-3 fatty acid measurements, the spirometry values from year 6 were used for the current analysis.	Fasting blood samples were collected and stored at -80℃. Fatty acids in plasma PL were measured at the Fred Hutchinson Cancer Research Center. A total of 45 fatty acids were identified with the unit of % of total fatty acids. PLs were separated from other lipids via 1-dimensional TLC. The fatty acids in PLs were trans-methylated and separated by 5890 GC (Agilent Technologies, Palo Alto, CA), with a SP-2560 fused-silica 100-m capillary column and a flame ionization detector. CVs of EPA, DPA, and DHA were all <3%. Measurement of plasma fatty acids across

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	Financing Administration (49).		different time points showed that 6-year correlations with baseline EPA, DPA and DHA were 0.55, 0.67, and 0.82, respectively (10).
FHS (Offspring)	Two Framingham Heart Study (FHS) generation cohorts were included in our study, the Offspring cohort and the Third Generation (Gen3) cohort. FHS is a U.S. family-based cohort in Framingham, MA, established in 1948. The Offspring cohort began in 1971 and is comprised of children of the original cohort and spouses of these children (52). Overall, 99.7% participants across all three generations were self-reported Caucasians (53, 54).	Spirometry testing was conducted at each exam, and 1994 ATS criteria was followed (55). In the 7th examination of the Offspring cohort, a 6-L water-filled Collins survey spirometer was used (Warren E. Collins Inc., Braintree, MA), connected to an S&M Instruments software (Doylestown, PA), and the spirometer was calibrated daily (56). Since Exam 8 of the Offspring Cohort, some participants in each cohort underwent post-bronchodilator spirometry testing, besides the regular spirometry testing that all participants performed, so as to differentiate participants with asthma (reversible disease) from those with COPD (fixed disease).	Red blood cells (RBCs) were separated from the whole blood after about a 12-hour fast and was stored at -80℃. Fatty acid composition in RBC was measured using the HS-Omega-3 index® methodology (57). Fatty acid methyl esters were first generated from RBCs and then separated by a CG2010 GC (Shimadzu Corporation, Columbia, MD), with a SP2560 100-m column. The concentration was expressed as % of total identified fatty acids. The inter-assay CV for both EPA and DHA was 4.9%. Omega-3 index (RBC EPA+DHA, expressed as weight % of total fatty acids) was also derived in FHS (58).
FHS (Gen3)	Two Framingham Heart Study (FHS) generation cohorts were included in our study, the Offspring cohort and the Third Generation (Gen3) cohort. Starting in 2002, 4,095 adults were enrolled in the Gen3 cohort given at least one of their parents were in the Offspring cohort. In addition, 103 parents of the Gen3 cohort participants were enrolled even though they were not in the Offspring cohort. Overall, 99.7% participants across all three generations were self-reported Caucasians (53, 54).	Spirometry testing was conducted at each exam, and 1994 ATS criteria was followed (55). In Exam 2 of the Generation 3 cohort, a dry rolling-sealed spirometer, connect to the CPL System (Warren E. Collins Inc., Braintree, MA), was used to measure pulmonary function, and the spirometer was calibrated daily (56).	Same as above.
MESA	The Multi-Ethnic Study of Atherosclerosis (MESA) is a population-based cohort consisting of 6,814 white, black, Hispanic and Asian men and women aged 45-84 yrs who were recruited from 6 sites in U.S., including St Paul, MN, Los Angeles, CA, northern Manhattan, NY, Forsyth County, NC, Chicago, IL, and Baltimore City and County, MD, from July 2000 to August	A dry rolling-sealed spirometer, connected to an automated quality control software (Occupational Marketing, Inc., Houston, TX) was used to carry out pulmonary function testing, in accordance with the 2005 ATS/ERS criteria (46). Each participant was required to have 3 or more acceptable maneuvers. A quality score lower than C, from a 5-point was based on a version of the National Lung Health Education Program, was viewed as low. All results were centrally	Fasting blood samples were stored at -70℃ (62), and fatty acids in the blood samples were analyzed at the Collaborative Studies Clinical Laboratory at Fairview-University Medical Center (Minneapolis, MN, USA). First, plasma PLs were extracted using chloroform/methanol, and then different lipids were separated by TLC (63). The fatty acids in PLs were trans-methylated and measured via a Hewlett Packard 5890 GC, configured for a single capillary Varian CP7420

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	2002 (59, 60). For this study, only whites and blacks were included.	reviewed. (61)	100-m column with a flame ionization detector (64). The concentration was expressed as % of total fatty acids (63).
RS	The Rotterdam Study (RS) is a population-based cohort which sent out invitation to all residents aged ≥ 55 yrs who lived at a Rotterdam suburb in the Netherlands in 1990-1993 for study participation (65). A total of 7,983 men and women were eventually enrolled in the study (~78% of those eligible) (36).	A SpiroPro® portable spirometer (Erich Jaeger GmbH, Hoechberg, Germany) was used to carry out spirometry from 2002 to 2009. The testing was performed by trained technicians, in accordance with ATS/ERS criteria (66). All measures, as collected from pre-bronchodilator testing, were centrally assessed and validated by researchers. (67)	Fasting blood samples were collected. The plasma was stored at -80°C. Fatty acids in the PL fraction were measured. Lipid extraction was conducted based on a standard method (68). First, plasma lipids were extracted using chloroform/methanol. Second, the PL fraction was separated from other lipid fractions using the solid-phase extraction by NH_2 columns. Third, the PL were methylated and fatty acid methyl esters were measured using high-resolution capillary gas-liquid chromatography (Shimadzu GC17A chromatograph; Shimadzu Benelux, 's-Hertogenbosch, NL), equipped with a 50-m fused silica column and a flame ionization detector. The fatty acids were quantified against the recovered amount of fatty acid methyl ester internal standard (19:0). Fatty acids were expressed as both mg/L plasma and % of total fatty acids. A difference between the values in % of total fatty acids also indicates a difference in absolute values (36).

Abbreviations: AGES = Age, Gene, Environment, Susceptibility Study – Reykjavik; ARIC = Atherosclerosis Risk in Communities; ATS = American Thoracic Society; CARDIA = Coronary Artery Risk Development in Young Adults; CE = Cholesterol ester; CHS = Cardiovascular Health Study; CV = Coefficient of variation; DHA = Docosahexaenoic acid; DPA = Docosapentaenoic acid; EPA = Eicosapentaenoic acid; ERS = European Respiratory Society; FA = Fatty acid; FHS (Offspring) = Framingham Heart Study – the Offspring Cohort; FHS (Gen3) = Framingham Heart Study – the Generation 3 Cohort; GC = Gas chromatograph; MESA = Multi-Ethnic Study of Atherosclerosis; PL = Phospholipid; RBC = Red blood cell; RS = Rotterdam Study, TLC = Thin layer chromatography.

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Table E5. Time of Measurement for Primary Study Variables in Each Cohort

Cohort	PFTs Collection Years	n-3 PUFA Biomarkers Collection Years	Smoking Status	Pack-Years	Height	Weight	Age
AGES	2002-2004	Concurrent with PFTs[*]	All the covariates are concurrent with PFTs.				
ARIC	1987-1989 (Baseline)	Concurrent with PFTs	All the covariates are concurrent with PFTs.				
CARDIA	2005-2006 (Year 20)	Concurrent with PFTs	All the covariates are concurrent with PFTs.				
CHS[†]	1993-1994 (Year 6)	1992-1993 (Year 5)	All the covariates are concurrent with n-3 PUFAs.[‡]				
FHS (Offspring)	1998-2001 (Exam 7)[§]/ 2005-2008 (Exam 8)	2005-2008 (Exam 8)	All the covariates are concurrent with PFTs.				
FHS (Gen 3)	2008-2011 (Exam 2)	Concurrent with PFTs	All the covariates are concurrent with PFTs.				
MESA	2004-2006 (Exam 4)	2000-2002 (Exam 1)	All the covariates are concurrent with PFTs.				
RSI	2002-2004 (Exam 4)	1997-1999 (Exam 3)	All the covariates are concurrent with PFTs.				

Abbreviations: AGES = Age, Gene, Environment, Susceptibility Study – Reykjavik; ARIC = Atherosclerosis Risk in Communities; CARDIA = Coronary Artery Risk Development in Young Adults; CHS = Cardiovascular Health Study; FHS (Offspring) = Framingham Heart Study – the Offspring Cohort; FHS (Gen3) = Framingham Heart Study – the Generation 3 Cohort; MESA = Multi-Ethnic Study of Atherosclerosis; n-3 PUFA = Omega-3 poly-unsaturated fatty acid; PFT = Pulmonary function test; RS = Rotterdam Study.

[*]In AGES, the blood samples were drawn at the time concurrent with PFTs (2002-2004). However, the n-3 PUFA biomarkers were measured from blood samples in 2013.

[†]In CHS, covariates from year 5 (concurrent with n-3 PUFA biomarkers) were used, but results were similar using covariates from either year 5 or year 6 (concurrent with PFT).

[‡]In CHS, the initial cohort (European and African ancestry participants) was enrolled in 1989-1990 and an additional cohort (African ancestry participants only) was recruited in 1992 and 1993. For the original cohort, pack-years in year 5 was extrapolated from that at baseline; for the additional cohort, pack-years in year 5 was calculated based on years and amount smoked. In addition, in CHS, height was only measured in year 5, but not in year 6.

[§]For the Offspring cohort, 2,165 participants had their PFT and other covariates measured at exam 8. However, 4 participants with PFT and other covariates measured at exam 7 were included in this study due to their missing data at exam 8.

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Table E6. Participant Characteristics Averaged across Cohorts[*]

Characteristics	Mean (SD) or Percent (%)[ll]	Range of Mean or Percent[**]
No. of Participants	16,134	141 – 3,254
Males, %	45.4	30.9 – 49.6
African ancestry, %	15.5	12.6 – 45.4[††]
Current Smoker, %	14.1	8.0 – 24.1
Former Smoker, %	37.6	13.5 – 57.5
Pack-Years[†]	21 (21)	11 – 30
Age, year	57 (13)	45 – 76
Height, m	1.69 (0.10)	1.64 – 1.72
Weight, kg[‡]	80.0 (18.5)	71.3 – 90.5
FEV_1, mL	2,831 (876)	1,765 – 3,388
FVC, mL	3,786 (1,104)	2,440 – 4,449
FEV_1/FVC (%)	74.7 (8.2)	69.6 – 79.7
ALA (% of total FAs)	0.17 (0.08)	0.14 – 0.23
EPA (% of total FAs)	0.76 (0.65)	0.56 – 2.87
DPA (% of total FAs)		
- Plasma Phospholipids	0.92 (0.20)	0.83 – 1.18
- RBC[‡‡]	2.64 (0.47)	2.55 – 2.76
DHA (% of total FAs)	3.67 (1.41)	2.81 – 6.33
Total n-3 PUFAs (% of total FAs)	6.08 (2.37)	4.41 – 10.60
Time Difference between PFT and n-3 PUFAs, days[§]	266 (580)	0 – 1,769

Abbreviations: AA = African ancestry; AGES = Age, Gene, Environment, Susceptibility Study—Reykjavik, Iceland; ALA = Alpha-linolenic acid; ARIC = Atherosclerosis Risk in Communities; CARDIA = Coronary Artery Risk Development in Young Adults; CHS = Cardiovascular Health Study; DHA = Docosahexaenoic acid; DPA = Docosapentaenoic acid; EA = European ancestry; EPA = Eicosapentaenoic acid; FA = Fatty acid; FEV_1 = 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; MESA = Multi-Ethnic Study of Atherosclerosis; n-3 PUFA = Omega-3 poly-unsaturated fatty acid; PFT = Pulmonary function test; RBC = Red blood cell; RS = Rotterdam (Netherlands) Study; SD = Standard Deviation.

[*]Data are presented as mean (SD) unless otherwise indicated. This table corresponds to the n-3 PUFA-PFT association analyses and thus includes all seven cohorts. The total sample size was 16,134 for the meta-analysis of omega-3 fatty acid biomarkers, in which 13,629 are European ancestry participants, and 2,505 are African ancestry participants. All the cohorts measured n-3 PUFAs in plasma phospholipids, except FHS, which measured n-3 PUFAs in red blood cells.

[†]Descriptive statistics of pack-years among ever smokers.

[‡]Number of participants with weight data was slightly different from the number of participants shown in this table for some cohorts. In CHS, 242 out of 243 AAs and 1,687 out of 1,690 EAs had weight data. In CARDIA, all 1,759 EAs and 1,456 out of 1,461 AAs had weight data.

[§]The time difference refers to the interval between measurement of PFT and n-3 PUFAs. If the difference is positive, n-3 PUFAs were measured before PFTs; if it is negative, n-3 PUFAs were measured after PFTs.

[ll]The mean (SD) or percentage was weighted by the sample size of each cohort.

[**]Range is presented for each ancestry-specific cohort, therefore 11 cohorts/sub-cohorts are included here (AGES-EA, ARIC-EA, CARDIA-EA, CARDIA-AA, CHS-EA, CHS-AA, MESA-EA, MESA-AA, RS-EA, FHS-Offspring-EA, and FHS-Gen3-EA).

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[††]Only CARDIA, CHS, and MESA contributed to the statistical analysis for AA participants and thus contributed to the percentages of AA participants here.

[‡‡]Only FHS-Offspring and FHS-Gen3 have DPA measured in RBCs.

Table E7. Omega-3 Fatty Acid Biomarker Levels by Smoking Status in Each Cohort

Cohorts	Mean ALA biomarker level (% of total fatty acids)			Mean EPA biomarker level (% of total fatty acids)			Mean DPA biomarker level (% of total fatty acids)			Mean DHA biomarker level (% of total fatty acids)		
	Never smoker	Former smoker	Current smoker	Never smoker	Former smoker	Current smoker	Never smoker	Former smoker	Current smoker	Never smoker	Former smoker	Current smoker
AGES-EA (N=424)	0.22	0.23	0.24	2.98	2.84	2.53	1.18	1.18	1.13	6.45	6.34	5.85
ARIC-EA (N=3,143)	0.15	0.14	0.14	0.57	0.58	0.53	0.92	0.90	0.88	2.94	2.85	2.54
CARDIA-EA (N=1,759)	0.19	0.20	0.19	0.87	0.86	0.73	0.95	0.93	0.93	3.18	3.19	2.59
CARIDA-AA (N=1,461)	0.17	0.17	0.17	0.70	0.71	0.63	0.93	0.91	0.93	3.39	3.48	2.94
CHS-EA (N = 1690)	0.15	0.15	0.14	0.58	0.62	0.58	0.84	0.84	0.79	2.94	3.05	2.76
CHS-AA (N = 243)	0.13	0.14	0.13	0.59	0.65	0.56	0.86	0.86	0.87	3.57	3.53	3.58
MESA-EA (N = 1140)	0.18	0.18	0.18	0.93	0.97	0.71	0.95	0.93	0.88	3.63	3.56	2.86
MESA-AA (N = 801)	0.16	0.15	0.16	0.96	0.90	0.76	0.97	0.94	0.91	4.46	4.30	3.67
RS-EA (N = 141)	0.18	0.16	0.15	0.81	0.87	0.85	0.94	0.94	0.94	3.63	3.52	3.32
FHS-Offspring-EA[*] (N = 2,169)	0.18	0.18	0.18	0.75	0.76	0.66	2.78	2.77	2.62	4.99	4.90	4.09
FHS-Gen3-EA[*] (N = 3,052)	0.17	0.17	0.16	0.66	0.71	0.57	2.56	2.57	2.49	4.29	4.24	3.43

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Abbreviations: AA = African ancestry; AGES = Age, Gene, Environment, Susceptibility Study—Reykjavik, Iceland; ALA = Alpha-linolenic acid; ARIC = Atherosclerosis Risk in Communities; CARDIA = Coronary Artery Risk Development in Young Adults; CHS = Cardiovascular Health Study; DHA = Docosahexaenoic acid; DPA = Docosapentaenoic acid; EA = European ancestry; EPA = Eicosapentaenoic acid; FHS (Offspring) = Framingham Heart Study—Offspring Cohort; FHS (Gen3) = Framingham Heart Study—Generation 3 Cohort; MESA = Multi-Ethnic Study of Atherosclerosis; RS = Rotterdam (Netherlands) Study.

*Omega-3 fatty acid biomarkers were measured in plasma in all cohorts, except those in FHS (measured in red blood cells).

Table E8. Meta-Analysis Results for the Primary Analyses of Each Omega-3 Fatty Acid Biomarker on Each Pulmonary Function Test Measure[*]

n-3 PUFA (Ancestry)	FEV$_1$				FVC				FEV$_1$/FVC (in percent)			
	β (mL)	SE	P-value	Effect per 1 SD increment[§]	β (mL)	SE	P-value	Effect per 1 SD increment[§]	β (%)	SE	P-value	Effect per 1 SD increment[§]
DHA (All)	14.3[†]	3.2	**<0.001**	20.3	8.4	3.7	**0.023**	11.9	0.03[†]	0.05	0.478	0.05
DHA (EA)	*15.4*	*3.4*	***<0.001***	*21.8*	*9.7*	*4.0*	***0.016***	*13.7*	*0.01[†]*	*0.05*	*0.816*	*0.02*
DHA (AA)	*8.4[‡]*	*8.1*	*0.300*	*11.8*	*1.3[†]*	*9.5*	*0.890*	*1.9*	*0.16[†]*	*0.12*	*0.192*	*0.23*
DPA (All)	39.3[†]	11.5	**<0.001**	8.1	32.4[‡]	13.3	**0.015**	6.7	-0.2	0.2	0.238	-0.04
DPA (EA)	*39.6[‡]*	*11.9*	***<0.001***	*8.1*	*35.7[‡]*	*13.8*	***0.010***	*7.3*	*-0.2*	*0.2*	*0.244*	*-0.04*
DPA (AA)	*35.6*	*41.0*	*0.384*	*7.3*	*-6.3*	*48.0*	*0.895*	*-1.3*	*-0.1*	*0.6*	*0.825*	*-0.03*
EPA (All)	2.9	6.6	0.658	1.9	2.8	7.7	0.711	1.9	-0.2	0.1	**0.016**	-0.16
EPA (EA)	*3.4*	*7.2*	*0.638*	*2.2*	*4.7*	*8.3*	*0.573*	*3.1*	*-0.3*	*0.1*	***0.007***	*-0.19*
EPA (AA)	*0.41*	*16.8*	*0.981*	*0.3*	*-7.5*	*19.7*	*0.703*	*-4.9*	*0.04*	*0.27*	*0.868*	*0.03*
ALA (All)	81.9	45.6	0.072	6.5	120.5	53.1	**0.023**	9.5	-2.9[†]	0.7	**<0.001**	-0.23
ALA (EA)	*54.3*	*49.1*	*0.270*	*4.3*	*95.4*	*57.3*	*0.096*	*7.5*	*-2.6[‡]*	*0.7*	***<0.001***	*-0.20*
ALA (AA)	*250.7*	*121.5*	***0.039***	*19.8*	*272.2[†]*	*140.8*	*0.053*	*21.5*	*-4.3*	*1.7*	***0.010***	*-0.34*

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Abbreviations: AA = African ancestry; ALA = Alpha-linolenic acid; DHA = Docosahexaenoic acid; DPA = Docosapentaenoic acid; EPA = Eicosapentaenoic acid; FEV_1 = Forced expiratory volume in the first second; FVC = Forced vital capacity; n-3 PUFA = Omega-3 poly-unsaturated fatty acid; SD = Standard deviation; SE = Standard error.

[*]The β coefficient corresponds to the association of each n-3 PUFA biomarker on the specific pulmonary function outcome from a meta-analysis across cohorts [individual cohort analyses adjusted for current and former smoking, with never smoking as the reference, pack-years, sex, age, age^2, height, $height^2$, weight (for the FVC outcome only), and study site (cohorts with >1 site)]. P-values that are ≤0.05 are bolded.

[†]Moderate heterogeneity with I^2 ranging from 33% to 60%.

[‡]Substantial heterogeneity with I^2 ranging from 62% to 82%.

[§]One standard deviation increments of DHA (all cohorts), DPA (all except FHS), EPA (all cohorts), and ALA (all cohorts) biomarkers are 1.41%, 0.20%, 0.65%, and 0.08% of total fatty acids, respectively.

Table E9. Meta-Analysis Results of the Interaction of Each Omega-3 Fatty Acid Biomarker and Smoking Status on Each Pulmonary Function Test Measure[*]

n-3 PUFA	Smoking status (vs. never smoking as reference)	FEV_1				FVC				FEV_1/FVC (in percent)			
		β (mL)	SE	P-value	Effect per 1 SD increment[§]	β (mL)	SE	P-value	Effect per 1 SD increment[§]	β (%)	SE	P-value	Effect per 1 SD increment[§]
DHA	*Current*	26.1	11.1	**0.019**	36.8	9.5	12.9	0.463	13.4	0.9	0.2	**<0.001**	1.2
	Former	3.5[†]	6.7	0.596	5.0	-0.6	7.7	0.937	-0.9	0.1	0.1	0.158	0.2
DPA	*Current*	44.8	40.4	0.268	9.0	43.3	46.6	0.353	8.7	1.1	0.6	0.060	0.2
	Former	39.3	24.1	0.104	7.9	30.0	27.9	0.282	6.0	0.4	0.4	0.208	0.1
EPA	*Current*	34.4	25.1	0.171	22.4	19.1	29.1	0.513	12.4	0.6	0.4	0.110	0.4
	Former	2.8[†]	14.1	0.841	1.8	-1.8[†]	16.4	0.912	-1.2	-0.0004	0.2222	0.999	-0.0003
ALA	*Current*	-109.1	144.1	0.449	-8.7	-151.0	167.6	0.367	-12.1	-0.09	2.06	0.965	-0.01
	Former	-147.2	106.4	0.167	-11.8	-68.2	123.5	0.581	-5.5	-2.2	1.6	0.169	-0.2

Abbreviations: ALA = Alpha-linolenic acid; DHA = Docosahexaenoic acid; DPA = Docosapentaenoic acid; EPA = Eicosapentaenoic acid; FEV_1 = Forced expiratory volume in the first second; FVC = Forced vital capacity; n-3 PUFA = Omega-3 poly-unsaturated fatty acid; SD = Standard deviation; SE = Standard error.

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[*]Fixed effect models were used. β (mL) and β (%) were the coefficients of the interaction terms only (the interaction of current smoking status with the n-3 PUFA biomarkers, and the interaction of former smoking status with the n-3 PUFA biomarkers), with never smokers as the reference group. P-values that are ≤0.05 are bolded. Coefficients were meta-analyzed across cohorts, and each cohort's analysis was adjusted for the following covariates: current and former smoking, with never smoking as the reference, pack-years, sex, age, age^2, height, $height^2$, weight (for the FVC outcome only), and study site (cohorts with >1 site).

[†]Moderate heterogeneity with I^2 ranging from 30% to 60%.

[§]One standard deviation increments of DHA (all cohorts), DPA (all except FHS), EPA (all cohorts), and ALA (all cohorts) biomarkers are 1.41%, 0.20%, 0.65%, and 0.08% of total fatty acids, respectively.

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Table E10. Previously Reported Lead SNPs at Genome-Wide Significant Loci for Either of the Omega-3 Fatty Acid Biomarkers (DHA or DPA) and Their Associations with FEV_1 and FVC in the Current Genome-Wide Joint 2df Meta-Analyses that Included Interaction with the N-3 Fatty Acid Biomarkers (DHA or DPA)

Chr	Position	SNP	Gene / nearby genes	Prior GWAS phenotype	Prior GWAS P	DHA interaction model for FEV_1			DPA interaction model for FEV_1			DHA interaction model for FVC			DPA interaction model for FVC		
						P_{main}	P_{int}	P_{2df}	P_{main}	P_{int}	P_{2df}	P_{main}	P_{int}	P_{2df}	P_{main}	P_{int}	P_{2df}
6	10994782	rs2236212	*ELOVL2*	DHA	$1.0×10^{-15}$	0.95	0.92	0.99	0.51	0.89	0.54	0.30	0.21	0.42	0.11	0.22	0.26
6	10968908	rs4713103	*SYCP2L*	DHA/ DPA	$8.0×10^{-14}$ / $3.0×10^{-36}$	0.80	0.92	0.90	0.76	0.51	0.70	0.67	0.44	0.54	0.54	0.62	0.83
6	11074114	rs4711171	*ELOVL2-AS1*	DHA	$5.0×10^{-13}$	0.68	0.62	0.87	0.36	0.58	0.59	0.11	0.062	0.16	0.093	0.15	0.24
2	27518370	rs780094	*GCKR*	DPA	$9.0×10^{-9}$	0.48	0.47	0.76	0.74	0.74	0.94	0.45	0.50	0.75	0.67	0.75	0.91
6	10982740	rs3734398	*ELOVL2*	DPA	$1.0×10^{-43}$	0.68	0.67	0.91	0.59	0.98	0.58	0.56	0.47	0.74	0.12	0.25	0.29
6	11075793	rs1321535	*ELOVL2-AS1*	DPA	$1.0×10^{-38}$	0.62	0.54	0.81	0.43	0.65	0.65	0.15	0.080	0.20	0.10	0.17	0.27
11	61723014	rs198426	*DAGLA*	DPA	$3.0×10^{-9}$	0.39	0.73	0.31	0.040	0.18	0.080	0.52	0.99	0.21	0.063	0.33	0.079
11	61783884	rs174535	*MYRF*	DPA	$1.0×10^{-151}$	0.84	0.56	0.57	0.24	0.96	0.095	0.59	0.35	0.44	0.12	0.67	0.063
11	61790331	rs102275	*TMEM258*	DPA	$8.0×10^{-153}$	0.94	0.57	0.23	0.030	0.49	$8.7×10^{-3}$	0.81	0.44	0.36	0.040	0.45	0.018
11	61796827	rs4246215	*FEN1*	DPA	$1.0×10^{-139}$	0.95	0.57	0.26	0.064	0.69	0.016	0.96	0.46	0.21	0.026	0.43	$7.6×10^{-3}$
11	61803311	rs174547	*FADS1*	DPA	$4.0×10^{-154}$	0.70	0.37	0.34	0.086	0.65	0.037	0.55	0.27	0.31	0.066	0.53	0.033
11	61830500	rs1535	*FADS2*	DPA	$3.0×10^{-152}$	0.98	0.61	0.45	0.055	0.49	0.034	0.83	0.48	0.41	0.036	0.38	0.024
11	61872101	rs174448	*FADS2/ FADS3*	DPA	$3.0×10^{-60}$	0.83	0.43	0.29	0.052	0.37	0.059	0.48	0.25	0.35	0.12	0.49	0.14
11	61896219	rs174468	*FADS3/ RAB3IL1*	DPA	$3.0×10^{-35}$	0.10	0.37	0.054	$2.2×10^{-3}$	0.091	**$1.8×10^{-3}$**	0.16	0.52	0.083	0.010	0.27	$3.9×10^{-3}$
11	61944003	rs2521572	*RAB3IL1*	DPA	$2.0×10^{-9}$	0.052	0.033	0.10	0.79	0.67	0.89	0.033	0.053	0.10	0.90	0.75	0.71

Abbreviations: chr = Chromosome; DHA = Docosahexaenoic acid; DPA = Docosapentaenoic acid; FEV_1 = Forced expiratory volume in the first second; FVC = Forced vital capacity; GWAS = Genome-wide association study; int = Interaction; NA = Not available; SNP = Single nucleotide polymorphism.

[*]SNPs with the smallest P values from each locus reported in the prior GWAS analysis (69) are shown and are sorted by DHA or DPA phenotype and then by chromosomal position (NCBI build 37). The SNP that passed the multiple testing correction (n of tests = 14, Bonferroni-corrected $P < 3.6×10^{-3}$) is bolded.

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Table E11. **Previously Reported Lead SNPs at Genome-Wide Significant Loci for any of the Pulmonary Function Test Measures (FEV$_1$, FVC, or FEV$_1$/FVC) and Their Associations in the Current Genome-Wide Joint 2df Meta-Analyses that Included Interaction with the N-3 Fatty Acid Biomarkers (DHA or DPA)[*]**

chr	Position	SNP	Gene / nearby genes	Prior GWAS phenotype	Prior GWAS best P	DHA interaction model for FEV$_1$			DPA interaction model for FEV$_1$			DHA interaction model for FVC			DPA interaction model for FVC		
						P_{main}	P_{int}	P_{2df}	P_{main}	P_{int}	P_{2df}	P_{main}	P_{int}	P_{2df}	P_{main}	P_{int}	P_{2df}
1	150586971	rs6681426	MCL1/ENSA	FEV$_1$	4.4×10^{-9} (70)	0.25	0.80	0.054	0.13	0.71	0.062	0.020	0.15	0.013	0.049	0.52	0.019
1	204434927	rs12092943	PIK3C2B	FEV$_1$	4.8×10^{-8} (71)	0.057	0.22	0.055	0.060	0.34	0.071	0.15	0.51	0.064	0.073	0.44	0.060
1	221765779	1:221765779: C_CA	C1orf140/ DUSP10	FEV$_1$	3.4×10^{-8} (71)	0.56	0.69	0.69	0.76	0.58	0.54	0.69	0.68	0.92	0.45	0.41	0.71
1	237941781	rs3766889	RYR2	FEV$_1$	4.1×10^{-8} (71)	6.3×10^{-4}	5.6×10^{-3}	6.4×10^{-4}	0.24	0.56	0.022	0.021	0.099	9.9×10^{-3}	0.13	0.33	0.025
2	42355947	rs963406	PKDCC/ EML4	FEV$_1$	3.2×10^{-8} (71)	0.56	0.95	0.20	0.28	0.86	0.15	0.27	0.55	0.24	0.11	0.37	0.16
2	218683154	rs2571445	TNS1	FEV$_1$	1.1×10^{-12} (72)	0.081	0.99	$\mathbf{6.0 \times 10^{-6}}$	2.4×10^{-3}	0.52	$\mathbf{5.5 \times 10^{-6}}$	0.57	0.20	$\mathbf{1.3 \times 10^{-5}}$	0.021	1.00	$\mathbf{3.5 \times 10^{-5}}$
3	57494433	rs79294353	DNAH12	FEV$_1$	4.8×10^{-9} (71)	0.41	0.65	0.50	0.84	0.66	0.46	0.59	0.61	0.86	0.70	0.72	0.93
3	98815640	rs6778584	DCBLD2/ MIR548G	FEV$_1$	4.5×10^{-8} (71)	0.27	0.35	0.52	0.046	0.037	0.11	0.074	0.16	0.15	0.010	0.020	0.036
3	169300219	rs1344555	MECOM	FEV$_1$	2.7×10^{-8} (73)	0.57	0.76	0.69	0.52	0.82	0.65	0.31	0.22	0.43	0.31	0.16	0.35
4	106137033	rs2047409	TET2	FEV$_1$	1.3×10^{-8} (74)	0.21	0.51	0.14	0.17	0.66	0.15	0.49	0.80	0.44	0.21	0.49	0.34
4	106531846	rs17035960	FLJ20184	FEV$_1$	9.4×10^{-14} (9)	0.11	0.83	$\mathbf{3.3 \times 10^{-6}}$	0.14	0.28	$\mathbf{6.9 \times 10^{-6}}$	0.10	0.81	4.2×10^{-4}	0.17	0.48	2.8×10^{-4}
4	106563379	rs17036052	FLJ20184	FEV$_1$	1.8×10^{-15} (9)	0.13	0.85	$\mathbf{1.1 \times 10^{-5}}$	0.19	0.29	$\mathbf{1.4 \times 10^{-5}}$	0.17	0.93	1.9×10^{-3}	0.29	0.42	9.0×10^{-4}
4	106593574	rs17036090	FLJ20184	FEV$_1$	5.6×10^{-15} (9)	0.23	0.57	$\mathbf{9.8 \times 10^{-6}}$	0.34	0.12	$\mathbf{9.7 \times 10^{-6}}$	0.17	0.89	2.2×10^{-3}	0.22	0.50	1.2×10^{-3}
4	106619140	rs11727189	INTS12	FEV$_1$	4.7×10^{-17} (9)	0.17	0.74	$\mathbf{2.1 \times 10^{-5}}$	0.19	0.33	$\mathbf{3.5 \times 10^{-5}}$	0.18	0.95	2.3×10^{-3}	0.14	0.71	1.8×10^{-3}
4	106688904	rs10516526	GSTCD	FEV$_1$	2.2×10^{-23} (72)	0.13	0.80	$\mathbf{9.6 \times 10^{-6}}$	0.14	0.38	$\mathbf{2.1 \times 10^{-5}}$	0.15	0.91	1.7×10^{-3}	0.12	0.76	1.3×10^{-3}
4	106729933	rs11097901	GSTCD	FEV$_1$	3.3×10^{-18} (9)	0.083	0.97	$\mathbf{1.4 \times 10^{-5}}$	0.18	0.30	$\mathbf{2.0 \times 10^{-5}}$	0.075	0.59	2.1×10^{-3}	0.15	0.66	1.5×10^{-3}

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4	106755996	rs11728716	GSTCD	FEV$_1$	7.2×10^{-18} (9)	0.18	0.69	$\mathbf{1.1\times10^{-5}}$	0.11	0.49	$\mathbf{3.1\times10^{-5}}$	0.18	0.90	4.0×10^{-3}	0.17	0.73	3.5×10^{-3}
4	106796829	rs17036341	GSTCD/ NPNT	FEV$_1$	2.2×10^{-15} (9)	0.023	0.38	$\mathbf{1.5\times10^{-4}}$	0.57	0.11	$\mathbf{1.8\times10^{-4}}$	0.056	0.33	0.012	0.45	0.43	0.015
4	106808107	rs17331332	GSTCD/ NPNT	FEV$_1$	5.7×10^{-15} (9, 72)	0.10	0.93	$\mathbf{1.3\times10^{-5}}$	0.11	0.51	$\mathbf{3.1\times10^{-5}}$	0.17	0.85	4.6×10^{-3}	0.19	0.68	3.9×10^{-3}
4	106819053	rs34712979	NPNT	FEV$_1$	9.6×10^{-16} (74)	0.061	0.34	0.022	0.012	0.16	0.014	0.28	0.57	0.32	0.037	0.13	0.093
4	146174040	rs111898810	OTUD4/ SMAD1	FEV$_1$	2.1×10^{-8} (71)	0.22	0.054	0.050	0.79	0.32	0.33	0.18	0.051	0.072	0.95	0.54	0.56
5	55922145	rs11748173	ANKRD55/ MAP3K1	FEV$_1$	3.9×10^{-10} (71)	0.50	0.73	0.57	0.43	0.76	0.56	0.61	0.86	0.66	0.88	0.43	0.45
5	77392117	rs252746	AP3B1	FEV$_1$	6.2×10^{-9} (71)	0.80	0.66	0.83	0.12	0.081	0.22	0.80	0.74	0.94	0.43	0.49	0.73
5	147845815	rs3995090	HTR4	FEV$_1$	4.3×10^{-9} (72)	8.5×10^{-4}	6.4×10^{-3}	2.2×10^{-3}	0.068	0.61	0.023	0.025	7.8×10^{-3}	0.024	0.75	0.58	0.82
5	147846707	rs6889822	HTR4	FEV$_1$	8.2×10^{-9} (72)	6.2×10^{-4}	6.5×10^{-3}	1.3×10^{-3}	0.015	0.29	7.6×10^{-3}	0.042	0.025	0.081	0.40	0.39	0.68
5	148596693	rs3839234	ABLIM3	FEV$_1$	4.5×10^{-11} (75)	0.54	0.35	0.53	0.50	0.64	0.77	1.00	0.79	0.78	0.62	0.83	0.81
6	28322296	rs6903823	ZKSCAN3/ ZNF323	FEV$_1$	2.2×10^{-10} (73)	0.91	0.42	0.15	0.84	0.28	0.18	0.94	0.71	0.72	0.61	0.38	0.58
6	32635592	rs9274600	HLA-DQB1/ HLA-DQA3	FEV$_1$	1.3×10^{-10} (74)	0.40	0.28	0.50	0.44	0.42	0.71	0.42	0.42	0.72	0.24	0.24	0.50
6	32648418	rs114229351[†]	HLA-DQB1/ HLA-DQA2	FEV$_1$	2.1×10^{-10} (75)	0.065	0.10	0.18	0.082	0.16	0.22	0.088	0.070	0.19	0.14	0.090	0.24
7	156127246	rs12698403	LOC389602/ LOC285889	FEV$_1$	1.1×10^{-13} (75)	0.84	0.39	0.16	0.85	0.54	0.30	0.67	0.21	0.050	0.75	0.40	0.093
9	4124377	rs7872188	GLIS3	FEV$_1$	1.6×10^{-10} (75)	0.24	0.62	0.16	0.057	0.29	0.091	0.13	0.43	0.080	0.013	0.12	0.026
10	65087468	rs7899503	JMJD1C	FEV$_1$	8.7×10^{-14} (71)	0.037	0.24	8.9×10^{-3}	0.028	0.47	5.4×10^{-3}	0.30	0.89	0.035	0.080	0.66	0.026
10	78315224	rs11001819	C10orf11	FEV$_1$	3.0×10^{-12} (73)	0.46	0.13	0.053	0.97	0.22	0.070	0.99	0.48	0.14	0.93	0.29	0.083
11	62310909	rs2509961	AHNAK	FEV$_1$	1.5×10^{-13} (75)	0.16	0.21	0.37	0.30	0.41	0.58	0.14	0.17	0.34	0.49	0.66	0.75
11	86442733	rs145729347	ME3/PRSS23	FEV$_1$	8.6×10^{-9} (75)	0.24	0.66	0.13	0.67	0.63	0.21	0.85	0.70	0.85	0.99	0.95	0.99
11	126008910	rs567508	CDON/	FEV$_1$	4.8×10^{-10}	0.63	0.28	0.20	0.85	0.28	0.21	0.63	0.96	0.47	0.93	0.36	0.25

			RPUSD4		(75)												
12	56390364	rs772920	*RAB5B*	FEV$_1$	2.5×10^{-8} (71)	0.87	0.80	0.95	0.44	0.30	0.57	0.48	0.67	0.63	0.92	0.65	0.57
12	65824670	rs1494502	*MSRB3*	FEV$_1$	9.8×10^{-10} (75)	0.044	0.069	0.13	0.48	0.80	0.59	0.31	0.39	0.58	0.68	0.93	0.80
12	114743533	chr12: 114743533	*RBM19/ TBX5*	FEV$_1$	1.2×10^{-8} (74)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
12	115201436	rs10850377	*TBX3*	FEV$_1$	2.5×10^{-12} (70)	0.60	0.96	0.28	0.88	0.24	0.12	0.58	0.86	0.12	0.36	0.82	0.084
12	125230287	rs11057793	*NCOR2\ SCARB1*	FEV$_1$	4.8×10^{-8} (71)	0.57	0.87	0.53	0.20	0.47	0.34	0.77	0.86	0.46	0.26	0.61	0.36
14	92485881	rs7155279	*TRIP11*	FEV$_1$	1.4×10^{-9} (70)	0.75	0.46	0.46	0.17	0.28	0.38	0.46	0.25	0.35	0.086	0.14	0.23
14	93118229	rs117068593	*RIN3*	FEV$_1$	2.3×10^{-8} (70)	0.21	0.76	0.029	0.31	0.65	0.020	0.44	0.80	0.33	0.75	0.63	0.33
17	29087285	rs62070631	*SUZ12P1*	FEV$_1$	2.6×10^{-8} (71)	0.070	0.38	0.021	0.11	0.80	0.029	0.30	0.74	0.16	0.25	0.78	0.20
17	43682323	rs186806998	*LOC644172/ CRHR1*	FEV1	3.5×10^{-10} (71)	0.19	0.95	4.2×10^{-3}	0.10	0.93	3.4×10^{-3}	0.21	0.88	9.7×10^{-3}	0.020	0.40	5.2×10^{-3}
17	43685698	rs143246821		FEV$_1$	9.1×10^{-10} (71)	0.082	0.61	3.1×10^{-3}	0.046	0.72	2.2×10^{-3}	0.11	0.59	9.8×10^{-3}	8.6×10^{-3}	0.20	3.7×10^{-3}
17	44339473	rs2532349	*KANSL1*	FEV$_1$	1.7×10^{-10} (70)	0.13	0.81	3.2×10^{-3}	0.056	0.80	2.4×10^{-3}	0.15	0.77	7.6×10^{-3}	0.012	0.28	3.8×10^{-3}
17	44847834	rs199525	*WNT3*	FVC, FEV$_1$	9.6×10^{-10} (71)	0.50	0.58	6.0×10^{-3}	0.098	0.93	6.1×10^{-3}	0.49	0.78	0.039	0.026	0.28	0.020
17	44863133	rs916888		FEV$_1$	3.8×10^{-9} (71)	0.81	0.39	0.014	0.32	0.67	0.024	0.96	0.31	0.033	0.096	0.54	0.070
17	69125606	rs11654749	*KCNJ2/ SOX9*	FEV$_1$	1.3×10^{-8} (4)	0.53	0.65	0.016	0.21	0.88	0.031	0.83	0.32	0.10	0.67	0.29	0.12
17	73513185	rs7218675	*TSEN54*	FEV$_1$	1.2×10^{-8} (74)	0.20	0.34	0.34	0.11	0.25	0.26	0.064	0.23	0.061	3.0×10^{-3}	0.022	0.010
18	8801351	rs513953	*SOGA2*	FEV$_1$	2.0×10^{-8} (71)	0.012	0.084	0.011	0.30	0.80	0.039	0.063	0.12	0.16	0.16	0.35	0.34
18	20148531	rs7243351	*CTAGE1/ RBBP8*	FEV$_1$	4.7×10^{-8} (71)	0.72	0.48	0.017	0.011	0.15	0.011	0.66	0.26	0.13	0.077	0.27	0.14
20	25669052	rs6138639	*ZNF337*	FEV$_1$	3.2×10^{-10} (71)	9.5×10^{-3}	0.20	3.0×10^{-4}	0.10	0.79	1.1×10^{-3}	0.014	0.15	2.0×10^{-3}	0.039	0.58	5.7×10^{-3}
20	31042176	rs1737889	*C20orf112*	FEV$_1$	4.2×10^{-8} (71)	0.16	0.31	0.25	0.64	0.80	0.39	0.39	0.72	0.33	0.15	0.43	0.24

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20	62363640	rs72448466	ZGPAT	FEV$_1$	4.3×10^{-13} (75)	0.66	0.86	0.22	0.62	0.69	0.19	0.55	0.91	0.40	0.89	0.58	0.39
22	18450287	rs11704827	MICAL3	FEV$_1$	8.3×10^{-13} (75)	0.29	0.48	0.44	0.74	0.82	0.58	0.71	0.90	0.79	0.48	0.66	0.75
22	28056338	rs134041	MN1	FEV$_1$	3.0×10^{-9} (70)	0.28	0.39	0.52	0.86	0.77	0.65	0.65	0.86	0.72	0.76	0.88	0.68
22	28181399	rs2283847	MN1	FEV$_1$	3.4×10^{-11} (75)	0.87	0.80	0.48	0.38	0.27	0.34	0.65	0.89	0.62	0.59	0.44	0.45
11	86376739	rs507211	ME3	longitudinal FEV$_1$	2.2×10^{-8} (76)	1.00	0.58	0.33	0.20	0.58	0.23	0.54	0.98	0.31	0.56	0.77	0.24
1	118862070	rs200154334	SPAG17/ TBX15	FVC	8.2×10^{-14} (75)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
1	146494027	rs12724426	LOC728989	FVC	3.0×10^{-8} (71)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
1	200085714	rs2821332	NR5A2	FVC	7.7×10^{-9} (71)	0.91	0.86	0.73	0.97	0.65	0.68	0.99	0.83	0.83	0.57	0.76	0.80
1	215095003	rs512597	CENPF/ KCNK2	FVC	3.9×10^{-9} (71)	0.61	0.80	0.72	0.22	0.31	0.47	0.35	0.77	0.18	0.15	0.49	0.20
1	221630555	rs6657854	C1orf140/ DUSP10	FVC	1.2×10^{-8} (71)	0.26	0.77	0.069	0.10	0.56	0.067	0.13	0.47	0.053	0.15	0.75	0.056
1	221635207	rs12046746		FVC	1.4×10^{-9} (71)	0.26	0.78	0.069	0.10	0.56	0.068	0.13	0.47	0.052	0.15	0.76	0.055
1	237929787	1:237929787: T_TCA	RYR2	FVC	4.5×10^{-8} (71)	0.59	0.36	0.43	0.14	0.23	0.33	0.59	0.37	0.46	0.16	0.24	0.38
2	56120853	rs1430193	EFEMP1	FVC	1.9×10^{-12} (77)	0.12	0.35	0.14	0.096	0.37	0.14	0.074	0.46	0.010	0.053	0.55	0.014
2	109571508	rs17034666	EDAR	FVC	1.8×10^{-8} (71)	0.34	0.24	0.48	0.54	0.52	0.81	0.082	0.065	0.18	0.94	0.99	0.99
2	119660943	rs114962105	EN1/ MARCO	FVC	3.8×10^{-8} (71)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2	147046592	rs6746679	DKFZp686O 1327/ PABPC1P2	FVC	2.2×10^{-8} (71)	0.18	0.15	0.36	0.96	0.89	0.98	0.13	0.16	0.32	0.59	0.77	0.82
3	67452043	rs1490265	SUCLG2	FVC	1.6×10^{-9} (75)	0.15	0.17	0.36	0.68	0.85	0.86	0.70	0.78	0.90	0.67	0.50	0.76
3	98806782	rs1404098	DCBLD2/ MIR548G	FVC	5.5×10^{-9} (71)	0.38	0.50	0.63	0.044	0.037	0.10	0.10	0.24	0.17	7.5×10^{-3}	0.017	0.028
3	158282459	rs6441207	RSRC1/ MLF1	FVC	1.3×10^{-13} (70)	0.27	0.79	0.066	0.36	0.86	0.11	0.089	0.18	0.20	0.75	0.73	0.49

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5	33334312	rs91731	*LOC340113/TARS*	FVC	4.3×10^{-13} (75)	0.84	0.75	0.36	0.70	0.79	0.47	0.63	0.95	0.30	0.26	0.58	0.39
5	53444498	rs2441026	*ARL15*	FVC	2.8×10^{-12} (75)	0.27	0.43	0.44	0.49	0.84	0.60	0.34	0.46	0.57	0.88	0.57	0.67
5	77450828	rs12513481	*AP3B1*	FVC	2.2×10^{-11} (71)	0.44	0.38	0.67	0.16	0.14	0.32	0.96	0.93	0.93	0.43	0.54	0.72
5	77440196	rs72776440		FVC	3.2×10^{-11} (71)	0.62	0.50	0.75	0.18	0.13	0.32	0.97	1.00	1.00	0.55	0.58	0.83
6	7801112	rs6923462	*BMP6*	FVC	5.9×10^{-13} (77)	0.13	0.29	0.21	0.58	0.76	0.28	0.18	0.57	0.074	0.89	0.13	0.025
6	126792095	rs11759026	*CENPW/RSPO3*	FVC	4.3×10^{-9} (71)	0.69	0.31	0.22	0.68	0.19	0.15	0.45	0.99	0.13	0.81	0.33	0.067
7	15506529	rs55905169	*AGMO*	FVC	1.3×10^{-8} (71)	0.39	0.074	0.011	0.96	0.14	0.019	0.94	0.54	0.13	0.82	0.40	0.11
9	1555835	rs771924	*DMRT2/SMARCA2*	FVC	7.2×10^{-9} (71)	0.080	0.47	9.1×10^{-3}	0.19	0.87	0.012	0.046	0.36	7.6×10^{-3}	0.22	0.77	0.016
9	1574877	rs9407640		FVC, FEV$_1$	2.9×10^{-8} (71)	0.21	0.72	0.033	0.55	0.43	0.027	0.24	0.68	0.092	0.76	0.39	0.080
9	139094805	rs2274116	*LHX3*	FVC	5.5×10^{-14} (70)	0.42	0.70	3.5×10^{-3}	0.31	0.42	3.0×10^{-3}	0.59	0.46	2.9×10^{-3}	0.27	0.47	3.2×10^{-3}
9	139257411	rs10870202	*DNLZ*	FVC	9.3×10^{-10} (75)	0.78	0.83	0.95	0.83	0.88	0.98	0.32	0.20	0.36	1.00	0.72	0.78
10	69957350	rs7095607	*MYPN*	FVC	8.7×10^{-15} (75)	0.77	0.54	0.58	0.83	0.36	0.31	0.71	0.56	0.75	0.67	0.35	0.47
10	77002679	10:77002679:TC_T	*COMTD1/ZNF503-AS1*	FVC	4.9×10^{-8} (71)	0.011	0.050	0.023	0.014	0.079	0.039	0.29	0.61	0.26	0.13	0.40	0.22
11	43648368	rs4237643	*HSD17B12*	FVC	3.5×10^{-8} (77)	0.33	0.66	0.28	0.80	0.64	0.36	0.11	0.53	0.021	0.66	0.34	0.028
11	45250732	rs2863171	*PRDM11/SYT13*	FVC	9.0×10^{-10} (77)	0.34	0.92	0.051	0.064	0.43	0.057	0.014	0.14	3.1×10^{-3}	2.5×10^{-3}	0.092	2.2×10^{-3}
11	127995904	rs73025192	*KIRREL3-AS3/ETS1*	FVC	1.6×10^{-8} (71)	0.47	0.35	0.58	0.73	0.58	0.83	0.54	0.64	0.79	0.66	0.86	0.85
12	28283187	rs11383346	*CCDC91*	FVC	9.5×10^{-18} (70)	0.62	0.91	0.23	0.93	0.42	0.16	0.18	0.55	0.069	0.34	0.98	0.10
12	85724305	rs7971039	*ALX1/RASSF9*	FVC, FEV$_1$	1.4×10^{-8} (71)	0.79	0.70	0.23	0.95	0.41	0.23	0.15	0.63	0.034	0.71	0.25	0.021
12	85724096	rs10779158		FVC	1.5×10^{-8} (71)	0.48	0.96	0.18	0.90	0.35	0.13	0.31	0.95	0.019	0.84	0.16	0.011
12	94184082	rs11107184	*CRADD*	FVC	3.9×10^{-8}	0.14	0.075	0.18	0.27	0.12	0.26	0.29	0.14	0.24	0.30	0.082	0.14

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12	94852628	rs10859698	CCDC41	FVC	3.5×10^{-8} (71)	0.67	0.34	0.27	0.34	0.75	0.37	0.92	0.49	0.29	0.41	0.91	0.32
12	115500691	rs35506	TBX3/ MED13L	FVC	9.9×10^{-10} (75)	0.16	0.32	0.27	0.38	0.83	0.40	0.058	0.17	0.092	0.27	0.80	0.22
15	46722435	rs4775429	SQRDL/ SEMA6D	FVC	2.5×10^{-8} (71)	0.14	0.039	0.027	0.86	0.58	0.26	0.16	0.078	0.12	0.41	0.29	0.40
15	67483276	rs8025774	SMAD3	FVC	9.3×10^{-13} (71)	0.45	0.88	0.24	0.56	0.72	0.19	0.47	0.85	0.047	0.29	0.79	0.035
16	70040398	rs3973397	PDXDC2P	FVC	3.3×10^{-8} (71)	0.031	0.074	0.078	0.60	0.83	0.32	1.9×10^{-3}	0.011	4.3×10^{-3}	0.40	0.68	0.088
16	72252097	rs55771535	PMFBP1/ ZFHX3	FVC	6.4×10^{-10} (71)	0.031	0.049	0.096	9.0×10^{-3}	8.7×10^{-3}	0.25	0.020	0.15	7.3×10^{-3}	1.5×10^{-3}	0.034	3.3×10^{-3}
16	78187138	rs1079572	WWOX	FVC	1.0×10^{-8} (77)	0.49	0.68	9.9×10^{-3}	0.17	0.94	0.015	0.11	0.48	0.028	0.16	0.95	0.031
17	37611352	rs8067511	MED1/ CDK12	FVC	1.1×10^{-8} (71)	0.11	0.29	0.14	0.063	0.31	0.090	0.055	0.15	0.10	0.023	0.13	0.050
17	43682405	rs150741403	LOC644172/ CRHR1	FVC	1.9×10^{-9} (71)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
17	68976415	rs6501431	KCNJ2	FVC	2.9×10^{-9} (77)	1.00	0.82	0.82	0.15	0.19	0.36	0.41	0.16	0.17	0.17	0.47	0.27
18	20728158	rs7238093	CABLES1	FVC	6.8×10^{-9} (71)	0.31	0.78	2.0×10^{-3}	0.031	0.58	3.4×10^{-3}	0.14	0.74	4.9×10^{-3}	4.0×10^{-3}	0.15	2.2×10^{-3}
18	50957922	rs8089865	DCC	FVC	2.0×10^{-10} (71)	0.86	0.96	0.94	0.85	0.99	0.92	0.42	0.83	0.24	0.89	0.42	0.18
20	6632901	rs6140050	CASC20/ BMP2	FVC	6.4×10^{-14} (75)	7.0×10^{-3}	0.016	0.025	5.6×10^{-3}	0.018	0.021	0.010	0.064	0.013	6.2×10^{-3}	0.086	0.011
20	45529571	rs2236519	EYA2	FVC	3.5×10^{-8} (71)	0.87	0.47	0.28	0.57	0.92	0.42	0.84	0.35	0.13	0.42	0.92	0.22
1	17306675	rs2284746	MFAP2	FEV$_1$/FVC	7.5×10^{-16} (73)	0.32	0.61	0.34	0.099	0.33	0.19	0.10	0.34	0.085	0.061	0.43	0.058
1	40035686	rs17513135	LOC 101929516	FEV$_1$/FVC	2.3×10^{-16} (75)	0.18	0.61	0.057	9.0×10^{-3}	0.11	0.014	0.38	0.54	0.59	0.094	0.17	0.24
1	92068967	rs1192404	CDC7/ TGFBR3	FEV$_1$/FVC	6.1×10^{-20} (75)	0.60	0.26	0.20	0.79	0.29	0.26	0.91	0.38	0.041	0.62	0.43	0.053
1	92374517	rs12140637	TGFBR3/ BRDT2	FEV$_1$/FVC	1.2×10^{-9} (75)	0.45	0.58	0.68	0.61	0.94	0.68	0.69	0.38	0.35	0.76	0.30	0.30
1	160206067	rs11591179	DCAF8	FEV$_1$/FVC	3.5×10^{-8} (71)	0.51	0.85	0.41	1.00	0.45	0.31	0.87	0.68	0.28	0.76	0.54	0.22

1	218860068	rs993925	TGFB2	FEV_1/FVC	1.2×10^{-8} (73)	0.56	0.53	5.4×10^{-3}	0.89	0.046	1.1×10^{-3}	0.29	0.93	0.024	0.60	0.35	0.021
1	219963090	rs201204531	LYPLAL1/RNUSF-1	FEV_1/FVC	2.7×10^{-10} (70)	0.40	0.52	0.66	0.65	0.79	0.88	0.96	0.91	0.92	0.44	0.52	0.75
1	239850588	rs6688537	CHRM3	FEV_1/FVC	6.7×10^{-22} (75)	0.52	0.52	0.81	0.26	0.19	0.43	0.20	0.13	0.30	0.12	0.05	0.14
2	10418806	rs139215025	C2orf48/HPCAL1	FEV_1/FVC	9.0×10^{-11} (71)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2	18292452	rs61067109	KCNS3/RDH14	FEV_1/FVC	1.4×10^{-15} (70)	0.32	0.53	0.45	0.50	0.99	0.45	0.34	0.49	0.55	0.59	0.97	0.63
2	157046432	rs72904209	KCNJ3/NR4A2	FEV_1/FVC	3.1×10^{-8} (71)	0.78	0.82	0.39	0.84	0.32	0.25	0.33	0.12	0.13	0.72	0.30	0.33
2	229502503	rs10498230	PID1	FEV_1/FVC	3.9×10^{-8} (9)	0.43	1.00	0.097	0.26	0.88	0.048	0.41	0.47	0.71	0.48	0.66	0.74
2	229510929	rs1435867	PID1	FEV_1/FVC	3.7×10^{-8} (9)	0.45	0.95	0.085	0.27	0.84	0.042	0.42	0.48	0.72	0.52	0.71	0.77
2	230224031	rs7594321	DNER	FEV_1/FVC	2.6×10^{-9} (4)	0.15	0.67	0.022	0.61	0.31	0.012	0.44	0.57	0.69	0.70	0.89	0.87
2	239316560	rs61332075	TRAF3IP1/ASB1	FEV_1/FVC	2.6×10^{-10} (75)	0.83	0.63	0.73	0.24	0.32	0.51	0.27	0.31	0.54	0.54	0.35	0.60
2	239877148	rs12477314	FLJ43879/HDAC4	FEV_1/FVC	1.7×10^{-12} (73)	0.35	0.94	0.020	0.56	0.28	5.8×10^{-3}	0.24	0.60	0.14	0.31	0.96	0.15
3	25520582	rs1529672	RARB	FEV_1/FVC	4.0×10^{-14} (73)	0.26	0.75	2.9×10^{-4}	0.017	0.53	5.5×10^{-4}	0.73	0.26	0.090	0.046	0.19	0.097
3	29431565	rs28723417	RBMS3	FEV_1/FVC	1.8×10^{-8} (71)	0.76	0.78	0.24	0.38	0.99	0.22	0.59	0.54	0.82	0.71	0.62	0.88
3	29469675	rs17666332		FEV_1/FVC	4.8×10^{-8} (71)	0.43	0.76	0.32	0.22	0.63	0.23	0.98	0.99	0.99	0.90	0.95	0.98
3	55150677	rs1458979	CACNA2D3/WNT5A	FEV_1/FVC	4.4×10^{-10} (75)	0.11	0.19	0.26	0.17	0.28	0.37	0.44	0.30	0.50	0.43	0.16	0.27
3	62386350	rs111793843	CADPS	FEV_1/FVC	2.0×10^{-8} (71)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
3	99359368	rs80217917	DCBLD2/MIR548G	FEV_1/FVC	2.6×10^{-8} (71)	0.81	0.50	0.43	0.27	0.50	0.46	0.32	0.19	0.35	0.55	0.77	0.77
3	127991527	rs2811415	EEFSEC	FEV_1/FVC	5.5×10^{-11} (75)	0.73	0.50	0.56	0.58	0.85	0.71	0.87	0.74	0.86	0.68	0.84	0.88
3	168715808	rs56341938	LOC100507661/MECOM	FEV_1/FVC	4.5×10^{-14} (75)	0.49	0.51	0.79	0.13	0.13	0.29	0.17	0.12	0.28	0.47	0.38	0.67
4	7846240	rs28520091	AFAP1	FEV_1/FVC	2.2×10^{-9}	0.33	0.33	0.61	0.15	0.82	0.22	0.49	0.44	0.74	0.40	0.26	0.51

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Chr	Position	SNP	Gene	Trait	P-value												
					(71)												
4	89777081	rs6830970	*FAM13A*	FEV_1/FVC	1.9×10^{-8} (9)	0.59	0.92	0.19	0.056	0.24	0.10	0.26	0.41	0.44	0.88	0.48	0.52
4	89815695	rs13110699	*FAM13A*	FEV_1/FVC	7.9×10^{-15} (75)	0.79	0.64	0.82	0.92	0.86	0.88	0.30	0.66	0.22	0.26	0.79	0.21
4	89869332	rs2869967	*FAM13A*	FEV_1/FVC	1.6×10^{-8} (9)	0.44	0.71	0.44	0.049	0.15	0.13	0.35	0.65	0.32	0.72	0.24	0.23
4	106841962	rs6856422	*NPNT*	FEV_1/FVC	1.5×10^{-23} (70)	0.33	0.96	0.050	0.093	0.51	0.065	0.87	0.65	0.25	0.17	0.53	0.22
4	145434584	rs1032295	*HHIP*	FEV_1/FVC	4.4×10^{-15} (9)	0.68	0.71	0.11	0.47	0.73	0.12	0.92	0.90	0.99	0.73	0.71	0.93
4	145436324	rs12504628	*HHIP*	FEV_1/FVC	6.5×10^{-13} (72)	0.64	0.53	0.018	0.35	0.63	0.023	0.58	0.62	0.86	0.85	0.93	0.97
4	145485738	rs1980057	*HHIP*	FEV_1/FVC	3.2×10^{-20} (9)	0.34	0.87	0.013	0.29	0.64	0.014	0.92	0.92	0.99	0.97	0.93	1.00
5	52195033	rs1551943	*ITGA1*	FEV_1/FVC	1.9×10^{-18} (75)	0.12	0.40	0.075	0.27	0.93	0.13	0.95	0.98	0.99	1.00	0.99	1.00
5	95036700	rs153916	*SPATA9*	FEV_1/FVC	2.1×10^{-8} (73)	0.19	0.24	0.042	0.12	0.15	0.29	0.52	0.35	0.54	0.96	0.77	0.80
5	131788334	rs7713065	*C5orf56*	FEV_1/FVC	2.8×10^{-11} (75)	0.34	0.86	0.085	0.012	0.086	0.028	0.66	0.55	0.79	0.19	0.18	0.38
5	147842353	rs11168048	*HTR4*	FEV_1/FVC	1.1×10^{-11} (9)	1.1×10^{-3}	9.9×10^{-3}	2.2×10^{-3}	0.062	0.64	0.016	0.035	0.016	0.052	0.63	0.55	0.84
5	147844392	rs7735184	*HTR4*	FEV_1/FVC	6.2×10^{-11} (9)	7.8×10^{-4}	6.4×10^{-3}	1.7×10^{-3}	0.051	0.57	0.015	0.026	0.011	0.039	0.56	0.50	0.79
5	156810072	rs10515750	*CYFIP2*	FEV_1/FVC	5.3×10^{-13} (75)	0.98	0.48	0.15	0.32	0.94	0.20	0.61	0.77	0.13	0.15	0.60	0.15
5	156932376	rs2277027	*ADAM19*	FEV_1/FVC	9.9×10^{-11} (9)	0.87	0.29	4.2×10^{-3}	0.51	0.30	5.0×10^{-3}	0.59	0.56	0.85	0.56	0.53	0.82
5	156936364	rs1422795	*ADAM19*	FEV_1/FVC	2.6×10^{-10} (9)	0.90	0.26	3.3×10^{-3}	0.51	0.29	4.1×10^{-3}	0.56	0.52	0.81	0.54	0.51	0.80
6	22017738	rs1928168	*LINC00340*	FEV_1/FVC	6.7×10^{-14} (71)	0.063	0.24	0.058	0.11	0.54	0.091	0.42	0.53	0.69	0.064	0.070	0.16
6	22021373	rs9350408		FEV_1/FVC	7.5×10^{-14} (71)	0.25	0.46	0.37	0.52	0.99	0.48	0.42	0.34	0.63	0.20	0.11	0.27
6	31556155	rs28986170	*LST1*	FEV_1/FVC	1.6×10^{-10} (75)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
6	31568469	rs2857595	*NCR3*	FEV_1/FVC	2.3×10^{-10} (73)	0.067	0.049	0.14	0.21	0.14	0.34	0.25	0.090	0.14	0.54	0.78	0.74

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6	32124424	rs10947233	*PPT2*	FEV$_1$/FVC	6.7×10^{-12} (9)	0.99	0.86	0.93	0.34	0.18	0.39	0.18	0.74	0.047	0.18	0.82	0.093
6	32151443	rs2070600	*AGER*	FEV$_1$/FVC	3.1×10^{-15} (9, 72)	0.56	0.65	0.83	0.34	0.14	0.29	0.38	0.89	0.052	0.14	0.73	0.074
6	32680576	rs7764819	*HLA-DQB1/ HLA-DQA2*	FEV$_1$/FVC	4.4×10^{-9} (4)	0.68	0.28	0.15	0.27	0.71	0.26	0.85	0.92	0.97	0.28	0.22	0.48
6	67863782	rs9351637	*SLC25A51P1 /BAI3*	FEV$_1$/FVC	2.9×10^{-8} (71)	0.54	0.78	0.59	0.90	0.74	0.67	0.20	0.76	0.027	0.23	0.90	0.036
6	73670095	rs141651520	*KCNQ5*	FEV$_1$/FVC	9.9×10^{-18} (75)	0.89	0.86	0.67	0.76	0.85	0.81	0.45	0.40	0.70	0.89	0.92	0.97
6	109268050	rs2798641	*ARMC2*	FEV$_1$/FVC	8.4×10^{-9} (73)	0.22	0.44	0.28	0.19	0.41	0.34	0.97	0.58	0.39	0.55	0.97	0.54
6	142691549	rs11155242	*GPR126*	FEV$_1$/FVC	9.1×10^{-9} (9)	0.061	0.10	0.17	0.10	0.18	0.26	0.26	0.21	0.45	0.34	0.26	0.53
6	142707133	rs6937121	*GPR126*	FEV$_1$/FVC	2.5×10^{-9} (9)	0.37	0.75	0.27	0.30	0.69	0.35	0.49	0.50	0.78	0.95	0.81	0.93
6	142750516	rs3817928	*GPR126*	FEV$_1$/FVC	2.6×10^{-10} (9)	0.13	0.23	0.27	0.088	0.18	0.23	0.37	0.32	0.61	0.24	0.16	0.38
6	142777064	rs7776375	*GPR126/ HIVEP2*	FEV$_1$/FVC	1.3×10^{-9} (9)	0.40	0.69	0.42	0.41	0.74	0.55	0.36	0.39	0.66	0.99	0.78	0.88
6	142838173	rs148274477	*GPR126*	FEV$_1$/FVC	9.6×10^{-26} (70)	0.30	0.29	0.56	0.81	0.84	0.96	0.091	0.17	0.20	0.16	0.25	0.22
7	7286445	rs10246303	*C1GALT1*	FEV$_1$/FVC	2.4×10^{-8} (75)	0.055	0.075	0.16	0.67	0.95	0.65	0.027	0.022	0.071	0.24	0.23	0.47
7	99635967	rs72615157	*ZKSCAN1*	FEV$_1$/FVC	2.0×10^{-9} (75)	0.72	0.81	0.90	0.45	0.24	0.43	0.86	0.76	0.90	0.42	0.42	0.71
7	146651409	rs1404154	*CNTNAP2*	FEV$_1$/FVC	2.8×10^{-8} (71)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
9	23588583	rs10965947	*FLJ35282/ ELAVL2*	FEV$_1$/FVC	2.7×10^{-9} (71)	0.18	0.51	0.13	0.080	0.44	0.078	0.78	0.75	0.28	0.23	0.67	0.23
9	98231008	rs16909898	*PTCH1*	FEV$_1$/FVC	1.8×10^{-8} (9)	0.32	0.12	0.15	0.87	0.42	0.43	0.96	0.39	0.059	0.79	0.092	0.022
9	98256309	rs10512249	*PTCH1*	FEV$_1$/FVC	2.8×10^{-8} (9)	0.35	0.19	0.32	0.51	0.26	0.45	0.71	0.66	0.11	0.73	0.096	0.033
9	109496630	rs2451951	*TMEM38B/ ZNF462*	FEV$_1$/FVC	2.4×10^{-8} (71)	0.30	0.40	0.56	0.34	0.49	0.61	0.30	0.17	0.31	0.38	0.16	0.30
9	119359372	rs34886460	*ASTN2*	FEV$_1$/FVC	4.7×10^{-11} (70)	0.17	0.29	0.30	0.92	0.61	0.43	0.88	0.66	0.68	0.67	0.94	0.70
10	12277992	rs7068966	*CDC123*	FEV$_1$/FVC	6.1×10^{-13}	0.13	0.68	6.6×	0.10	0.96	6.0×	0.72	1.00	0.62	0.95	0.64	0.59

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									10^{-3}			10^{-3}						
					(73)													
10	30267810	rs3847402	SVIL/ KIAA1462	FEV$_1$/FVC	7.7×10^{-11} (75)	0.39	0.43	0.69	0.33	0.41	0.62	0.47	0.73	0.51	0.26	0.53	0.43
10	64916064	rs75159994	JMJD1C	FEV$_1$/FVC	6.1×10^{-9} (71)	0.067	0.35	0.015	0.059	0.62	0.011	0.17	0.70	0.019	0.050	0.54	0.016
10	124273671	rs2293871	HTRA1	FEV$_1$/FVC	1.5×10^{-8} (71)	0.54	0.32	0.44	0.51	0.19	0.28	0.36	0.34	0.63	0.37	0.31	0.59
11	73280955	11:73280955: GA_G	FAM168A	FEV$_1$/FVC	2.7×10^{-8} (71)	0.10	0.11	0.26	0.84	0.45	0.52	0.12	0.19	0.28	0.98	0.58	0.53
12	57527283	rs11172113	LRP1	FEV$_1$/FVC	1.2×10^{-8} (73)	4.1×10^{-3}	0.030	6.7×10^{-3}	0.60	0.39	0.033	0.047	0.18	0.054	0.40	0.86	0.15
12	95554771	rs113745635	FGD6	FEV$_1$/FVC	8.5×10^{-18} (75)	0.91	0.62	0.25	0.25	0.70	0.25	0.82	0.96	0.77	0.11	0.15	0.27
12	96271428	rs1036429	CCDC38	FEV$_1$/FVC	2.3×10^{-11} (73)	0.44	0.35	0.62	0.57	0.42	0.70	0.65	0.71	0.099	0.92	0.26	0.067
14	54410919	rs4444235	DDHD1\ MIR5580	FEV$_1$/FVC	4.0×10^{-8} (71)	0.18	0.61	0.065	0.042	0.32	0.050	0.52	0.85	0.47	0.068	0.14	0.19
14	84309664	rs1698268	LINC01467/L INC00911	FEV$_1$/FVC	3.2×10^{-8} (75)	0.80	0.85	0.96	0.44	0.24	0.44	0.73	0.80	0.92	0.62	0.35	0.54
15	41977690	rs72724130	MGA	FEV$_1$/FVC	9.6×10^{-10} (75)	0.45	0.36	0.63	0.30	0.14	0.30	0.81	0.81	0.44	0.54	0.15	0.16
15	50555681	rs180930492	HDC	FEV$_1$/FVC	2.6×10^{-9} (71)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
15	71645120	rs12899618	THSD4	FEV$_1$/FVC	7.2×10^{-15} (72)	0.20	0.53	0.14	0.52	0.76	0.19	0.73	0.87	0.86	0.99	0.87	0.95
15	71788387	rs12591467	THSD4	FEV$_1$/FVC	5.7×10^{-10} (75)	0.97	0.87	0.87	0.24	0.28	0.49	0.32	0.17	0.31	0.15	0.034	0.079
15	84261689	rs66650179	SH3GL3	FEV$_1$/FVC	3.7×10^{-12} (75)	0.22	0.27	0.46	0.46	0.56	0.65	0.26	0.27	0.52	0.049	0.050	0.14
16	10706328	rs12149828	EMP2/ TEKT5	FEV$_1$/FVC	7.7×10^{-10} (70)	9.6×10^{-3}	0.023	0.031	0.16	0.44	0.26	0.058	0.038	0.12	0.37	0.30	0.59
16	58075282	rs12447804	MMP15	FEV$_1$/FVC	3.6×10^{-8} (73)	0.052	0.17	0.078	0.13	0.48	0.16	0.99	0.73	0.66	0.37	0.17	0.35
16	66060569	rs144296676	LOC283867/ CDH5	FEV$_1$/FVC	5.4×10^{-9} (71)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
16	75390316	rs2865531	CFDP1	FEV$_1$/FVC	1.8×10^{-11} (73)	0.34	0.98	0.025	0.30	0.78	0.039	0.53	0.80	0.56	0.56	0.91	0.62
17	28263980	rs62070270	EFCAB5	FEV$_1$/FVC	7.3×10^{-18} (75)	0.28	0.34	0.56	0.90	0.65	0.78	0.58	0.80	0.69	0.99	0.61	0.60

17	36886828	rs11658500	*CISD3*	FEV$_1$/FVC	7.2×10^{-11} (75)	0.034	0.12	0.054	0.01	0.04	0.02	0.13	0.20	0.31	0.084	0.12	0.22
19	31829613	rs9636166	*TSHZ3*	FEV$_1$/FVC	3.3×10^{-9} (71)	0.58	0.74	0.78	0.099	0.13	0.25	0.60	0.51	0.79	0.25	0.17	0.39
19	31846907	rs1353531		FEV$_1$/FVC	4.5×10^{-8} (71)	0.48	0.87	0.34	0.029	0.10	0.079	0.47	0.71	0.55	0.029	0.057	0.091
19	41124155	rs113473882	*LTBP4*	FEV$_1$/FVC	1.0×10^{-12} (70)	0.72	0.59	0.79	0.80	0.77	0.96	0.85	0.49	0.24	0.70	0.92	0.61
19	50213396	rs147472287	*CPT1C*	FEV$_1$/FVC	3.3×10^{-8} (71)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
21	35652239	rs9978142	*MRPS6/ KCNE2*	FEV$_1$/FVC	2.7×10^{-8} (73)	0.56	0.32	0.39	0.83	0.51	0.61	0.082	0.10	0.22	0.46	0.70	0.67
22	20854161	rs4820216	*KLHL22/ MED15*	FEV$_1$/FVC	2.6×10^{-8} (71)	4.1×10^{-3}	0.015	0.013	0.019	0.071	0.060	0.048	0.057	0.14	0.11	0.12	0.27
X	15964845	rs7050036	*APIS2/GRPR*	FEV$_1$/FVC	4.1×10^{-8} (70)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Abbreviations: chr = Chromosome; DHA = Docosahexaenoic acid; DPA = Docosapentaenoic acid; FEV$_1$ = Forced expiratory volume in the first second; FVC = Forced vital capacity; GWAS = Genome-wide association study; int = Interaction; NA = Not available; SNP = Single nucleotide polymorphism.

[*]SNPs with the smallest P values from each locus reported in the prior GWAS analysis are shown and are sorted by the originally indicated PFT measure and then by chromosomal position (NCBI build 37). SNPs that passed the multiple testing correction (*n* of tests = 199, Bonferroni-corrected $P<2.5\times10^{-4}$) are bolded.

[†]Originally reported SNP rs114229351 has merged into rs9275068.

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Table E12. HaploReg v4.1 Functional Annotation of rs11693320 and Variants with $r^2 > 0.8$ in the 1000 Genomes European (EUR) Reference Panel[*]

Chr. 2 position (hg38)	LD (r^2)	LD (D')	Variant	Reference allele	Alternative allele	AFR freq	EUR freq	Enhancer histone marks	Motifs changed	dbSNP functional annotation
114547473	0.8	0.93	rs7581096	C	G	0.59	0.18	GI	HDAC2, Ik-2, NF-AT1, NF-I, Pou2f2, Pou3f3, TATA	intronic
114547629	0.8	0.93	rs7606971	G	T	0.6	0.18	GI	Foxf1, Foxi1, Foxp1	intronic
114548134	0.85	0.98	rs1430112	A	G	0.49	0.19	GI, PANC	ATF2, CEBPA, CEBPB, E4BP4, Evi-1, Rad21	intronic
114548855	0.85	0.98	rs6738538	C	T	0.54	0.19	ESC, GI, PANC		intronic
114549091	0.85	0.98	rs2033305	G	A	0.45	0.81	ESC, IPSC, GI, PANC, LNG, LIV	BDP1, GR, Ik-1, Ik-2, Ik-3, Pax-4	intronic
114549684	0.85	0.98	rs201802986	A	AG	0.17	0.19	BLD, GI, LNG, LIV		intronic
114549695	0.83	0.98	rs66601344	GAAAT	G	0.45	0.81	BLD, GI, LNG, LIV	Dbx1, Evi-1, Foxd3, Foxi1, Foxj2, Foxk1, Foxl1, Foxo, Foxp1, HDAC2, Hoxb9, Irf, Nkx6-2, Pou1f1, TATA, Zfp105, p300	intronic
114550803	0.83	0.95	rs13008052	G	A	0.16	0.18	GI	FXR, GR	intronic
114552197	0.84	0.96	rs4289198	G	A	0.15	0.18	LIV	Irf	intronic
114552344	0.84	0.96	rs5833551	GT	G	0.45	0.82		DBP, Smad3	intronic
114552481	0.84	0.96	rs2082131	C	T	0.35	0.18		Cdc5	intronic
114553326	0.84	0.96	rs11886546	A	G	0.15	0.18		HNF1, Ncx	intronic
114557050	0.86	0.98	rs12711799	G	A	0.45	0.81		HMG-IY	intronic
114562002	0.86	0.98	rs1864437	A	G	0.58	0.19			intronic
114562416	0.86	0.98	rs1367183	G	A	0.54	0.19		Arid3a, Dbx1, HP1-site-factor, Lhx3, Ncx, Pou2f2, Pou3f4, Pou5f1, Sox, TATA	intronic
114563156	0.86	0.98	rs1835330	A	G	0.59	0.19		FXR, HDAC2, HNF4, NR4A, RAR, RXRA	intronic
114566124	0.86	0.98	rs35463802	G	C	0.21	0.19	GI	HDAC2, Pou6f1, Spz1	intronic
114567030	0.86	0.98	rs11683255	T	C	0.28	0.19	ESDR	ZBTB33	intronic
114568698	0.85	0.97	rs6746835	G	A	0.58	0.19	BRN	Foxa, Foxd1, Foxf2, Foxi1, HDAC2, Homez, TCF12, p300	intronic
114573143	1	1	rs6735899	C	T	0.39	0.83		ERalpha-a, NRSF	intronic
114574293	1	1	rs11693320	A	G	0.21	0.17		Glis2	intronic

114574534	1	1	rs11694667	T	G	0.18	0.17		HNF1, PLZF	intronic
114576974	0.98	1	rs1835329	C	T	0.59	0.17		Isl2	intronic
114579673	0.96	0.99	rs10496466	G	A	0.14	0.17			intronic

Abbreviations: AFR = African populations from 1000 Genomes; BLD = Blood tissue; BRN = Brain tissue; chr = Chromosome; dbSNP = Single Nucleotide Polymorphism database; ESC = Embryonic stem cells; ESDR = ESC-derived cells; EUR = European populations from 1000 Genomes; freq = Frequency; GENCODE = Reference human genome annotation for the ENCODE project; GI = Gastrointestinal tissue; IPSC = Induced pluripotent stem cells; LD = Linkage disequilibrium; LIV = Liver tissue; LNG = Lung tissue; PANC = Pancreas tissue.

*All variants are annotated to the *DPP10* gene.

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Table E13. *DPP10* SNPs Implicated at $P_{2df} < 5 \times 10^{-6}$ in Our Cross-Ancestry Genome-Wide Joint 2df Meta-Analysis of FVC with DHA Interaction (Discovery N=11,962) and Tested for Association in Prior HapMap-Imputed GWAS Analyses of FVC or DHA in Cohorts of European Ancestry from the CHARGE Consortium[*]

SNP and coded allele	Effect allele freq[†]	r^2 / D' with rs11693320[‡] in 1000 Genomes European (EUR) panel	r^2 / D' with rs11693320[‡] in 1000 Genomes African (AFR) panel	Joint 2df meta-analysis of FVC, accounting for DHA interaction (N=11,962)		GWAS meta-analysis of FVC (N=52,253) (77)		GWAS meta-analysis of DHA (N=8,866) (69)	
				β_{2df} direction	P_{2df}	β direction	P	β direction	P
rs1835329-C	0.78	0.99 / 1	0.17 / 0.99	-	5.0×10^{-8}	-	0.087	+	0.57
rs6746835-G	0.77	0.85 / 0.96	0.15 / 0.90	-	1.2×10^{-7}	-	0.060	+	0.55
rs1864437-A	0.77	0.85 / 0.97	0.14 / 0.88	-	1.2×10^{-7}	-	0.085	+	0.64
rs2082131-C	0.79	0.85 / 0.96	0.09 / 0.44	-	1.3×10^{-7}	-	0.100	+	0.63
rs6738538-C	0.77	0.87 / 0.99	0.04 / 0.42	-	1.4×10^{-7}	-	0.083	+	0.66
rs1367183-G	0.77	0.85 / 0.96	0.05 / 0.46	-	1.6×10^{-7}	-	0.091	+	0.55
rs11683255-T	0.80	0.88 / 0.99	0.39 / 0.82	-	1.7×10^{-7}	-	0.085	+	0.55
rs2033305-A	0.77	0.87 / 0.99	0.03 / 0.36	-	1.7×10^{-7}	-	0.080	+	0.64
rs1430112-A	0.77	0.88 / 0.99	0.01 / 0.23	-	4.9×10^{-7}	-	0.083	+	0.71
rs10496466-G	0.83	0.98 / 0.99	0.46 / 0.80	-	1.2×10^{-6}	-	0.082	+	0.71
rs7581096-C	0.76	NA[§]	NA[§]	-	1.3×10^{-6}	-	0.075	+	0.68

Abbreviations: DHA = Docosahexaenoic acid; freq = Frequency; FVC = Forced vital capacity; GWAS = Genome-wide association study; NA = Not available; SNP = Single nucleotide polymorphism.
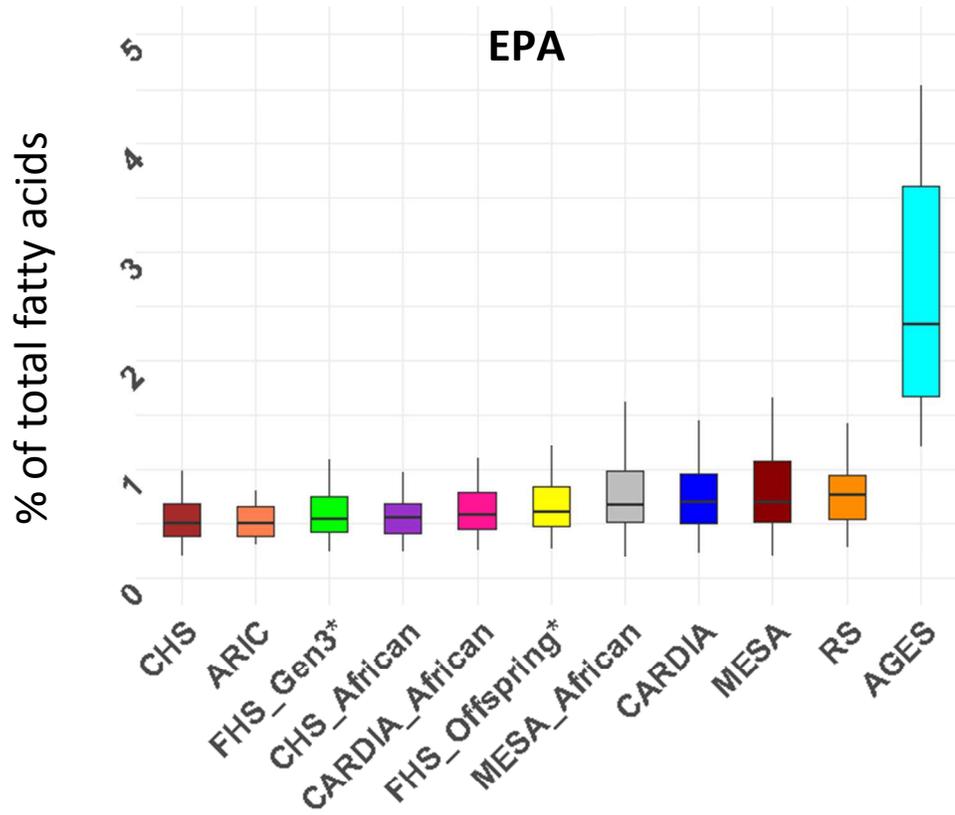
[*]The SNPs, which are all located in the same intron as the 1000 Genomes-imputed SNP rs11693320, are sorted by P_{2df} values. Linkage disequilibrium is presented with the top *DPP10* SNP rs11693320. Linkage disequilibrium estimates with rs11693320 correspond to 1000 Genomes phase 3 panels of European (EUR) or African (AFR) ancestry, as computed in LDlink (78).

[†]Coded allele frequency weighted by sample size of cohorts in the joint 2df meta-analysis.

[‡]As a 1000 Genomes-imputed SNP, rs11693320 was not tested in the prior HapMap-based GWAS of FVC or DHA.

[§]NA, not available. Linkage disequilibrium estimates were not computed due to rs7581096 being a multi-allelic SNP.

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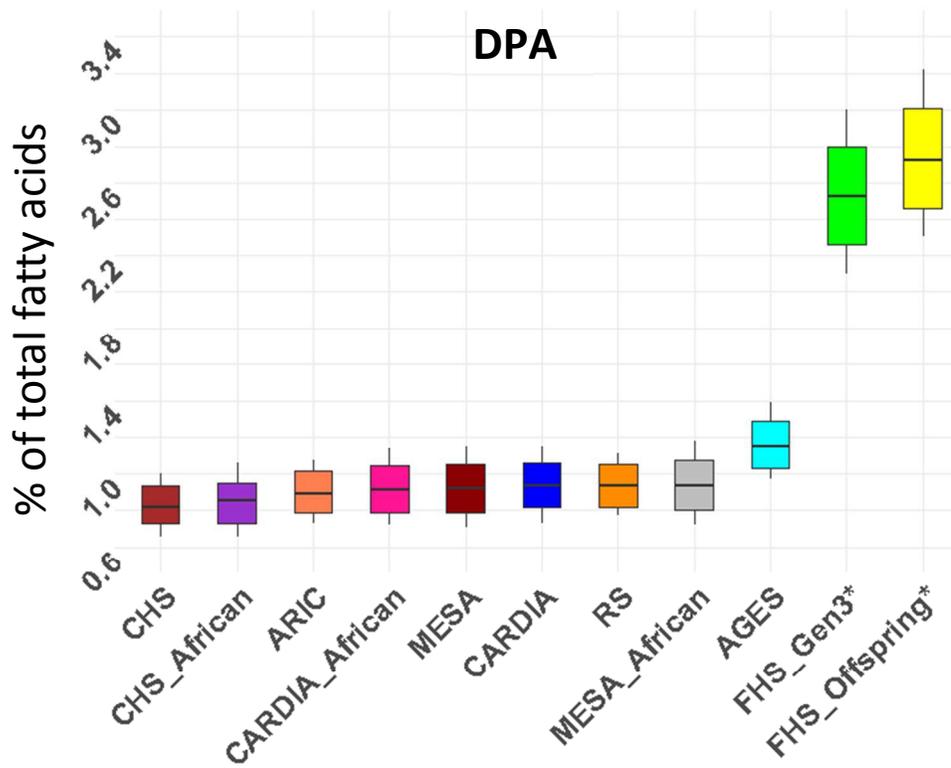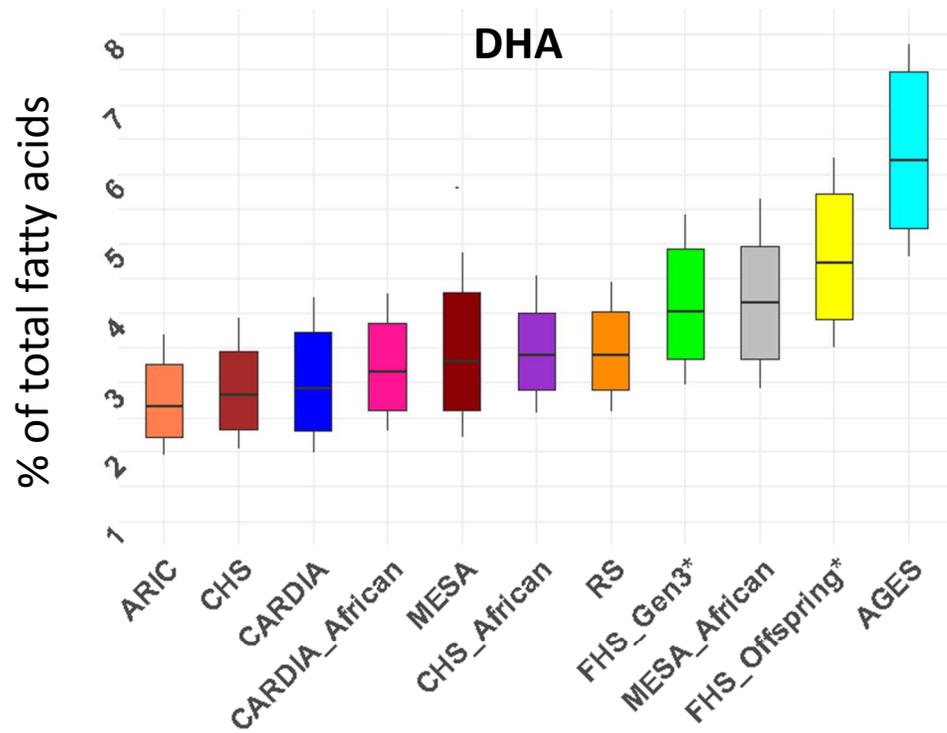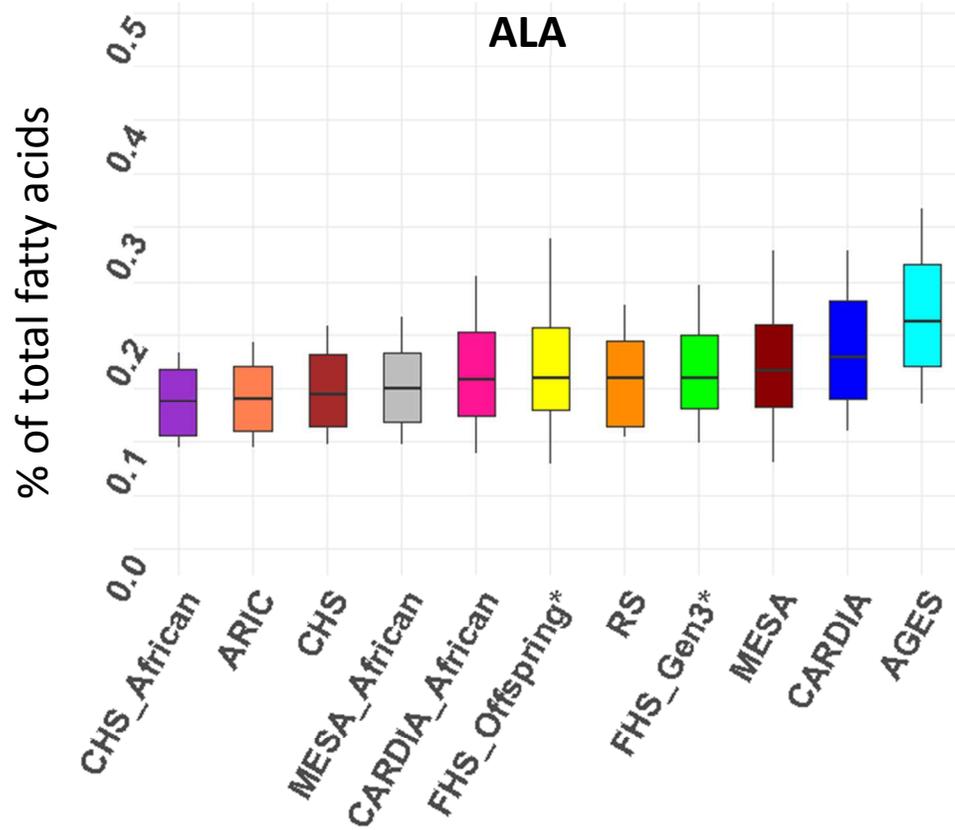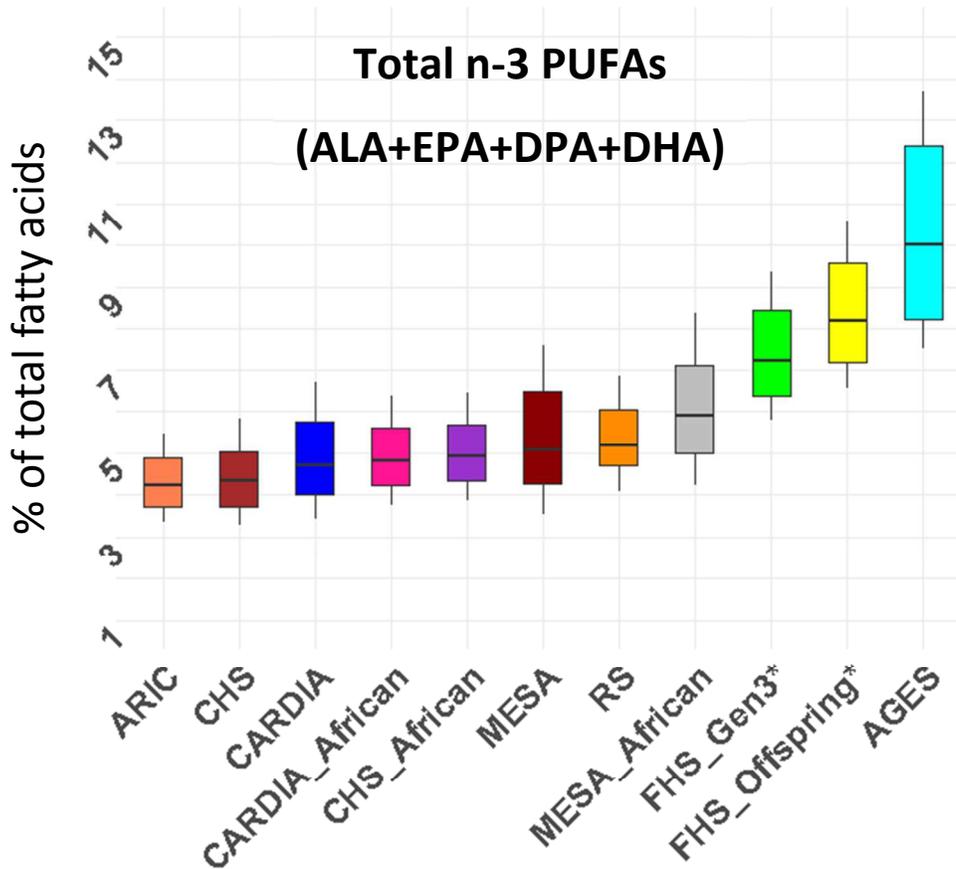
Figure E1. Distribution of Omega-3 Fatty Acid Biomarkers in Each Cohort. The middle bar is the median of each n-3 PUFA biomarker; the lower and upper bars of the box represent the 25th and 75th percentile values, respectively, of each n-3 PUFA biomarker; the minimum and maximum of the whisker were calculated as mean - SD, and mean + SD, respectively. Each cohort represents the European ancestry participants in that cohort, unless otherwise indicated. *FHS has omega-3 fatty acid biomarkers measured in red blood cells, rather than plasma phospholipids.

Abbreviations: AGES = Age, Gene, Environment, Susceptibility Study – Reykjavik; ALA = Alpha-linolenic acid; ARIC = Atherosclerosis Risk in Communities; CARDIA = Coronary Artery Risk Development in Young Adults; CHS = Cardiovascular Health Study; DHA = Docosahexaenoic acid; DPA = Docosapentaenoic acid; EPA = Eicosapentaenoic acid; FHS (Offspring) = Framingham Heart Study – the Offspring Cohort; FHS (Gen3) = Framingham Heart Study – the Generation 3 Cohort; MESA= Multi-Ethnic Study of Atherosclerosis; n-3 PUFA = Omega-3 poly-unsaturated fatty acid; RS = Rotterdam Study; SD = Standard deviation.

A   **DPA-FVC**   β [95% CI   ]

AGES_EA (N = 424)   41.3 [-215.5, 298.1]
ARIC_EA (N = 3252)   254.2 [145.1, 363.2]
CARDIA_AA (N = 1454)   -29.8 [-158.6, 99.1]
CARDIA_EA (N = 1758)   35.4 [-83.9, 154.8]
CHS_AA (N = 242)   155.9 [-156.2, 467.9]
CHS_EA (N = 1687)   192.7 [42.0, 343.4]
MESA_AA (N = 797)   -12.2 [-165.3, 140.8]
MESA_EA (N = 1140)   145.4 [3.8, 287.0]
RS_EA (N = 140)   178.0 [-448.1, 804.2]

Summarized Effect   105.4 [54.1, 156.8]

-500.0   100.0   700.0

B   **DPA-FEV$_1$**   β [95% CI   ]

AGES_EA (N = 424)   80.9 [-144.5, 306.3]
ARIC_EA (N = 3244)   149.1 [52.6, 245.6]
CARDIA_AA (N = 1460)   16.4 [-97.0, 129.8]
CARDIA_EA (N = 1754)   97.3 [-1.1, 195.7]
CHS_AA (N = 243)   2.3 [-242.8, 247.3]
CHS_EA (N = 1690)   211.8 [86.3, 337.2]
MESA_AA (N = 797)   69.5 [-58.9, 197.9]
MESA_EA (N = 1137)   119.3 [-1.6, 240.2]
RS_EA (N = 141)   -169.2 [-726.1, 387.7]

Summarized Effect   104.2 [60.4, 148.0]

-800.0   -400.0   0.0   400.0   800.0

Figure E2. Forest Plots of Meta-Analysis of the DPA Plasma Biomarker on Pulmonary Function (Sensitivity Analysis). Associations are presented for the DPA plasma biomarker on (A) FVC and (B) FEV$_1$. β (unit: mL) denotes the coefficient from the fixed-effects meta-analysis for DPA plasma biomarker on the pulmonary function test measure per 1% (of total fatty acids) increment, with its 95% confidence interval. The vertical line in the center means no effect of the DPA plasma biomarker on pulmonary function; β value to the right of the line means positive effect, while β value to the left of the line means negative effect. The size of black square for each cohort represents the variance of the β coefficient, so that cohorts with smaller variances have larger black squares. Cohorts listed in the forest plots are ordered based on alphabetical order, with sample size of each cohort shown in the parenthesis.

Abbreviations: AA = African ancestry; AGES = Age, Gene, Environment, Susceptibility Study—Reykjavik, Iceland; ARIC = Atherosclerosis Risk in Communities; CARDIA = Coronary Artery Risk Development in Young Adults; CHS = Cardiovascular Health Study; CI = Confidence interval; DPA = Docosapentaenoic acid; EA = European ancestry; FEV$_1$ = Forced expiratory volume in the first second; FVC = Forced vital capacity; MESA = Multi-Ethnic Study of Atherosclerosis; RS = Rotterdam (Netherlands) Study.
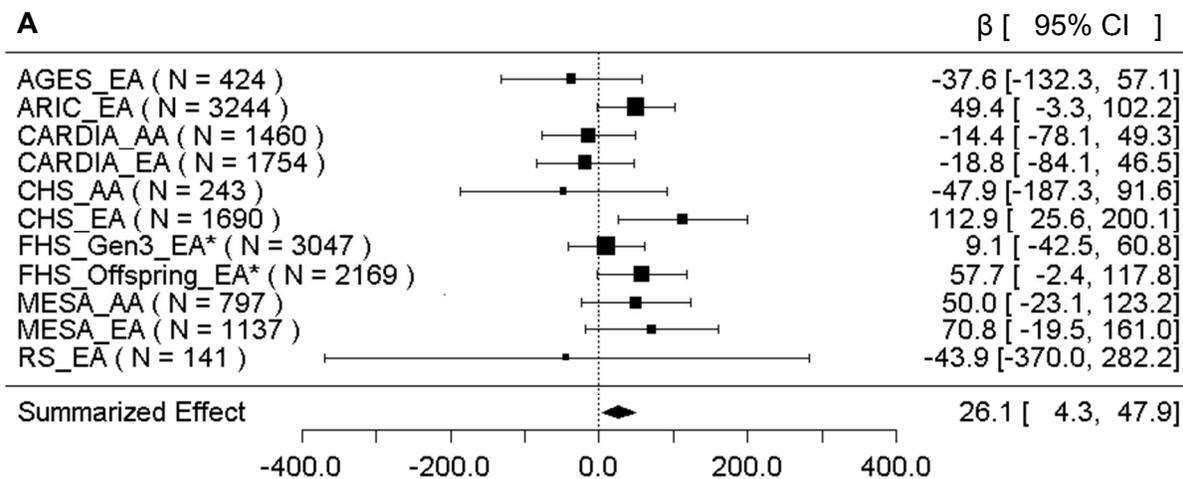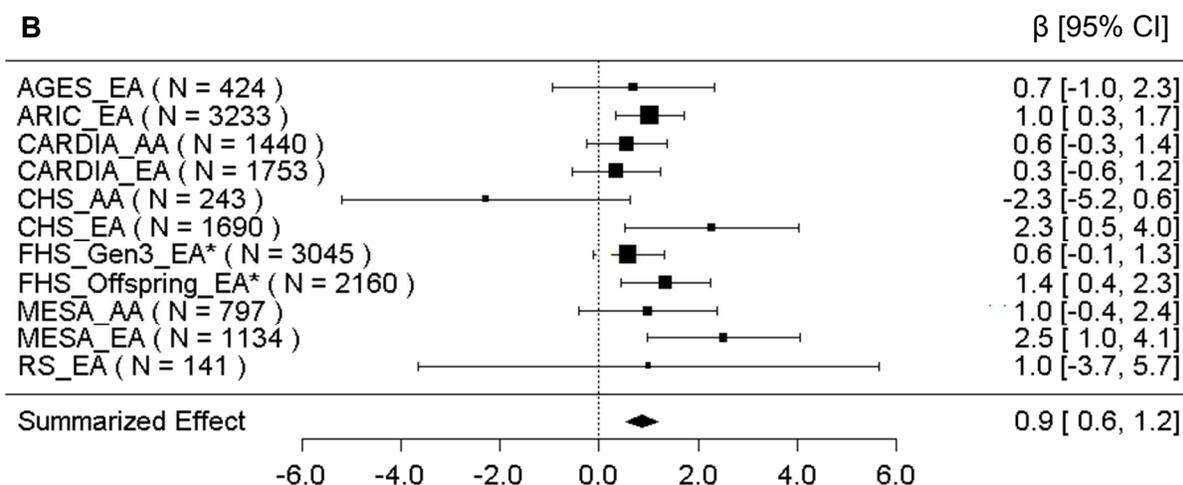
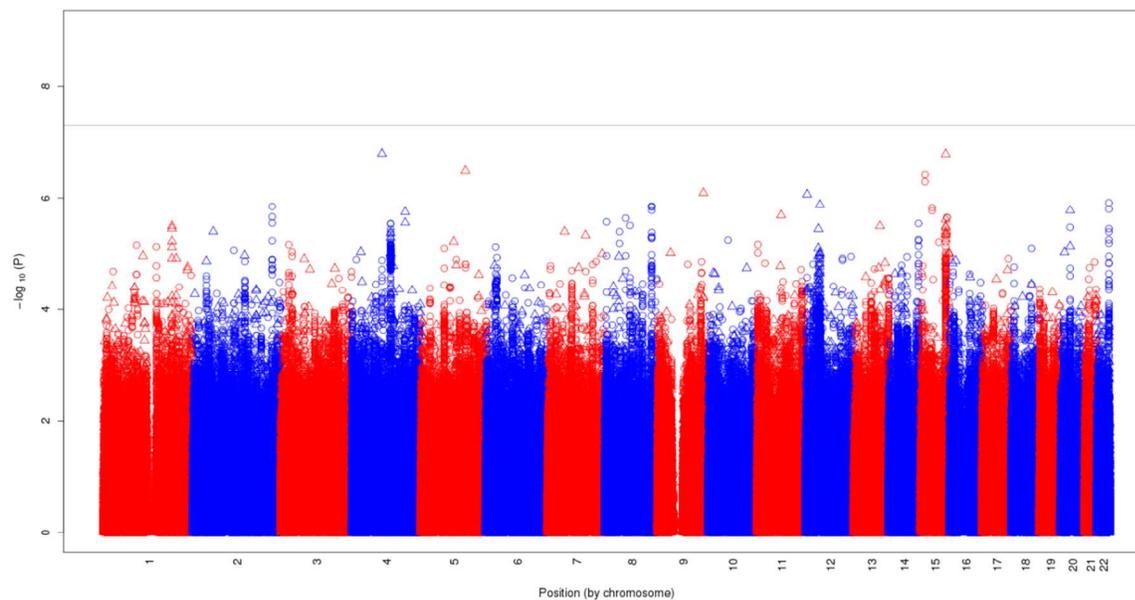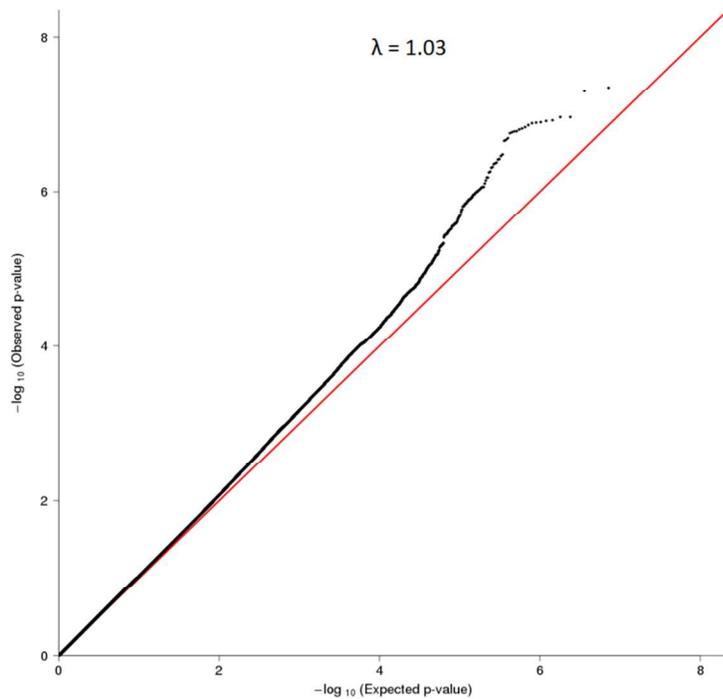AJRCCM Articles in Press. Published on 10-September-2018 as 10.1164/rccm.201802-0304OC

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A   DHA-FVC outcome   β [95% CI]

Cohort	β [95% CI]
AGES_EA (N = 424)	13.3 [-21.0, 47.6]
ARIC_EA (N = 3252)	22.8 [1.4, 44.2]
CARDIA_AA (N = 1454)	20.4 [-7.5, 48.3]
CARDIA_EA (N = 1758)	11.9 [-11.2, 34.9]
CHS_AA (N = 242)	-18.7 [-79.8, 42.5]
CHS_EA (N = 1687)	13.1 [-15.0, 41.2]
FHS_Gen3_EA* (N = 3050)	0.8 [-14.0, 15.6]
FHS_Offspring_EA* (N = 2167)	19.1 [2.7, 35.6]
Summarized Effect	12.2 [4.3, 20.1]

X-axis: -100.0   -40.0   -10.0   20.0   50.0

B   DHA-FEV$_1$ outcome   β [95% CI]

Cohort	β [95% CI]
AGES_EA (N = 424)	13.5 [-16.5, 43.5]
ARIC_EA (N = 3244)	34.2 [15.2, 53.1]
CARDIA_AA (N = 1460)	38.9 [14.4, 63.5]
CARDIA_EA (N = 1754)	13.4 [-5.6, 32.4]
CHS_AA (N = 243)	-29.8 [-77.5, 17.8]
CHS_EA (N = 1690)	12.7 [-10.7, 36.1]
FHS_Gen3_EA* (N = 3047)	11.7 [-1.0, 24.5]
FHS_Offspring_EA* (N = 2169)	20.8 [6.6, 35.0]
Summarized Effect	18.3 [11.5, 25.1]

X-axis: -100.0   -60.0   -20.0   20.0   60.0   100.0

Figure E3. Forest Plots of Meta-Analysis of the DHA Biomarker on Pulmonary Function (Sensitivity Analysis of Measurement Time). Associations are presented for the DHA biomarker on (A) FVC and (B) FEV$_1$, only for the cohorts in which the spirometry test and omega-3 fatty acid biomarkers were measured within an average of one year. β (unit: mL) denotes the coefficient from the fixed-effects meta-analysis for DHA biomarker on the pulmonary function outcome per 1% (of total fatty acids) increment, with its 95% confidence interval. The vertical line in the center means no effect of the DHA biomarker on pulmonary function; β value to the right of the line means positive effect, while β value to the left of the line means negative effect. The size of black square for each cohort represents the variance of the β coefficient, so that cohorts with smaller variances have larger black squares. Cohorts listed in the forest plots are ordered based on alphabetical order, with sample size of each cohort shown in the parenthesis. *FHS has omega-3 fatty acid biomarkers measured in red blood cells, rather than plasma phospholipids.

Abbreviations: AA = African ancestry; AGES = Age, Gene, Environment, Susceptibility Study—Reykjavik, Iceland; ARIC = Atherosclerosis Risk in Communities; CARDIA = Coronary Artery Risk Development in Young Adults; CHS = Cardiovascular Health Study; CI = Confidence interval; DHA = Docosahexaenoic acid; EA = European ancestry; FEV$_1$ = Forced expiratory volume in the first second; FVC = Forced vital capacity.

A

β [95% CI]

AGES_EA (N = 424)	-37.6 [-132.3, 57.1]
ARIC_EA (N = 3244)	49.4 [-3.3, 102.2]
CARDIA_AA (N = 1460)	-14.4 [-78.1, 49.3]
CARDIA_EA (N = 1754)	-18.8 [-84.1, 46.5]
CHS_AA (N = 243)	-47.9 [-187.3, 91.6]
CHS_EA (N = 1690)	112.9 [25.6, 200.1]
FHS_Gen3_EA* (N = 3047)	9.1 [-42.5, 60.8]
FHS_Offspring_EA* (N = 2169)	57.7 [-2.4, 117.8]
MESA_AA (N = 797)	50.0 [-23.1, 123.2]
MESA_EA (N = 1137)	70.8 [-19.5, 161.0]
RS_EA (N = 141)	-43.9 [-370.0, 282.2]
Summarized Effect	26.1 [4.3, 47.9]

-400.0 -200.0 0.0 200.0 400.0

Interaction coefficient of DHA biomarker and current smoking on FEV$_1$

B

β [95% CI]

AGES_EA (N = 424)	0.7 [-1.0, 2.3]
ARIC_EA (N = 3233)	1.0 [0.3, 1.7]
CARDIA_AA (N = 1440)	0.6 [-0.3, 1.4]
CARDIA_EA (N = 1753)	0.3 [-0.6, 1.2]
CHS_AA (N = 243)	-2.3 [-5.2, 0.6]
CHS_EA (N = 1690)	2.3 [0.5, 4.0]
FHS_Gen3_EA* (N = 3045)	0.6 [-0.1, 1.3]
FHS_Offspring_EA* (N = 2160)	1.4 [0.4, 2.3]
MESA_AA (N = 797)	1.0 [-0.4, 2.4]
MESA_EA (N = 1134)	2.5 [1.0, 4.1]
RS_EA (N = 141)	1.0 [-3.7, 5.7]
Summarized Effect	0.9 [0.6, 1.2]

-6.0 -4.0 -2.0 0.0 2.0 4.0 6.0

Interaction coefficient of DHA biomarker and current smoking on FEV$_1$/FVC

Figure E4. Forest Plots of the Interaction Meta-Analysis of DHA Biomarker with Current Smoking Status on Pulmonary Function. β denotes the interaction term coefficient of DHA biomarker with current smoking status on (A) FEV$_1$, and (B) FEV$_1$/FVC, compared to never smoking, from the fixed-effects meta-analysis, per 1% (of total fatty acids) increment of DHA biomarker, with its 95% confidence interval. The vertical line in the center means no effect of DHA on the pulmonary function outcome; β value to the right of the line means positive effect, while β value to the left of the line means negative effect. The size of black square for each cohort represents the variance of the β coefficient, so that cohorts with smaller variances have larger black squares. Cohorts listed in the forest plots are ordered based on alphabetical order, with sample size of each cohort shown in the parenthesis. *FHS has omega-3 fatty acid biomarkers measured in red blood cells, rather than plasma phospholipids.

Abbreviations: AA = African Ancestry; AGES = Age, Gene, Environment, Susceptibility Study—Reykjavik, Iceland; ARIC = Atherosclerosis Risk in Communities; CARDIA = Coronary Artery Risk Development in Young

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Adults; CHS = Cardiovascular Health Study; CI = Confidence interval; DHA = Docosahexaenoic acid; EA = European ancestry; FEV_1 = 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; MESA = Multi-Ethnic Study of Atherosclerosis; RS = Rotterdam (Netherlands) Study.

(A)

(B)

Figure E5. **Genome-Wide SNP/Indel Associations with FEV$_1$, Accounting for Interaction with DHA, in Cross-Ancestry Meta-Analysis.** The -log$_{10}$ (meta-analysis P$_{2df}$) for 7.2 million SNPs/indels with minor allele frequency > 5% and imputation quality > 0.3 are plotted against (A) expected P values where the red line depicts the null hypothesis of no association and (B) chromosomal position where the solid black line depicts the genome-wide statistical significance threshold (P < 5×10^{-8}). SNPs/indels failing to achieve minimal frequency and imputation quality in all but one cohort were excluded from results.

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(A)

(B)
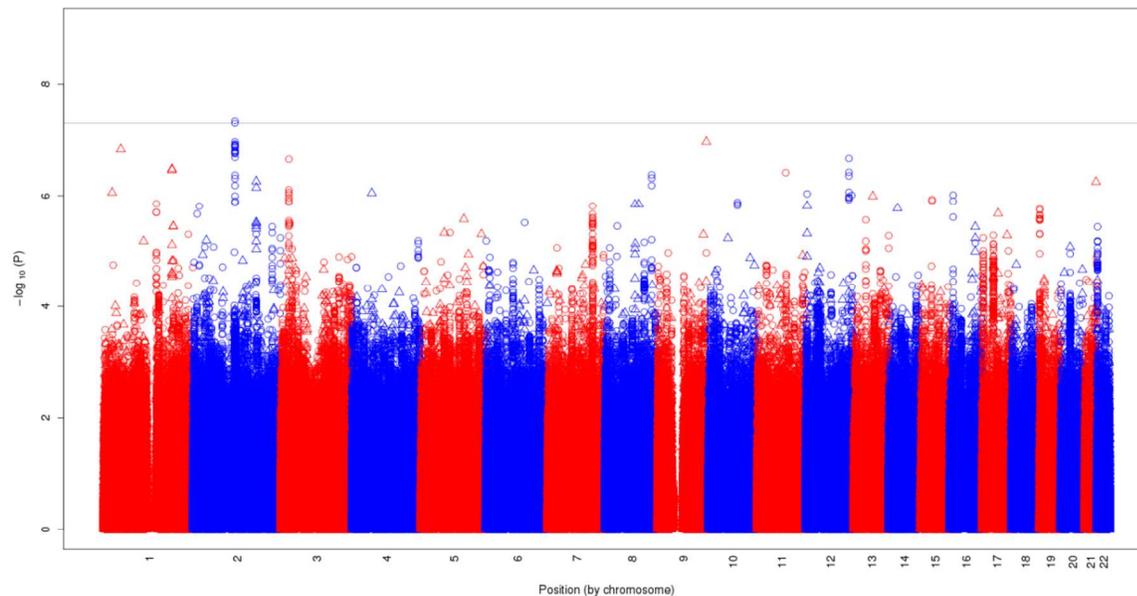
Figure E6. **Genome-Wide SNP/Indel Associations with FVC, Accounting for Interaction with DHA, in Cross-Ancestry Meta-Analysis.** The $-\log_{10}$ (meta-analysis P_{2df}) for 7.2 million SNPs/indels with minor allele frequency > 5% and imputation quality > 0.3 are plotted against (A) expected P values where the red line depicts the null hypothesis of no association and (B) chromosomal position where the solid black line depicts the genome-wide statistical significance threshold ($P < 5 \times 10^{-8}$). SNPs/indels failing to achieve minimal frequency and imputation quality in all but one cohort were excluded from results.

(A)
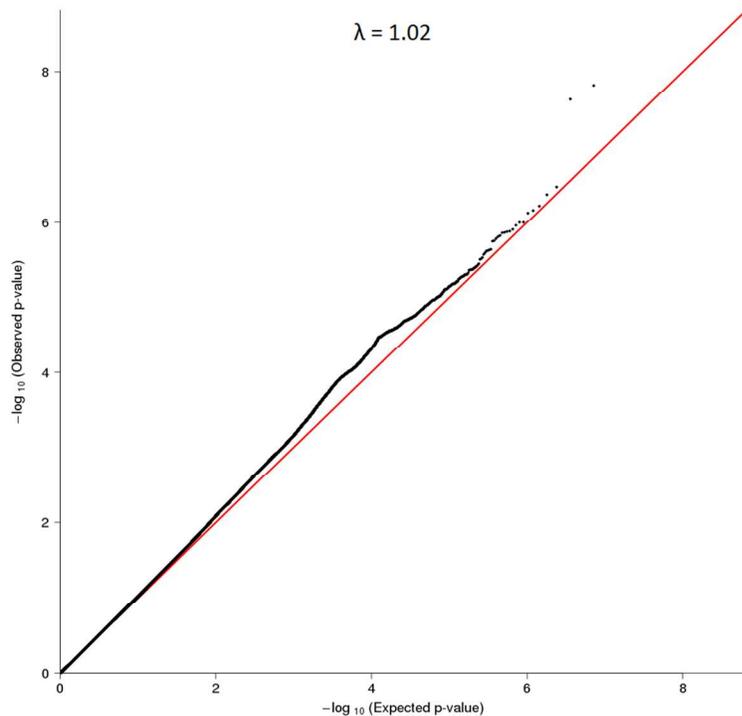
(B)
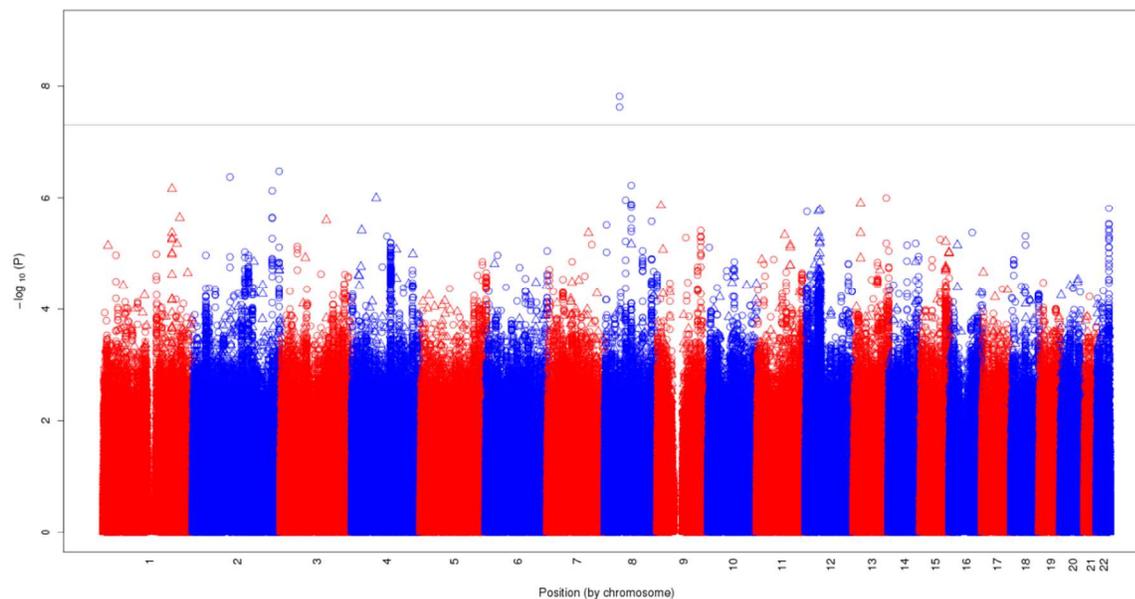
Figure E7. **Genome-Wide SNP/Indel Associations with FEV$_1$, Accounting for Interaction with DPA, in Cross-Ancestry Meta-Analysis.** The -log$_{10}$ (meta-analysis P$_{2df}$) for 7.2 million SNPs/indels with minor allele frequency > 5% and imputation quality > 0.3 are plotted against (A) expected P values where the red line depicts the null hypothesis of no association and (B) chromosomal position where the solid black line depicts the genome-wide statistical significance threshold (P < 5×10^{-8}). SNPs/indels failing to achieve minimal frequency and imputation quality in all but one cohort were excluded from results.

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(A)
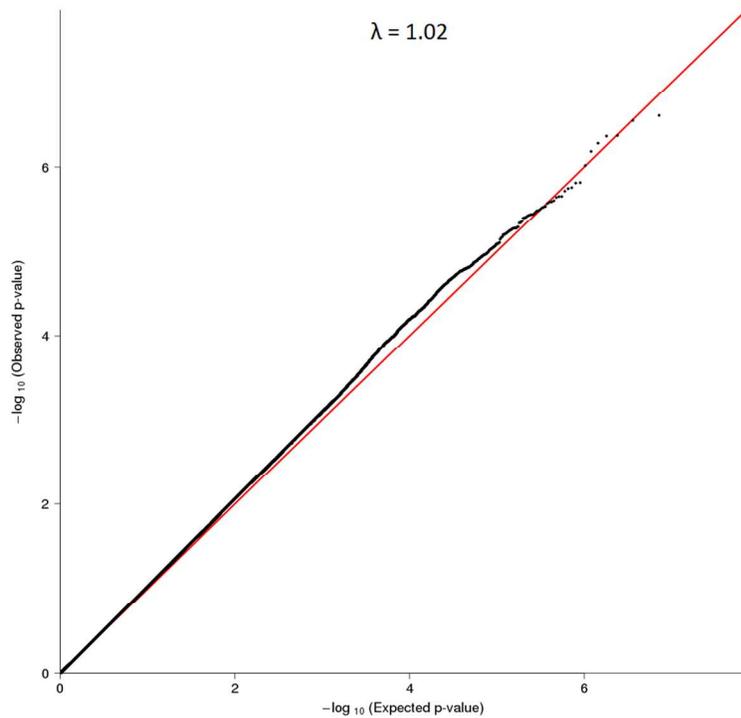
(B)
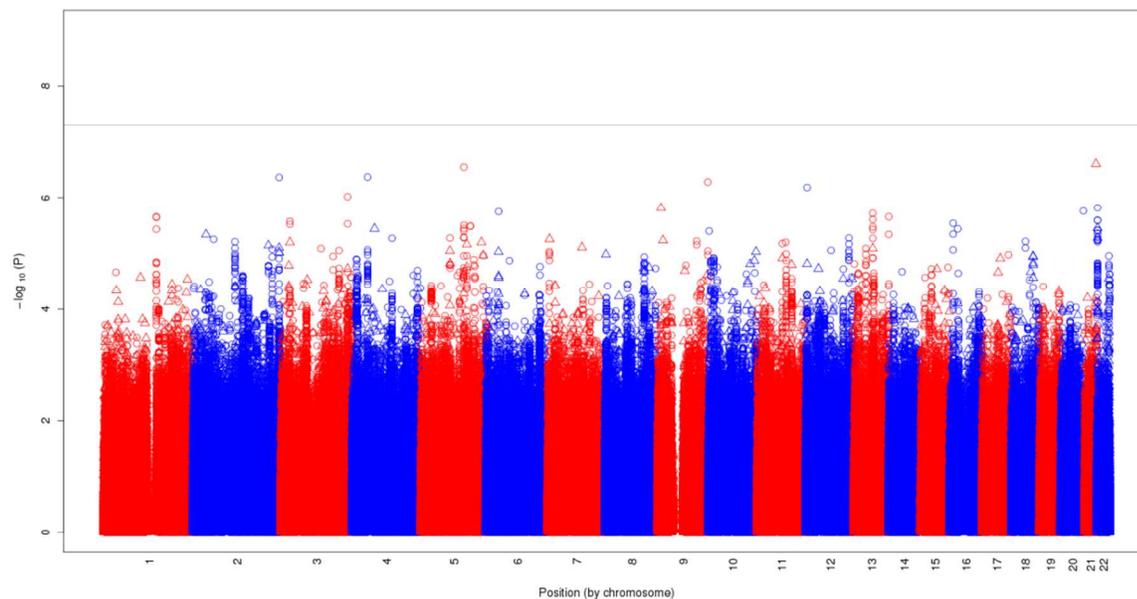
Figure E8. **Genome-Wide SNP/Indel Associations with FVC, Accounting for Interaction with DPA, in Cross-Ancestry Meta-Analysis.** The -$\log_{10}$ (meta-analysis P_{2df}) for 7.2 million SNPs/indels with minor allele frequency > 5% and imputation quality > 0.3 are plotted against (A) expected P values where the red line depicts the null hypothesis of no association and (B) chromosomal position where the solid black line depicts the genome-wide statistical significance threshold ($P < 5×10^{-8}$). SNPs/indels failing to achieve minimal frequency and imputation quality in all but one cohort were excluded from results.

(A)
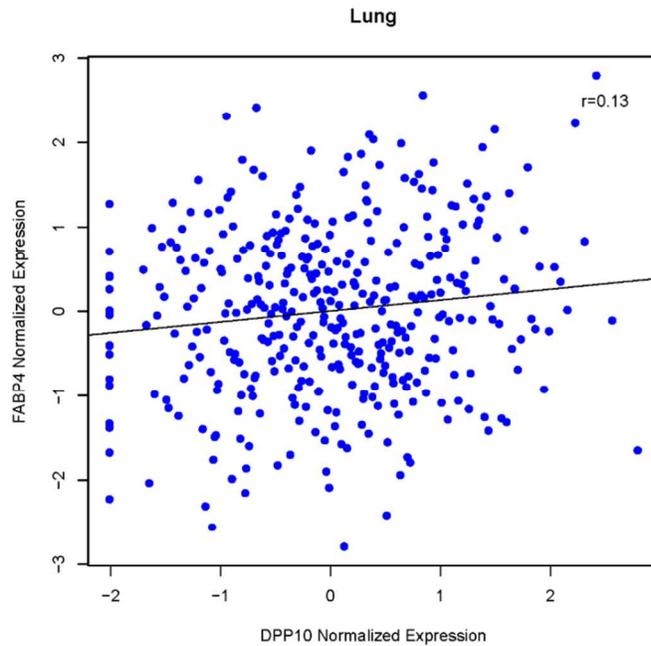
(B)
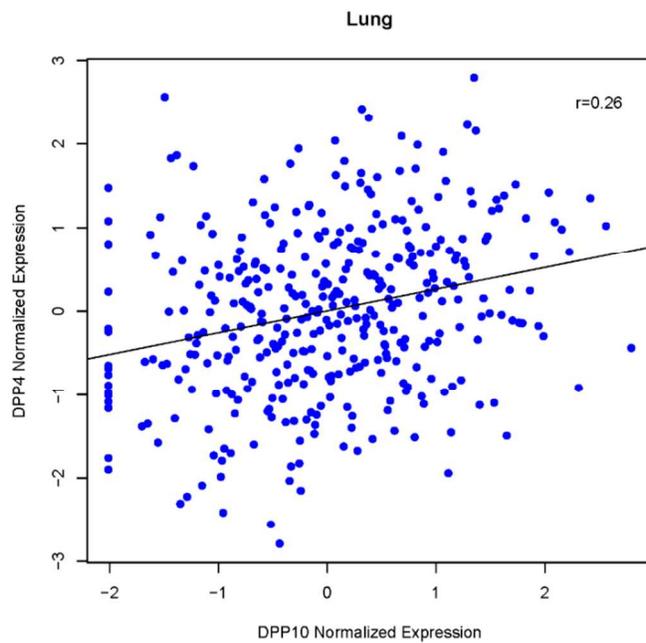
Figure E9. **Co-Expressed Genes with *DPP10* in Lung Tissue.** Scatterplots show the correlation between expression levels of *DPP10* and (A) *FABP4*, as well as (B) *DPP4*. Data are based on GTEx v7 RNA-Seq data (fully processed, filtered and normalized expression data, as previous described (28)). Pearson correlation coefficient, *r*, is shown.

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