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## Supplementary appendix

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# Supplementary Note

## Table of Contents


Individual Study Information……2
Funding and Acknowledgements……..5
Supplementary Methods…….....…11
Supplementary Tables
- Table S1……...……12
- Table S2……...13
- Table S3……...14
- Table S4……...16
- Table S5……...17
- Table S6……...18

Supplementary Figures
- Figure S1……..19
- Figure S2……..20
- Figure S3……..21
- Figure S4……..22
- Figure S5……..23
- Figure S6……..24
- Figure S7……..25
- Figure S8……..27
- Figure S9……..28
- Figure S10……..…..29
- Figure S11……..……..30
- Figure S12……..……..33

References……34

## Individual Study Information

This section describes each study and provides details about measurements and genotyping. All participants gave informed consent and study protocols were approved by local Research Ethics Committees and Institutional Review Boards.

### COPDGene

COPDGene is a multicenter observational study which primarily consists of smokers with and without COPD[1]. Subjects in COPDGene have at least 10 pack-years of smoking (except for a smaller group of nonsmoking controls, who were excluded from the analyses in this manuscript). Illumina (San Diego, CA) performed genotyping on the HumanOmniExpress array. Genotyping at the Z and S alleles was performed in all subjects. Subjects with severe alpha-1 antitrypsin deficiency were excluded. Imputation was performed the Michigan Imputation Server to the Haplotype Resource Consortium[2] and 1000 Genomes Phase I v3 Cosmopolitan reference panels, for whites and African Americans, respectively. Variants with an r2 value of $\leq 0.3$ were removed.

### GenKOLS

The Genetics of Chronic Obstructive Lung Disease (GenKOLS) is a single-center case-control study based in Bergen, Norway[3,4]. Subjects with > 2.5 pack years of smoking history were included; severe alpha-1 antitrypsin deficiency and other lung diseases were excluded. The Regional Committee for Medical Research Ethics (REK Vest), the Norwegian Data Inspectorate and the Norwegian Department of Health approved the case–control study. Written informed consent was obtained from all participants. Genotyping was performed using Illumina HumanHap 550 arrays (Illumina, San Diego, CA). Genotype imputation was the Michigan Imputation Server and Haplotype Resource Consortium[2] reference panel.

### NETT/NAS

The National Emphysema Treatment Trial (NETT) was a multicenter randomized clinical trial comparing lung-volume-reduction surgery and medical therapy for severe emphysema[5]. All subjects in NETT were former smokers with severe COPD ($FEV_1 \leq 45\%$ predicted). The Normative Aging Study (NAS) is a longitudinal study of health and aging[6,7]. We included NAS participants with normal spirometry and at least 10 pack-years of cigarette smoking history as control subjects in NETT/NAS. Genotyping for NETT-NAS was performed using the Illumina Quad 610 array (Illumina, San Diego, CA).[8,9] Imputation was performed using the Michigan Imputation Server and Haplotype Resource Consortium[2] reference panel.

### ECLIPSE

The Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) study was a case-control study of smokers with ≥ 10 pack years of smoking history, aged 40-75 years, and without other respiratory diseases.[10] Genotyping was performed using the Illumina HumanHap 550 V3 (Illumina, San Diego, CA). Subjects and markers with a call rate of < 95% were excluded. Imputation was performed using the Michigan Imputation Server and Haplotype Resource Consortium[2] reference panel.

**MESA**

The Multi-Ethnic Study of Atherosclerosis (MESA) was a longitudinal study of subclinical cardiovascular disease and risk factors that predict progression to clinically overt cardiovascular disease or progression of the subclinical disease.[11] Further details have been previously reported.[12] Genotyping was performed at Affymetrix (Santa Clara, California, USA) and the Broad Institute of Harvard and MIT (Boston, Massachusetts, USA) using the Affymetrix Genome-Wide Human SNP Array 6.0.

**CHS**

The Cardiovascular Health Study (CHS) is a population-based cohort study of risk factors for coronary heart disease and stroke in adults ≥65 years conducted across four field centers.[13] The original predominantly European ancestry cohort of 5,201 persons was recruited in 1989-1990 from random samples of the Medicare eligibility lists; subsequently, an additional predominantly African-American cohort of 687 persons was enrolled in 1992-1993 for a total sample of 5,888. Blood samples were drawn from all participants at their baseline examination and DNA was subsequently extracted from available samples. Genotyping was performed at the General Clinical Research Center's Phenotyping/Genotyping Laboratory at Cedars-Sinai among CHS participants who consented to genetic testing and had DNA available using the Illumina 370CNV BeadChip system (for European ancestry participants, in 2007) or the Illumina HumanOmni1-Quad_v1 BeadChip system (for African-American participants, in 2010). European ancestry participants were excluded from the GWAS study sample due to the presence at study baseline of coronary heart disease, congestive heart failure, peripheral vascular disease, valvular heart disease, stroke or transient ischemic attack or lack of available DNA. Imputation to the HRC r1.1 2016 panel was performed on the Michigan imputation server. SNPs were excluded for variance on the allele dosage ≤0.01. Pulmonary measures were taken at the 1989-1990 examination for the first cohort and at the 1993-1994 examination for the second cohort. CHS was approved by institutional review committees at each field center and individuals in the present analysis had available DNA and gave informed consent including consent to use of genetic information for the study of cardiovascular disease.

**Rotterdam**

The Rotterdam study (RS) is a prospective population-based cohort study conducted in a suburb of Rotterdam, Netherlands.[14] The first cohort (RS-I) enrolled 7,983 participants, aged 55 years and over. The second cohort (RS-II) recruited in 2000. The third cohort (RS-III) consisted of 3,932 participants, aged 45 years and over and was recruited in 2006. A total of 6,291 subjects for RS I, 2,157 for RS II and 3,048 for RS III passed genotyping quality control.

**SPIROMICS**

The Subpopulations and intermediate outcome measures in COPD study (SPIROMICS) study. Participants of the NHLBI SPIROMICS study were 40-80 years of age at baseline with a smoking history ≥20 pack-years. Recruitment included non-smokers, smokers without COPD, mild-moderate COPD, and severe COPD.[15] Genomewide genotyping was performed using the Illumina OmniExpress HumanExome BeadChip using standard techniques in the first 571 subjects with COPD and 175 smoking controls. Imputation was performed against 1000 Genomes reference panels using Impute-v2.30 using a quality cutoff of 0.9.

**KWU**

The KWU data consisted of Koreans who visited Kang-Won National University Hospital and Seoul National University Gangnam Center. All subjects were genotyped by using their blood with the Korea Biobank Array version 1.0 (Affymetrix customized SNP chip).[16] SNPs were excluded if any of the following conditions were satisfied; the genotype call rate was less than 95%; the Hardy-Weinberg equilibrium (HWE) test gave $P < 1\times10^{-5}$; MAFs were less than 0.05. Also, subjects were discarded if X chromosome homozygosity were between 0.2 and 0.8; genotype call rates were < 95%; or heterozygosity rates of SNPs were outside the average of heterozygosity rate ± 3 standard deviations. Then untyped SNPs were imputed using the Michigan imputation server (https://imputationserver.sph.umich.edu). Only 'not European' or 'mixed' population of Haplotype Reference Consortium release v1.1 were used as a reference. Pre-phasing and imputation were conducted with Eagle2[17] and Minimac4[18] respectively. Imputed SNPs were removed if there were duplicated SNPs; missing genotype rates were larger than 0.05; P-values for HWE were less than $1\times10^{-5}$; MAFs were less than 0.05. Also, subjects whose identity-by-descent (IBS) was larger than 0.9 and PC scores were outside the median ± 5×IQR were removed. After quality controls, 794 COPD patients and 1600 normal subjects with 4,922,773 SNPs genotyped were analyzed.

**LHS**

The Lung Health Study (LHS) was initially a randomized clinical trial across 10 clinical centers in North America, that enrolled 5,887 smokers, 35-60 years of age with COPD. Two-thirds were assigned to smoking intervention and one-third to usual care. Further details have been reported.[19,20] Genotyping was performed using Illumina Human660WQuad v.1_A BeadChip. Imputation was performed with the Michigan Imputation Server [18] using the Haplotype Reference Consortium[2] panel. Variants with r2 < 0.5 and minor allele frequency < 1% were removed.

**CAMP**

The Childhood Asthma Management Program (CAMP) study was a randomized, placebo-controlled trial of inhaled anti-inflammatory therapies in 1,041 mild-to-moderate childhood asthmatics with three phases of observational follow-up; follow up phases included at least annual pre- and post-bronchodilator spirometry. 684 participants had follow up spirometry after 23 years, and two independent

investigators classified individuals as having one of four lung function growth and decline patterns: normal growth, normal growth with early decline, reduced growth, and reduced growth with early decline.[21] Genome-wide SNP genotyping was performed using Illumina's HumanHAP550 Genotyping BeadChip (Illumina, Inc., San Diego, CA). Imputation was performed using Markov Chain Haplotyping software (MaCH) [22] and variants with minor allele frequency < 1% were removed.

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**UK Biobank**
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## Supplementary Methods

Derivation of polygenic risk scores

The PRS was penalized using lasso regression. Lasso regression is a form of L1 penalized regression where absolute values of coefficients that are closer to zero are more strongly penalized. As a result, certain coefficients can be shrunk to zero, which provides for a simpler model. The lassosum R package extends this concept. The shrinkage parameter is estimated from the covariance matrix, and the lambda is estimated from the PRS that most strongly correlates with the phenotype in the validation set (i.e. GenKOLS in this study). In addition, this takes into account linkage disequilibrium with a moderate degree of clumping and thresholding.[23]

A clinical risk score (CRS) was derived in UK Biobank. We included participants with ≥ 10 pack-years of smoking history, as this is similar exposure as the COPDGene and ECLIPSE testing cohorts. We then constructed a logistic regression model in which the outcome was moderate-to-severe COPD and the predictors included age, sex, and pack-years of cigarette smoking. This model was used to calculate CRSs in COPDGene and ECLIPSE.

## Supplementary Tables

Table S1: Association of PRS with frequent (> 1 exacerbation in 12 months) and severe exacerbations (exacerbation requiring emergency room visit or hospitalization). Logistic regression models were adjusted for age, sex, pack years of smoking, ± lung function ($FEV_1$ and $FEV_1$/FVC).

| Outcome | Model | *COPDGene* | | *ECLIPSE* | |
|---|---|---|---|---|---|
| | | *OR (95% CI)* | *P* | *OR (95% CI)* | *P* |
| Severe Exacerbations | Adj. (age, sex, pack years) | 1.26 (1.12 - 1.42) | 0.00011 | 1.12 (1.01 - 1.23) | 0.027 |
| | Adj. (age, sex, pack years, lung function) | 0.99 (0.87 - 1.13) | 0.89 | 1.01 (0.9 - 1.12) | 0.92 |
| Frequent Exacerbations | Adj. (age, sex, pack years) | 1.04 (1.02 - 1.05) | 6.80E-07 | 1.03 (1.01 - 1.05) | 0.015 |
| | Adj. (age, sex, pack years, lung function) | 1 (0.98 - 1.01) | 0.5 | 1 (0.97 - 1.02) | 0.66 |

Table S2: Meta-analysis of AUCs in European cohorts comparing models with only combined PRS, only clinical risk factors, and clinical risk factors with combined PRS. The model with both clinical risk factors and PRS had a significantly higher AUC than the model with clinical risk factors alone (p = 1.6e-39). AUCs were meta-analyzed by two methods: (1) inverse variance weighting, and (2) effective sample size weighting.

| *Model* | *AUC weighted by inverse variance (95% CI)* | *AUC weighted by sample size (95% CI)* |
|---|---|---|
| Combined polygenic score (PRS) | 0.67 (0.663-0.681) | 0.66 (0.635-0.687) |
| Risk factors (age, sex, and smoking pack-years) | 0.76 (0.748-0.763) | 0.73 (0.706-0.752) |
| Risk factors and PRS | 0.80 (0.791-0.806) | 0.77 (0.75-0.793) |

Table S3: AUC, confidence intervals, and p-values for each model and comparison in Figure 4.

| *Model* | *Cohort* | *AUC* | *AUC lower 95% CI* | *AUC upper 95% CI* | *P (risk factors vs PRS)* | *P (PRS+risk factors vs. risk factors)* |
|---|---|---|---|---|---|---|
| Combined polygenic score (PRS) | COPDGene NHW | 0.689 | 0.673 | 0.704 | NA | NA |
| Risk factors (age, sex, and smoking pack-years) | COPDGene NHW | 0.764 | 0.75 | 0.778 | 2.69E-13 | 2.70E-25 |
| Risk factors and PRS | COPDGene NHW | 0.811 | 0.798 | 0.823 | NA | NA |
| Combined polygenic score (PRS) | ECLIPSE | 0.713 | 0.671 | 0.756 | NA | NA |
| Risk factors (age, sex, and smoking pack-years) | ECLIPSE | 0.824 | 0.788 | 0.86 | 5.41E-05 | 0.0042 |
| Risk factors and PRS | ECLIPSE | 0.852 | 0.818 | 0.887 | NA | NA |
| Combined polygenic score (PRS) | NETT/NAS | 0.745 | 0.711 | 0.779 | NA | NA |
| Risk factors (age, sex, and smoking pack-years) | NETT/NAS | 0.899 | 0.879 | 0.92 | 9.12E-19 | 0.0104 |
| Risk factors and PRS | NETT/NAS | 0.912 | 0.893 | 0.931 | NA | NA |
| Risk factors (age, sex, and smoking pack-years) | CHS EA | 0.758 | 0.734 | 0.781 | 1.63E-06 | 6.66E-06 |
| Combined polygenic score (PRS) | CHS EA | 0.669 | 0.643 | 0.695 | NA | NA |
| Risk factors and PRS | CHS EA | 0.798 | 0.777 | 0.82 | NA | NA |
| Risk factors (age, sex, and smoking pack-years) | MESA NHW | 0.741 | 0.703 | 0.779 | 0.0215 | 0.000603 |
| Combined polygenic score (PRS) | MESA NHW | 0.673 | 0.632 | 0.714 | NA | NA |
| Risk factors and PRS | MESA NHW | 0.794 | 0.76 | 0.828 | NA | NA |
| Risk factors (age, sex, and smoking pack-years) | LHS | 0.576 | 0.553 | 0.598 | 0.542 | 3.47E-05 |
| Combined polygenic score (PRS) | LHS | 0.585 | 0.563 | 0.608 | NA | NA |
| Risk factors and PRS | LHS | 0.617 | 0.594 | 0.639 | NA | NA |
| Risk factors (age, sex, and smoking pack-years) | SPIROMICS NHW | 0.666 | 0.637 | 0.694 | 0.425 | 3.16E-09 |
| Combined polygenic score (PRS) | SPIROMICS NHW | 0.682 | 0.654 | 0.71 | NA | NA |

| | | | | | | |
|---|---|---|---|---|---|---|
| | SPIROMICS | | | | | |
| Risk factors and PRS | NHW | 0.742 | 0.716 | 0.768 | NA | NA |
| Risk factors (age, sex, and smoking pack-years) | RS1 | 0.716 | 0.67 | 0.763 | 0.494 | 0.0013 |
| Combined polygenic score (PRS) | RS1 | 0.692 | 0.642 | 0.741 | NA | NA |
| Risk factors and PRS | RS1 | 0.781 | 0.74 | 0.823 | NA | NA |
| Risk factors (age, sex, and smoking pack-years) | RS2 | 0.79 | 0.742 | 0.838 | 2.14E-05 | 0.115 |
| Combined polygenic score (PRS) | RS2 | 0.628 | 0.568 | 0.687 | NA | NA |
| Risk factors and PRS | RS2 | 0.808 | 0.763 | 0.854 | NA | NA |
| Risk factors (age, sex, and smoking pack-years) | RS3 | 0.804 | 0.766 | 0.842 | 0.00118 | 0.0662 |
| Combined polygenic score (PRS) | RS3 | 0.7 | 0.652 | 0.749 | NA | NA |
| Risk factors and PRS | RS3 | 0.833 | 0.796 | 0.869 | NA | NA |

Table S4: Performance characteristics of a clinical risk score (CRS) trained in UK Biobank participants with ≥ 10 pack-years of smoking history, the PRS, and both the CRS and PRS combined. The threshold was chosen by optimal Youden index. "PPV" = positive predictive value. "NPV" = negative predictive value.

| *Score* | *Threshold* | *Accuracy* | *PPV* | *NPV* | *Sensitivity* | *Specificity* |
|---|---|---|---|---|---|---|
| CRS | 0.55 | 0.6 | 0.62 | 0.52 | 0.85 | 0.23 |
| PRS | 0.5 | 0.65 | 0.67 | 0.61 | 0.82 | 0.4 |
| CRS + PRS | 0.49 | 0.73 | 0.75 | 0.7 | 0.82 | 0.61 |

Table S5: The association of the PRS with % LAA < -950 HU and WAP after adjusting for baseline $FEV_1$ % predicted.

| *Score* | *trait* | *Beta* | *Se* | *p* |
|---|---|---|---|---|
| PRS | % LAA < -950 HU | -0.03 | 0.017 | 0.08 |
| PRS | WAP | 0.37 | 0.042 | 4.1E-18 |

Table S6: Results of ordinal logistic regression showing association of the combined polygenic risk score with visual emphysema severity category. [24]

| Predictor | OR (95% CI) | p-value |
|---|---|---|
| Combined PRS | 1.2 (1.13 - 1.27) | 2.70E-10 |
| Age | 1.04 (1.03 - 1.04) | 9.10E-27 |
| Gender | 1.06 (0.95 - 1.19) | 0.3 |
| Pack-years | 1.03 (1.02 - 1.03) | 5.00E-89 |
| Principal component 1 | 0 (0 - 0) | 1.90E-05 |
| 0\|1 | 18.02 (11.36 - 28.59) | 1.10E-34 |
| 1\|2 | 39.72 (24.92 - 63.29) | 4.20E-54 |
| 2\|3 | 102.17 (63.61 - 164.12) | 1.30E-81 |
| 3\|4 | 297.53 (183.35 - 482.83) | 1.20E-117 |
| 4\|5 | 1397.13 (839.12 - 2326.22) | 1.30E-170 |

## Supplementary Figures

Figure S1: Flow diagram of participants included in this analysis

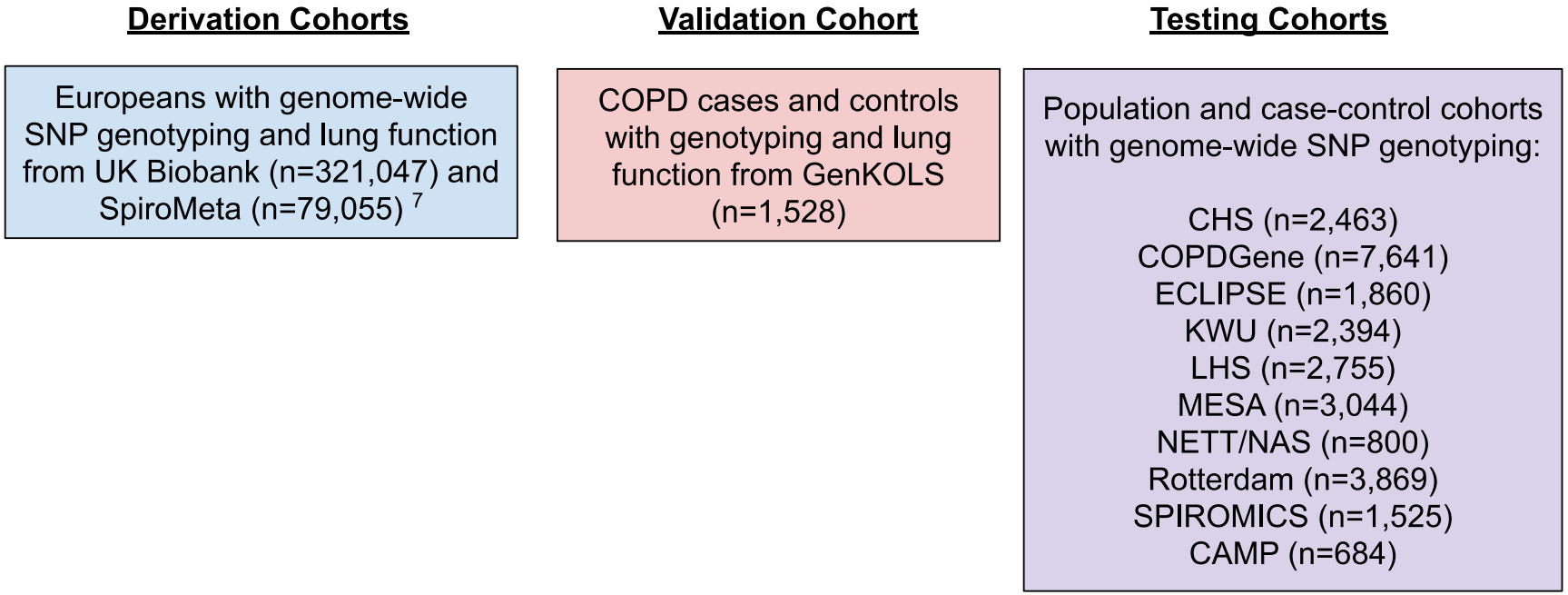


Figure S2: Flow diagram of variants included in the polygenic risk scores

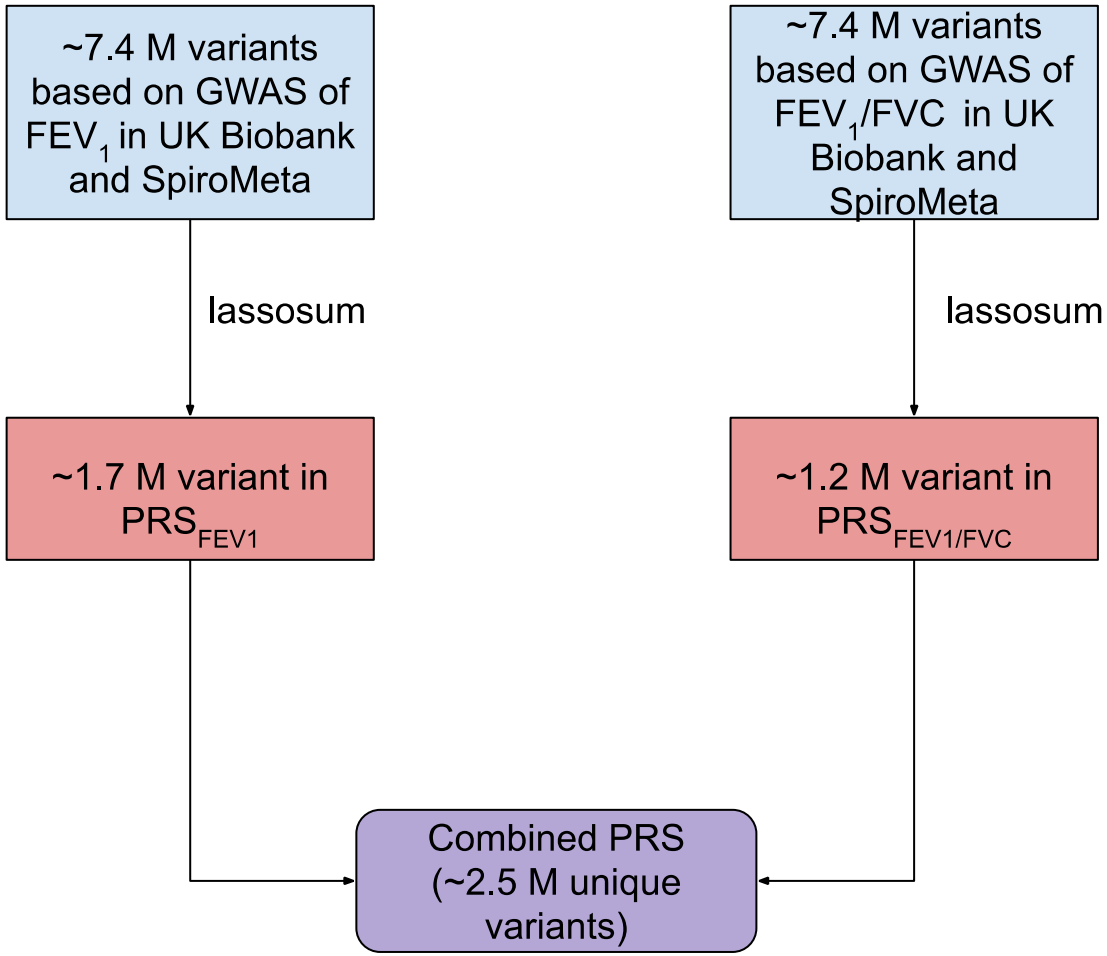


Figure S3: Plot showing effect sizes of genetic loci associated with $FEV_1/FVC$ in meta-analysis of UK Biobank and SpiroMeta.

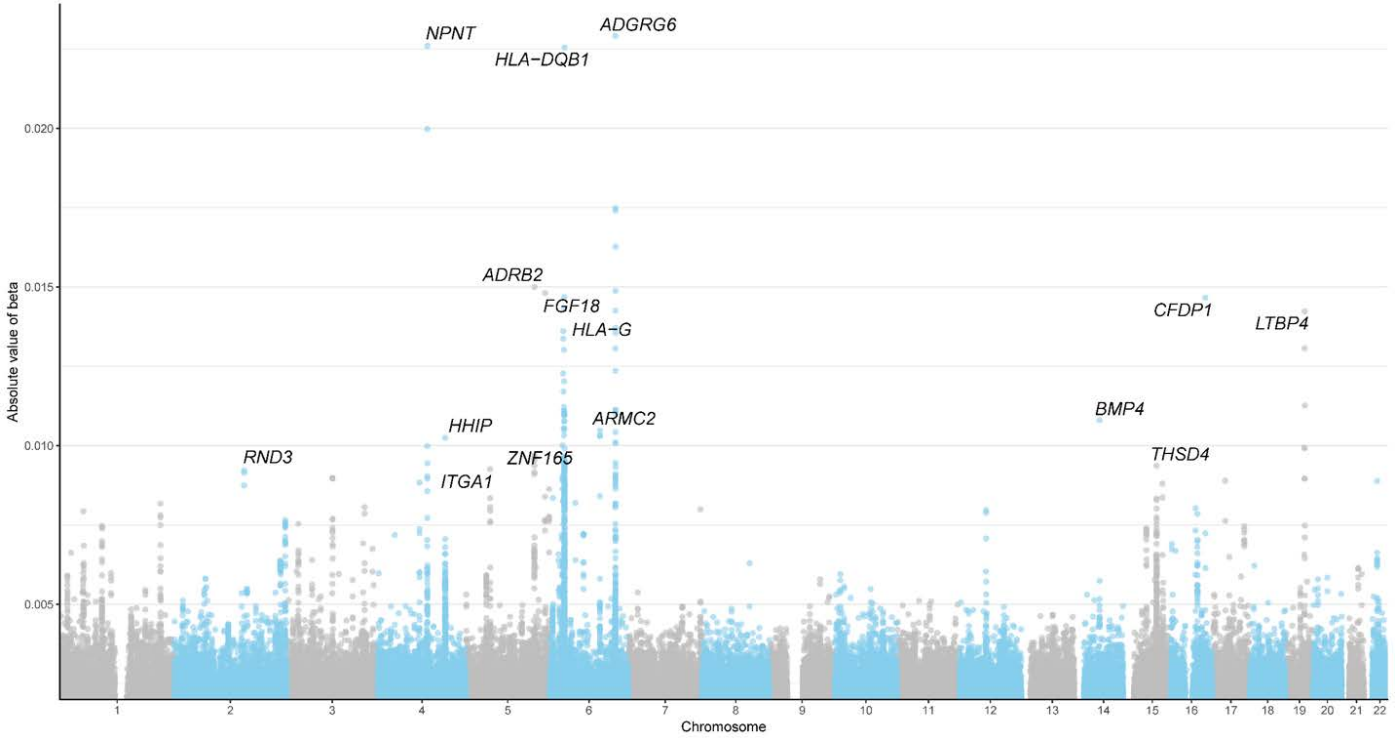


Figure S4: Area-under-the-curve (AUC) measures to predict COPD for PRSs validated in one cohort and tested in others. "PRSfev1" indicates a PRS using FEV1, "PRSratio" using ratio, and "PRSfev1AndRatio" the combined score used as the main analysis in the manuscript. The suffixes indicate the cohort used for validation. "ASP" indicates that the model was adjusted for age, sex, and pack-years of smoking. The AUC for measures are the measures calculated in testing cohorts, labeled on the x-axis. "cgNhw" = COPDGene NHW, "cgAa" = COPDGene AA.

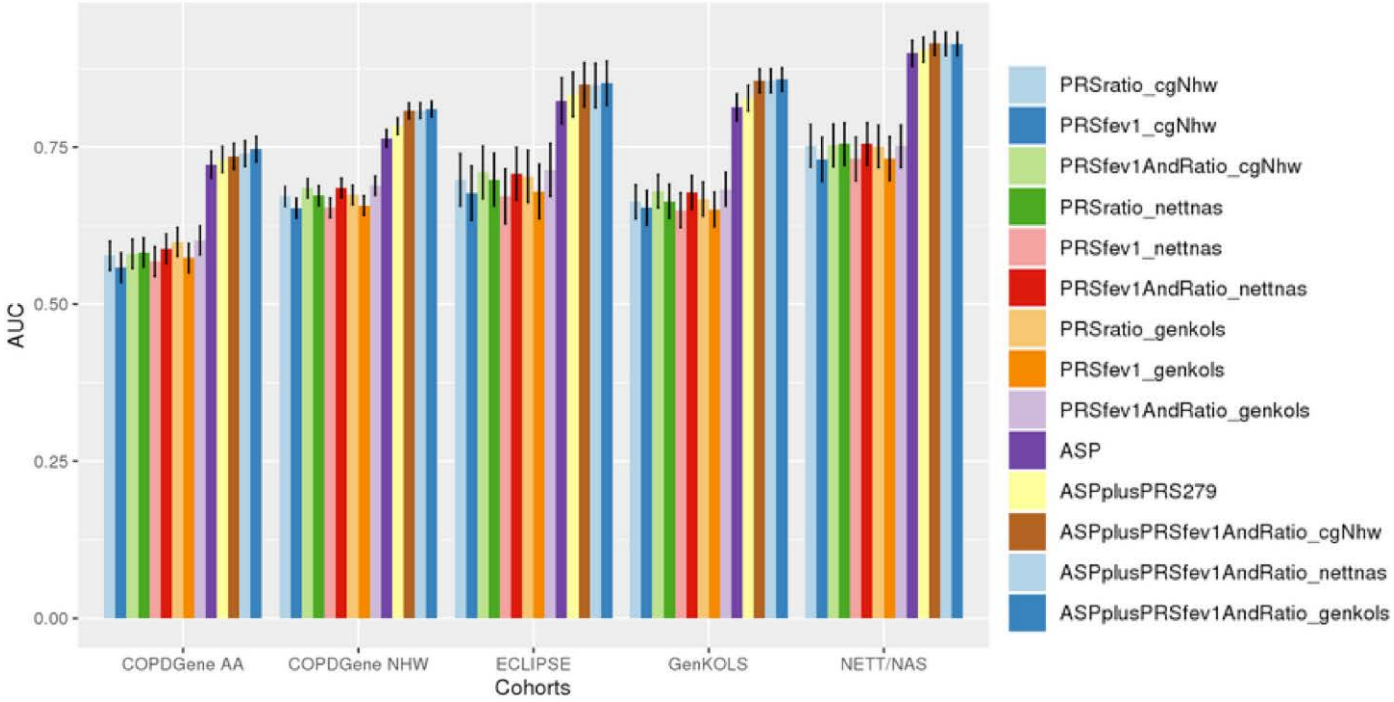


Figure S5: Representative scatterplot showing minimal correlation between the combined $FEV_1$ and $FEV_1/FVC$ PRS in the COPDGene NHW population with smoking intensity. Similar scatterplots were observed in COPDGene AA, GenKOLS, ECLIPSE, and NETT/NAS.

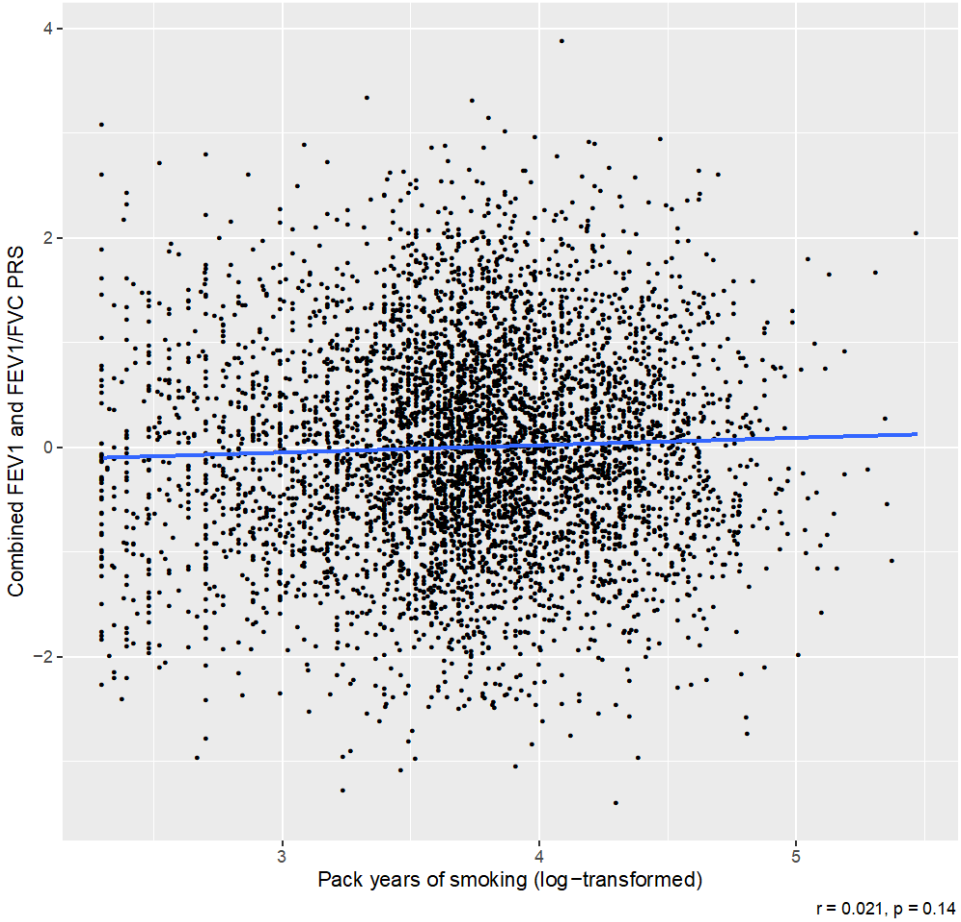


Figure S6: Funnel plot of the combined $FEV_1$ and $FEV_1/FVC$ PRS effect sizes versus standard errors for each cohort.

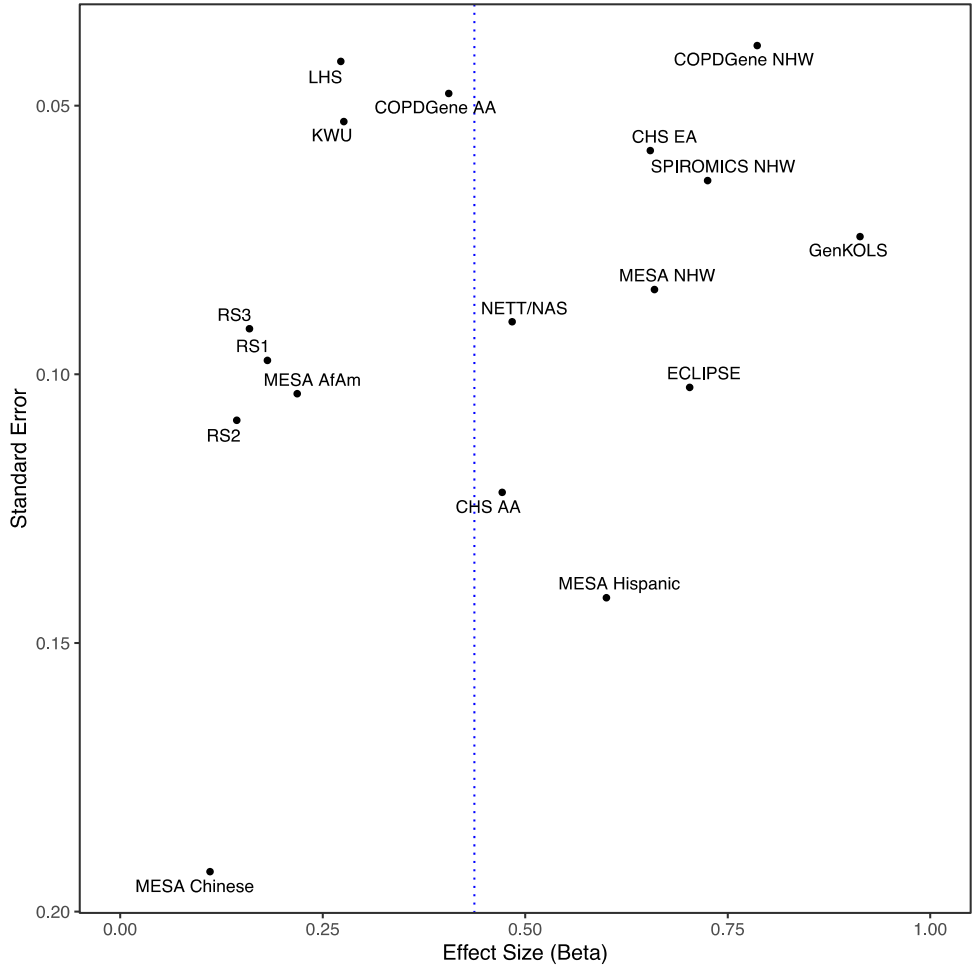
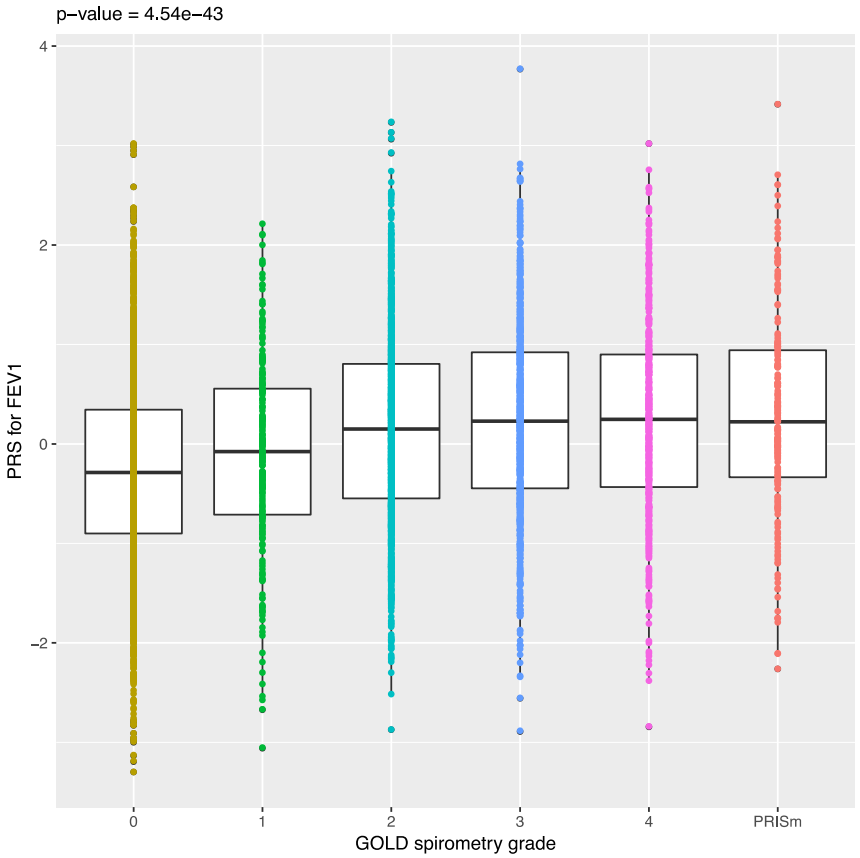


Figure S7: Correlation of FEV1 and FEV1/FVC PRSs with GOLD spirometry grades in COPDGene NHW population. PRISm = preserved ratio with impaired spirometry.

A)



B)

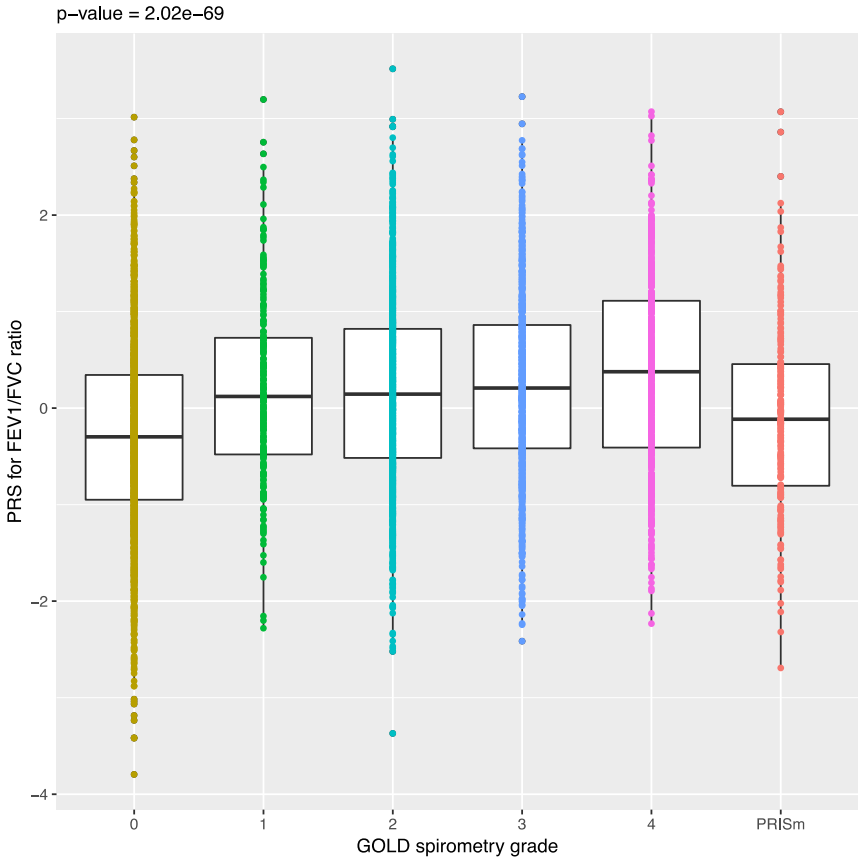

p–value = 2.02e–69
PRS for FEV1/FVC ratio
2
0
–2
–4
0
1
2
3
4
PRISm
GOLD spirometry grade

Figure S8: Scatterplot of controls and COPD cases in the COPDGene NHW cohort based on pack-years of smoking and polygenic risk based on PRS.

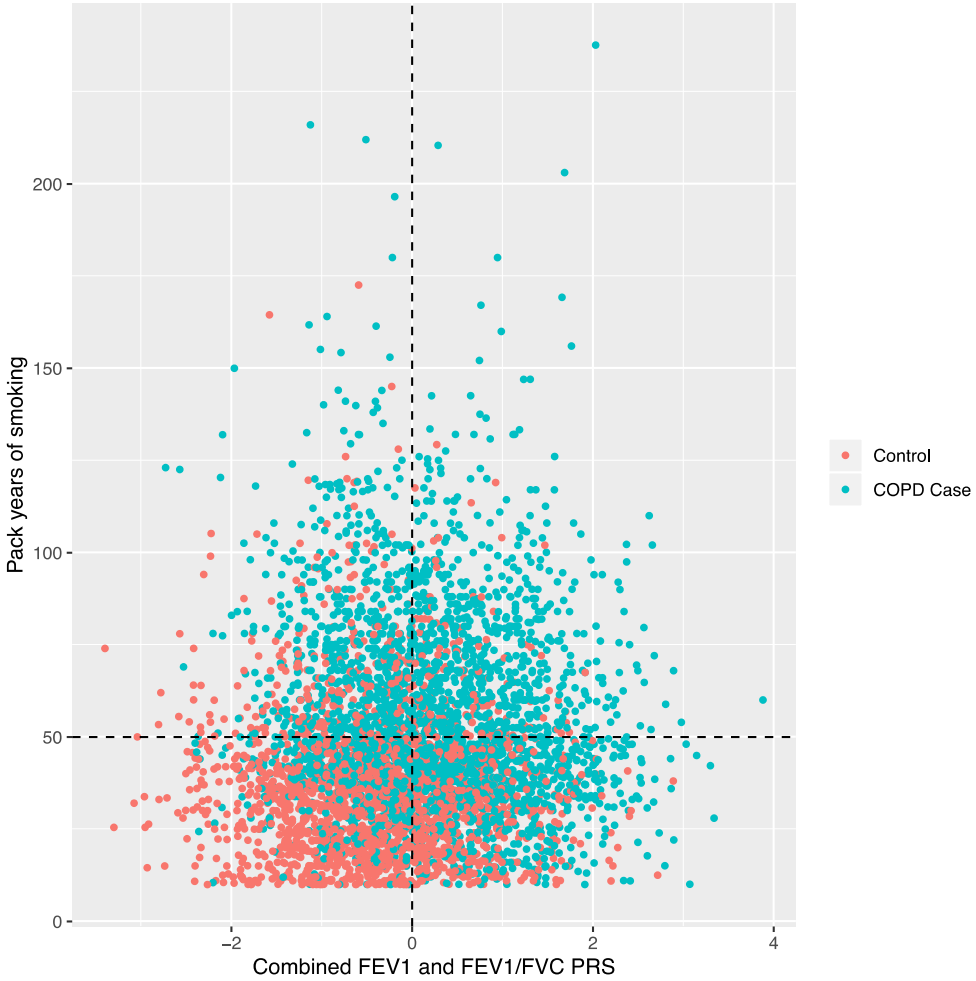


Figure S9: Comparison of AUCs for each of three PRSs across all cohorts.

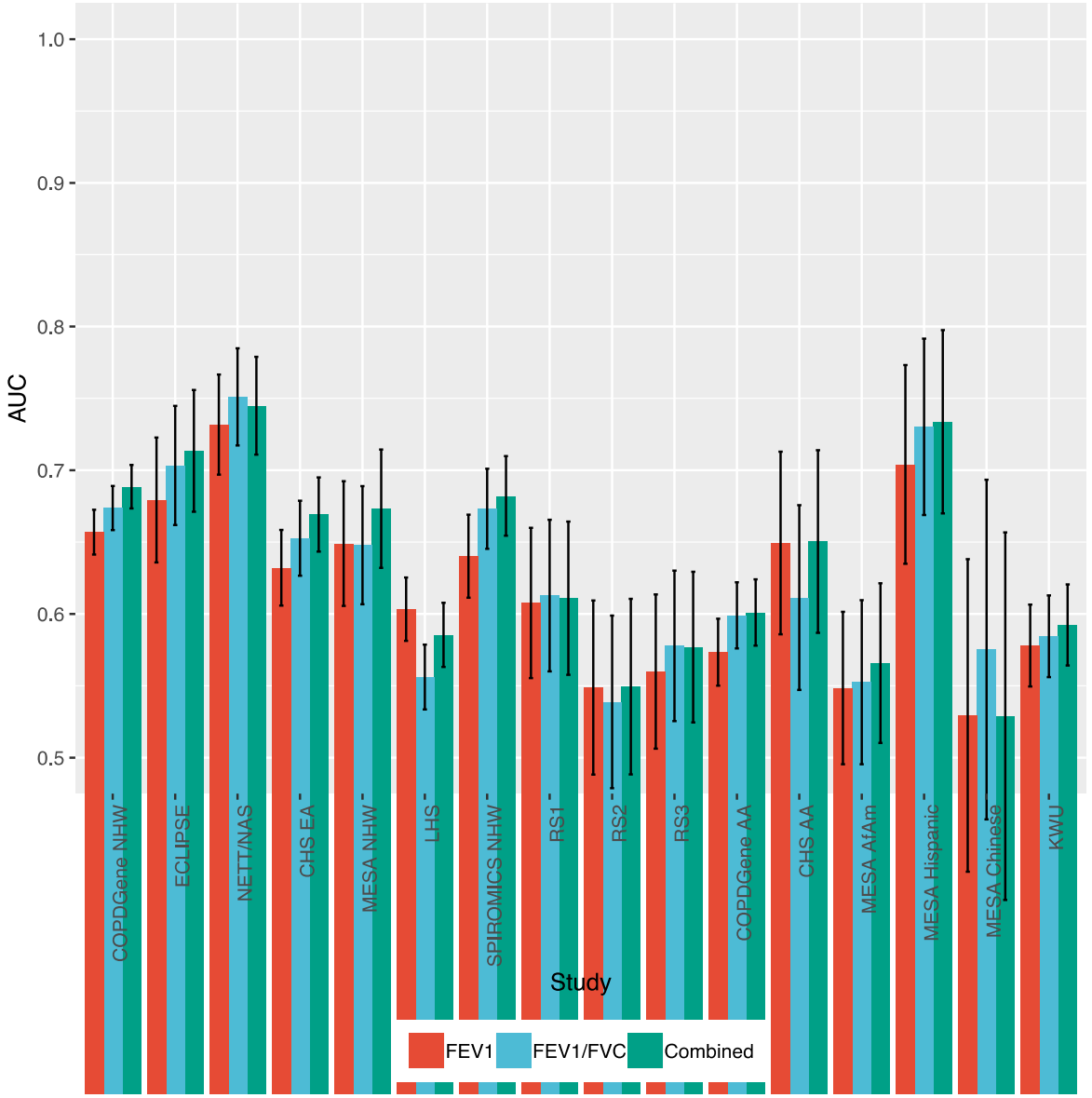


Figure S10: Receiver operator characteristic (ROC) curves for a clinical risk score (CRS) trained in UK Biobank participants with ≥ 10 pack years of cigarette smoking, the PRS, and both the CRS and PRS together, tested in the COPDGene and ECLIPSE cohorts. COPDGene p-value (AUC PRS vs CRS) = 1.1e-36; ECLIPSE p-value (AUC PRS vs CRS) = 3.0e-5. COPDGene p-value (AUC PRS+CRS vs PRS) = 3.9e-64; ECLIPSE (AUC PRS+CRS vs PRS) = 5.8e-11.

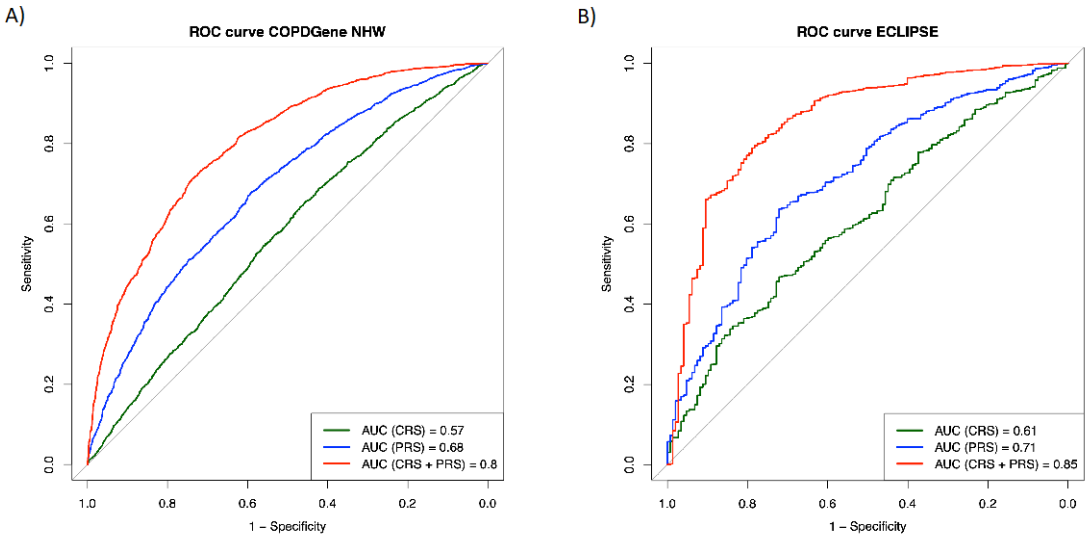
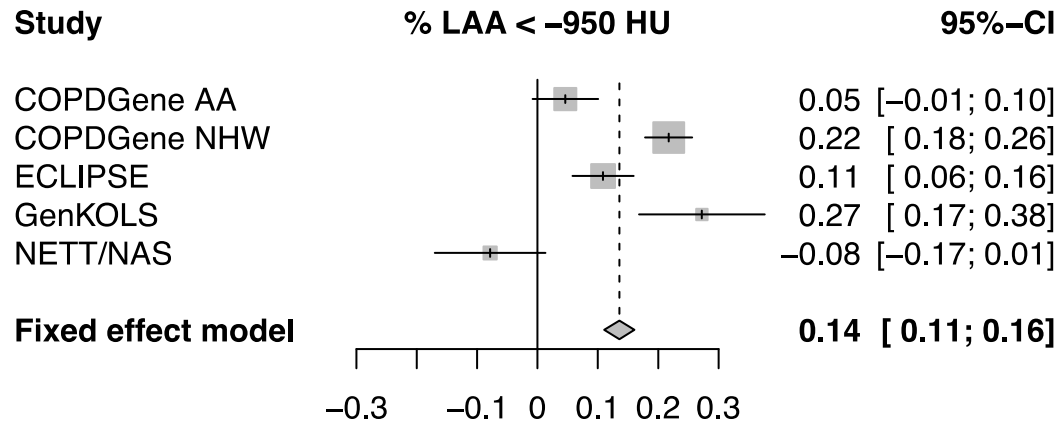
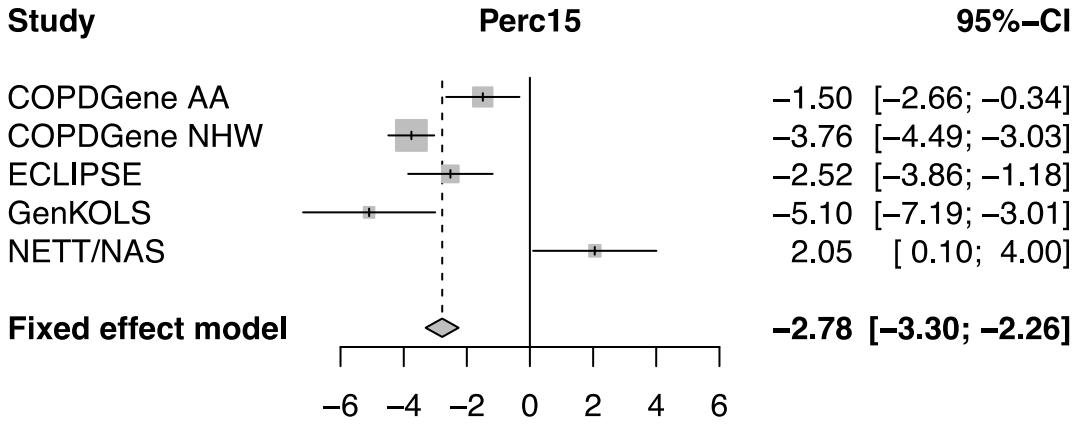


Figure S11: Association of PRS with CT imaging phenotypes. Meta-analysis beta coefficients are shown. "*" indicates that p-value is below Bonferroni-corrected significance level of 0.0025 (0.05/20 imaging comparisons).

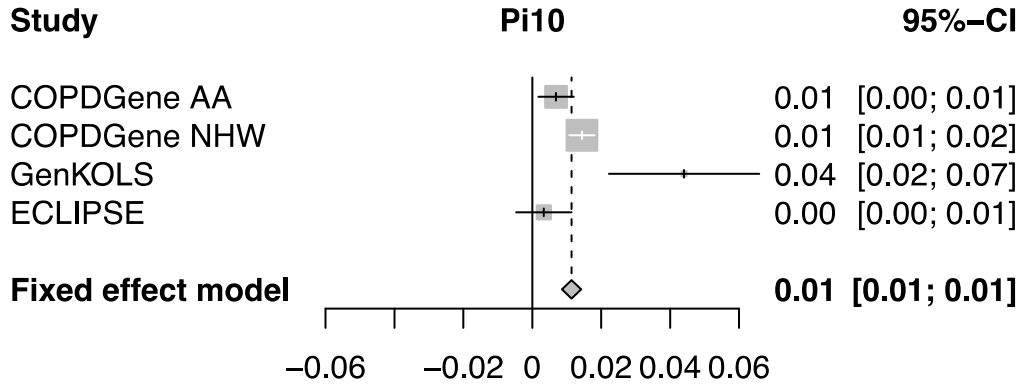
A: %LAA < -950 HU (n=9,340); CI (Bonferroni-adjusted): 0.1-0.17; p = 2.3e-26*



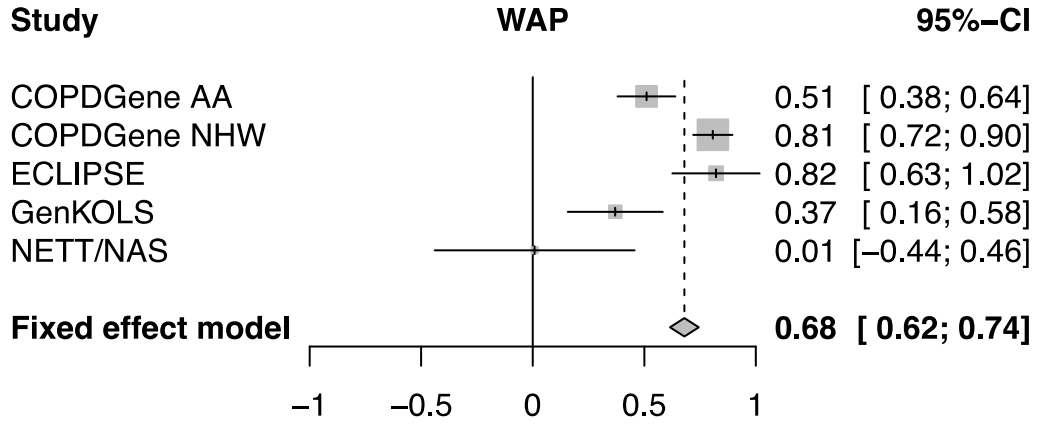

B: Perc15 (n=9,340); CI (Bonferroni-adjusted): -3.5--2.0; p = 1.1e-25*



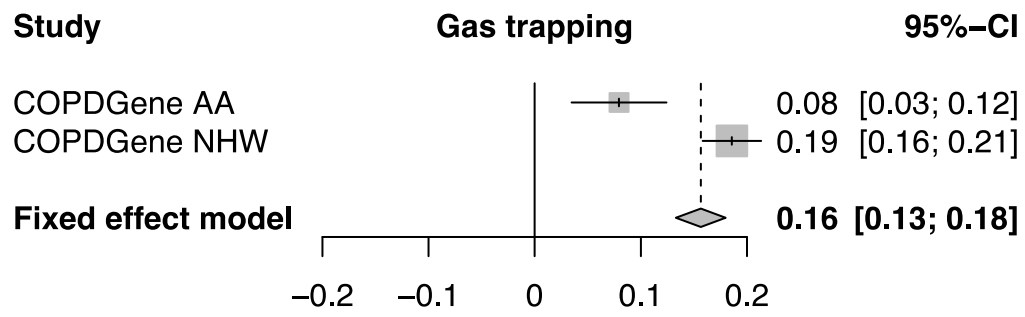
C: Pi10 (n=8,820); CI (Bonferroni-adjusted): 0.0074-0.015; p = 8.8e-16*




D: WAP (n=9,310); CI (Bonferroni-adjusted): 0.59-0.77; p = 1.4e-95*




E: Gas trapping (n=6,110); CI (Bonferroni-adjusted): 0.12-0.19; p = 6.1e-39*




F: Qualitative emphysema (n=2,600); CI (Bonferroni-adjusted): -0.03-0.13; p=0.08

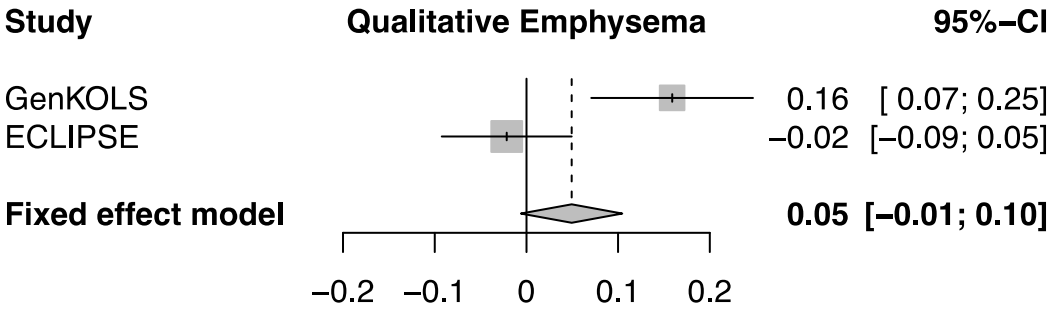
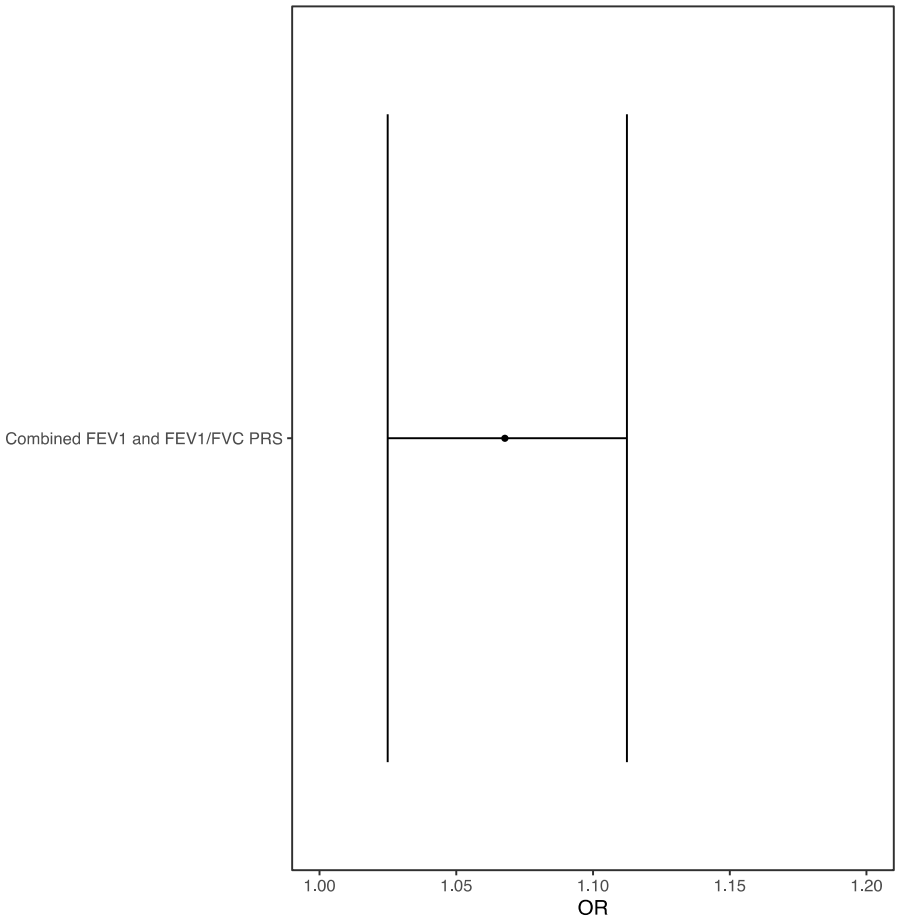


Figure S12: Odds ratio for the combined polygenic risk score and the association with reduced compared to normal lung function growth curves in the CAMP study.



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