Genome-wide association and large scale follow-up identifies 16 new loci influencing lung function

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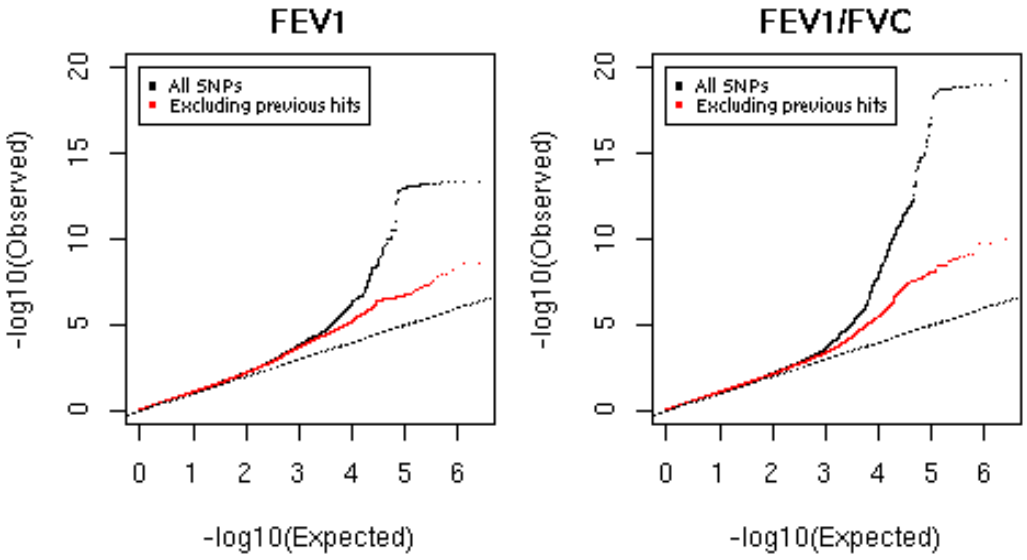
Supplementary Figures

Supplementary Figure 1 Association test statistics for FEV_1 and FEV_1/FVC.

A) Quantile-Quantile (QQ) plots show $-\log_{10}(P)$ of observed genome-wide association results against expected association results for FEV_1 and FEV_1/FVC. λ_{GC} before genomic control was 1.12 for FEV_1 and 1.09 for FEV_1/FVC. The QQ plot for all SNPs is shown in black. The QQ plot for remaining SNPs after exclusion of SNPs from loci previously reported by the SpiroMeta and CHARGE consortia[1,2] is shown in red; SNPs within 500kb of the lead reported SNP were excluded. The previously reported loci were *TNS1*, *FAM13A*, *GSTCD*/*NPNT*, *HHIP*, *HTR4*, *ADAM19*, *AGER*, *GPR126*, *PTCH1*, and *TSHD4.*



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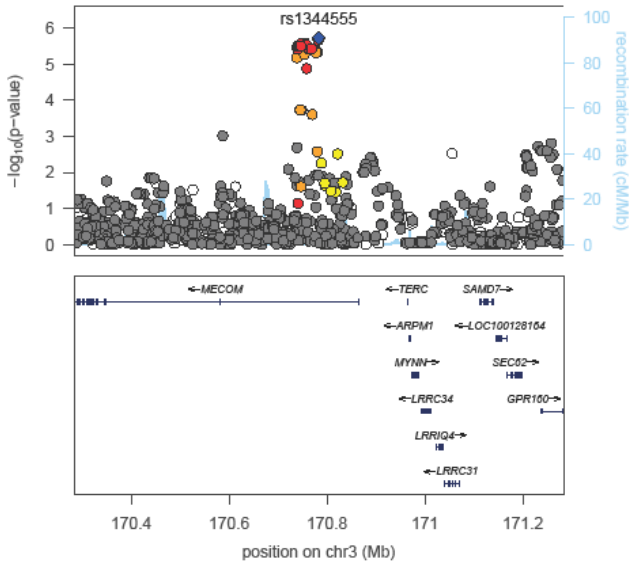
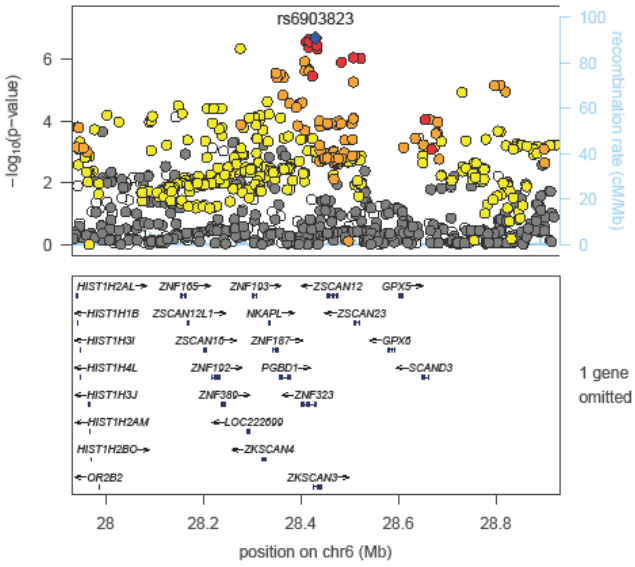
B) Regional association plots of 16 novel lung function-associated loci. Statistical significance of each SNP on the $-\log_{10}(P)$ scale as a function of chromosome position (NCBI Build 36) in the meta-analysis of Stage 1 data alone. The sentinel SNP at each locus is shown in blue with the correlations (r^2) of surrounding SNPs to the sentinel indicated by colour (red: r^2>0.8, orange: r^2>0.5, yellow: r^2>0.2, grey: r^2<0.2, white: r^2 unknown). The fine scale recombination rate is shown in blue.

FEV_1 only





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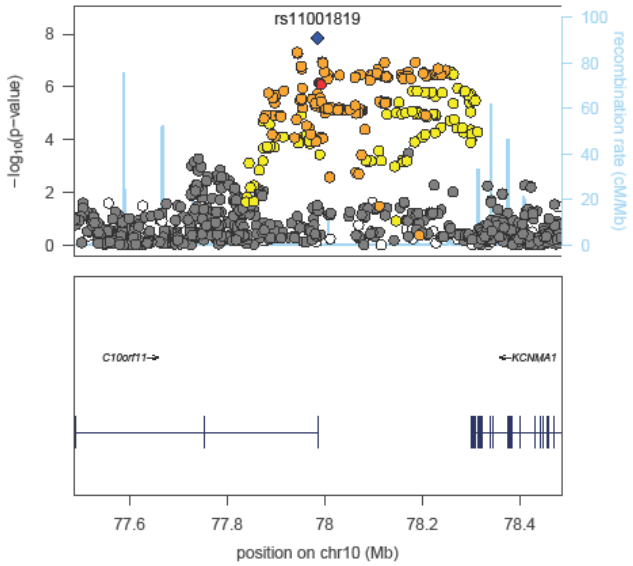

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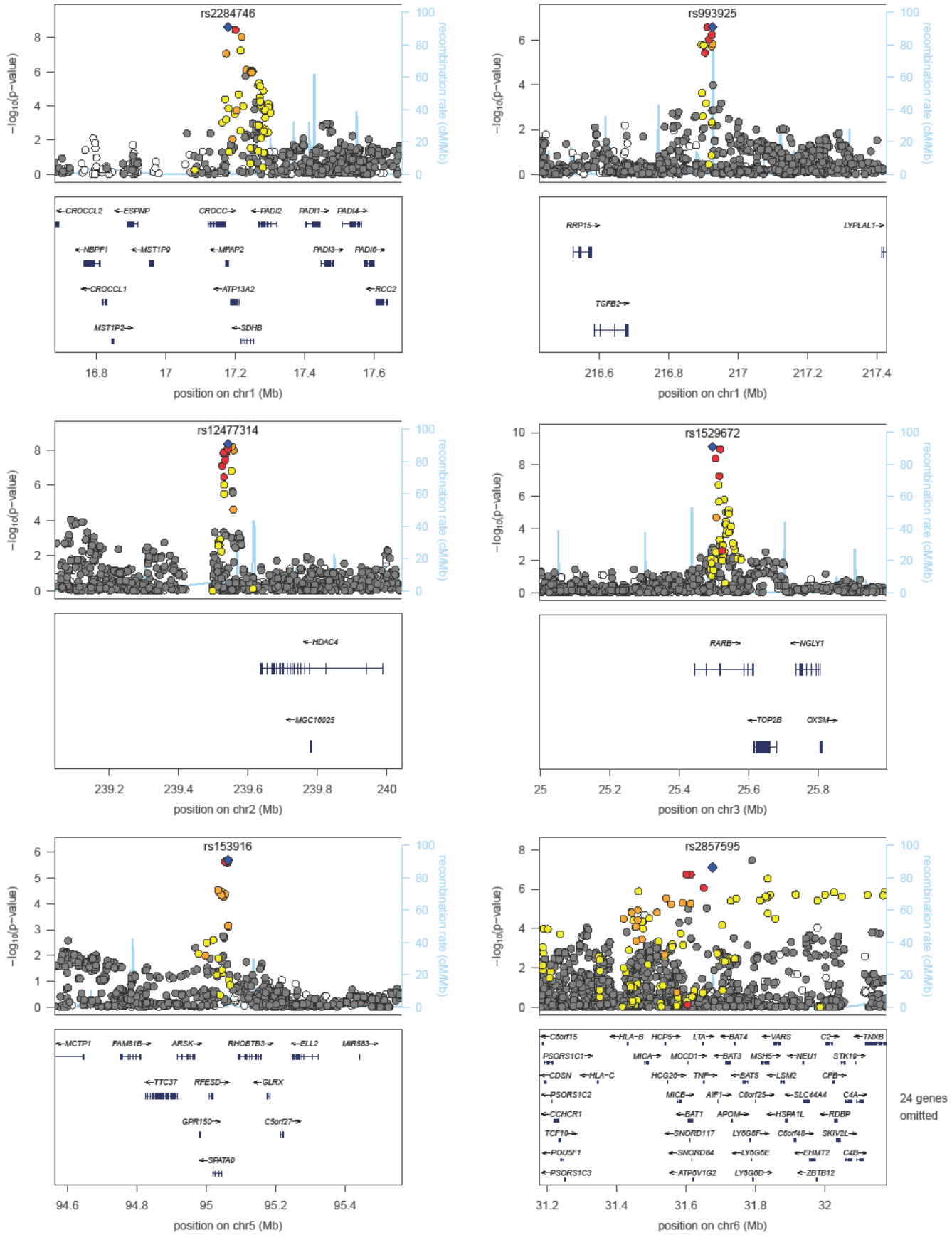
FEV$_1$/FVC only



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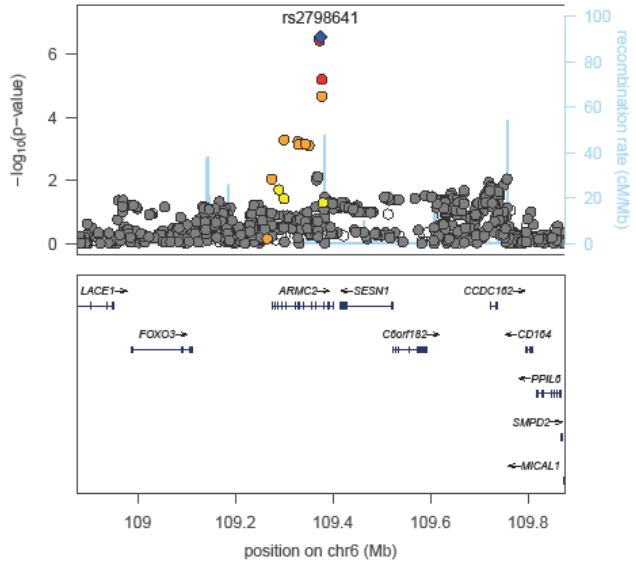

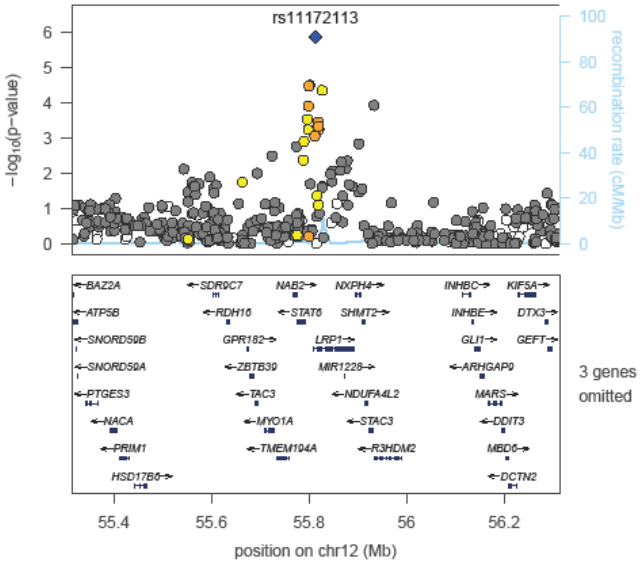

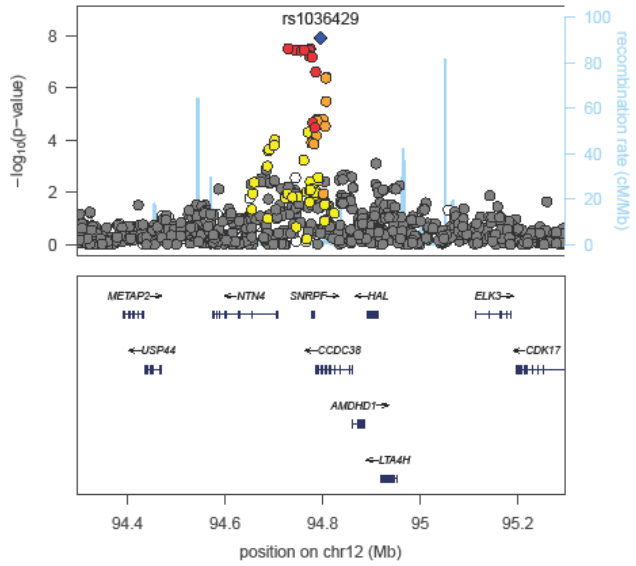

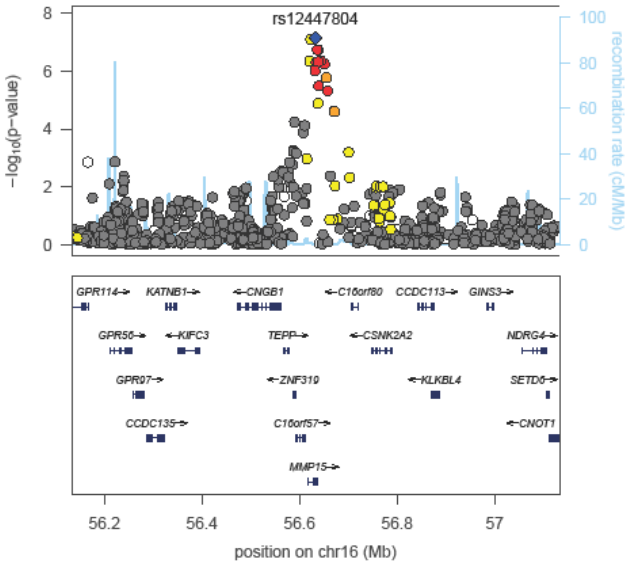

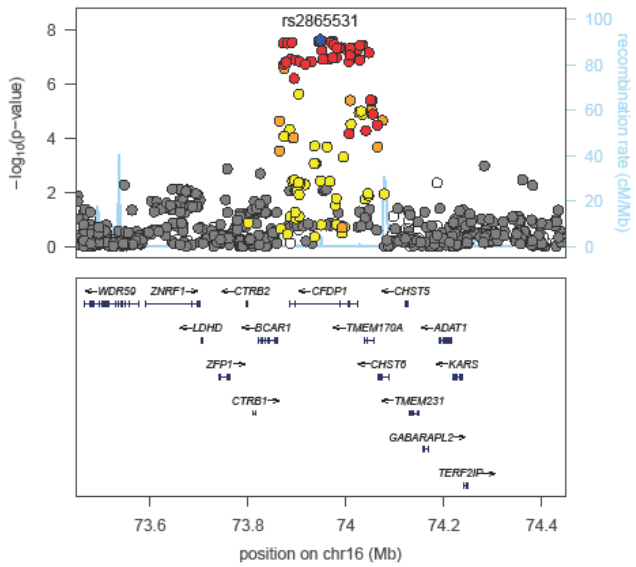

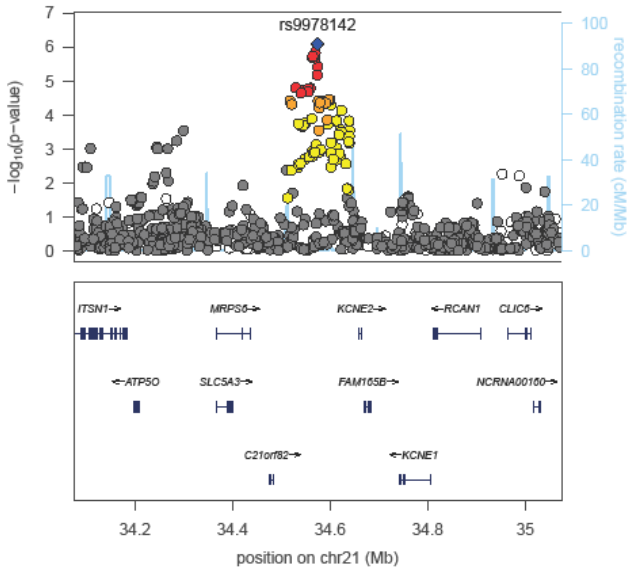

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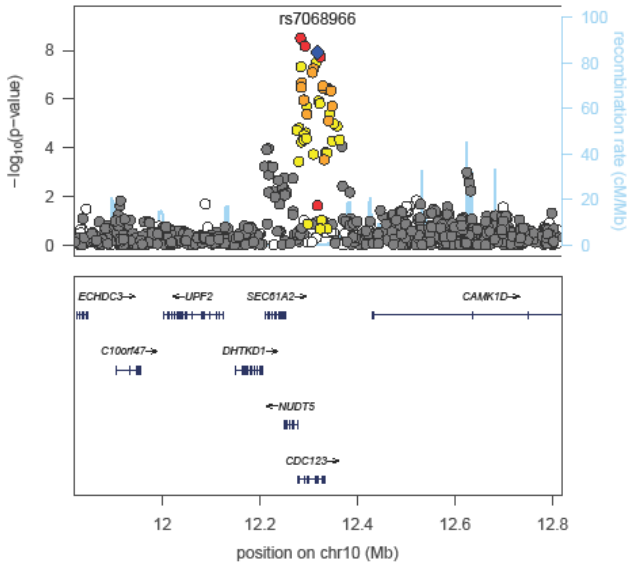
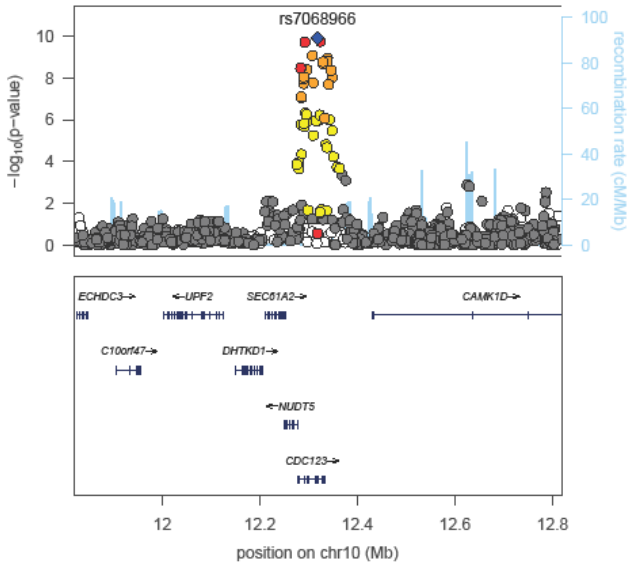
Both FEV_1 and FEV_1/FVC

FEV_1



FEV_1/FVC



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C) Forest plots for the 16 loci associated with lung function for Stage 1 and Stage 2 separately. Each of the SNPs included in the figure showed genome-wide significant association ($P<5\times10^{-8}$) with either FEV_1 or FEV_1/FVC in the data from Stages 1 and 2. For each SNP there is a plot for the meta-analysis of the Stage 1 data and another for the meta-analysis of the Stage 2 data. The contributing effect (transformed beta) from each study is shown by a square, with confidence intervals indicated by horizontal lines. The contributing weight of each study to the meta-analysis is indicated by the size of the square. The combined meta-analysis estimate is shown at the bottom of each graph.

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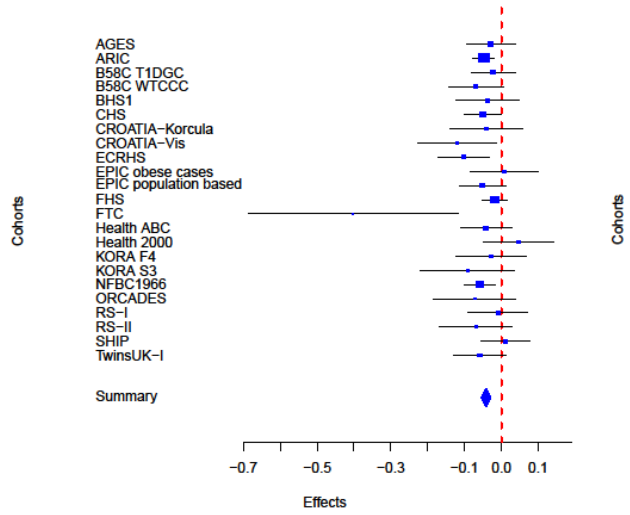
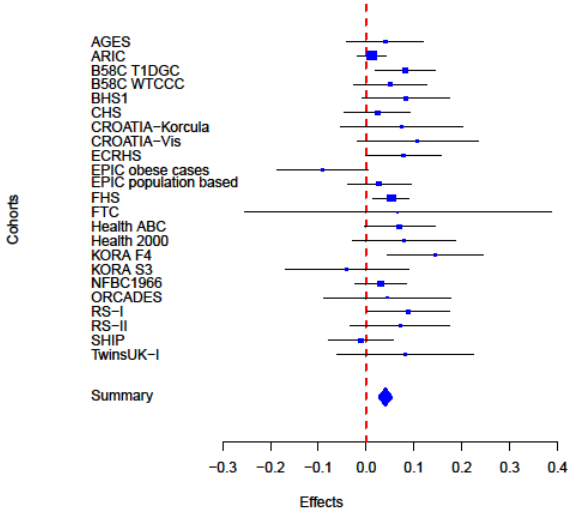
Stage 1

FEV1/FVC rs2284746



FEV1/FVC rs993925



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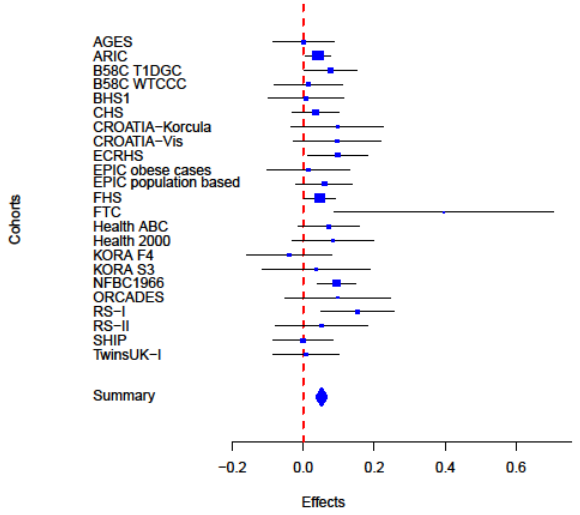
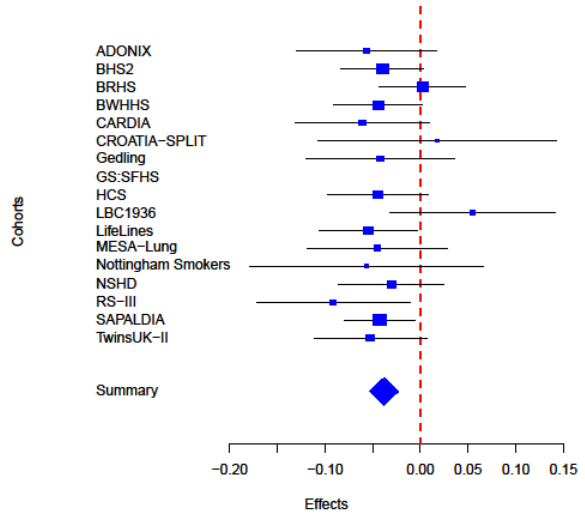


Stage 2

FEV1/FVC rs2284746



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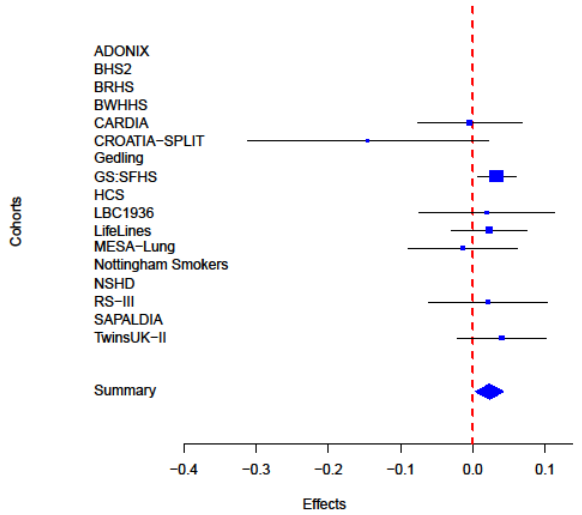

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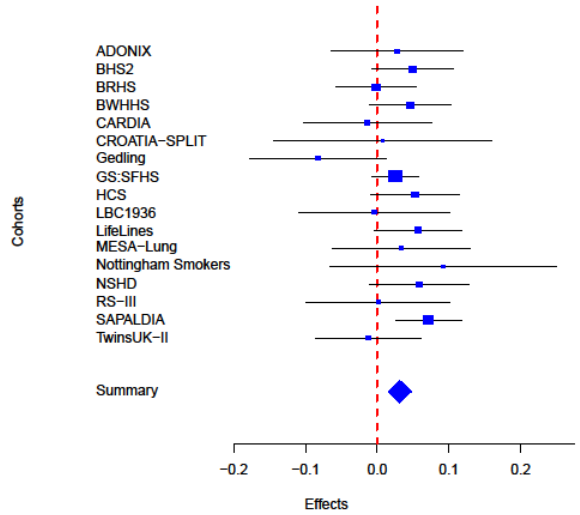

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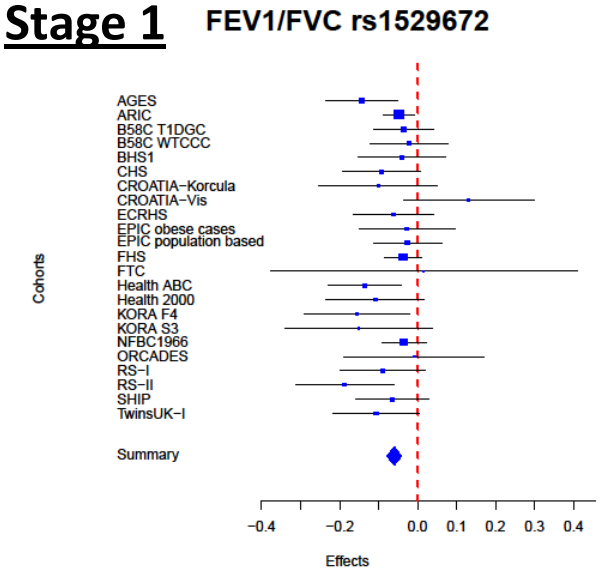
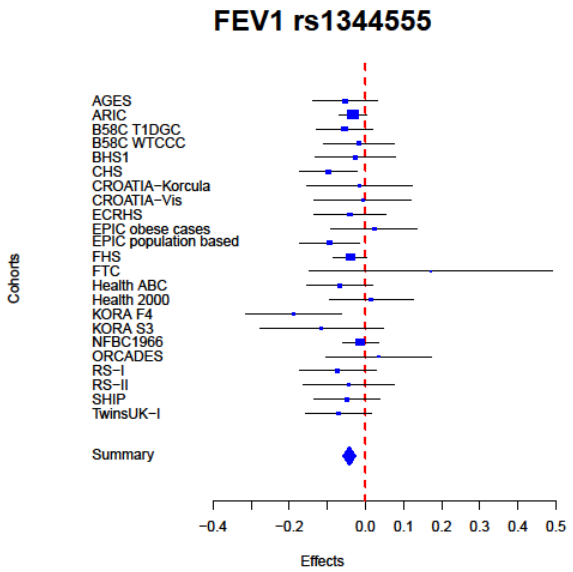
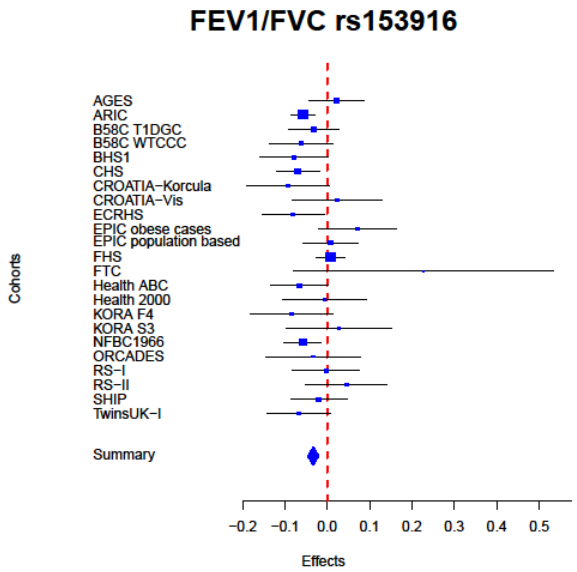
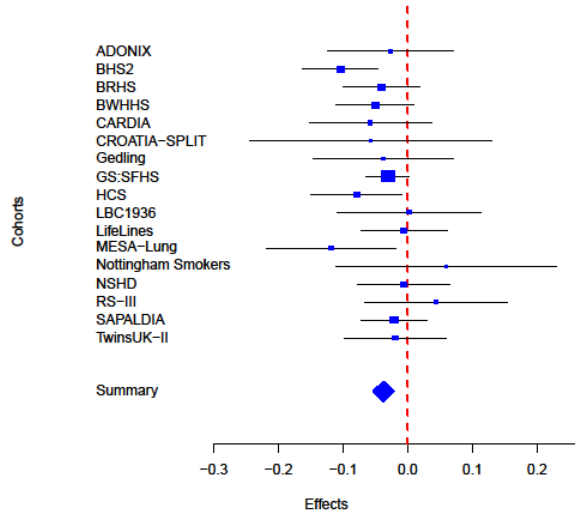
Stage 1

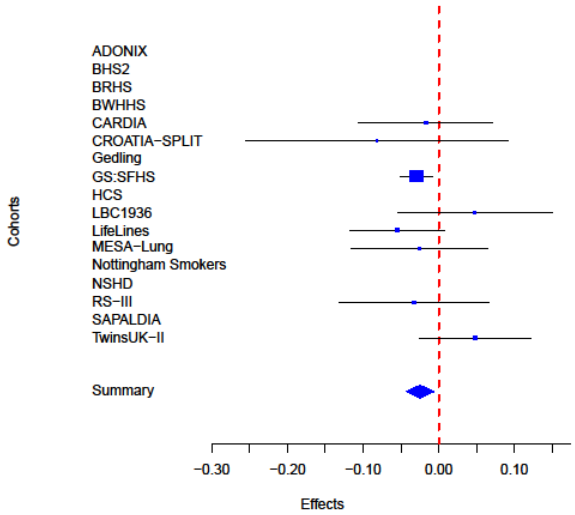


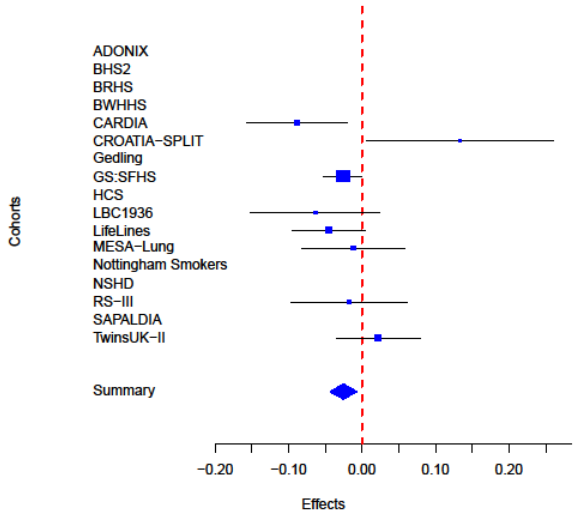




Stage 2







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Stage 1

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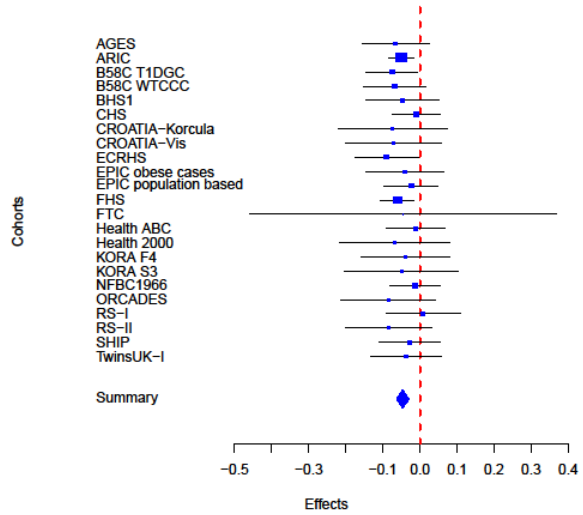

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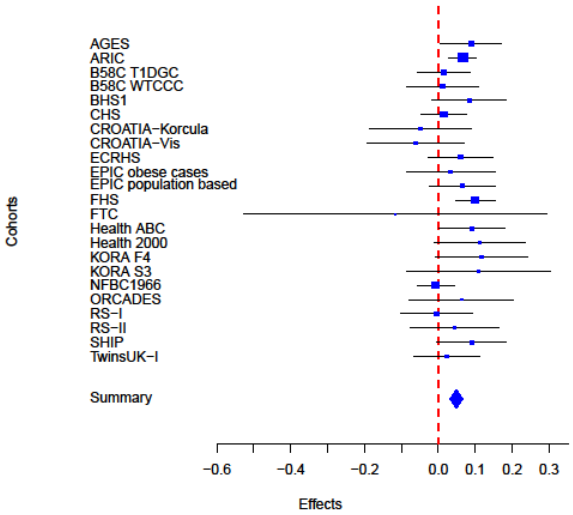

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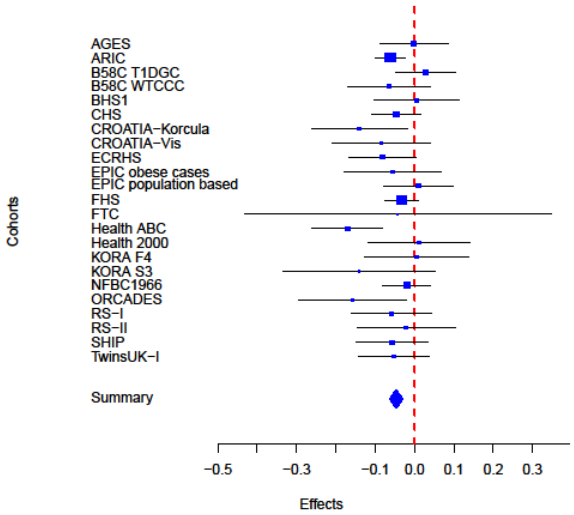

Stage 2

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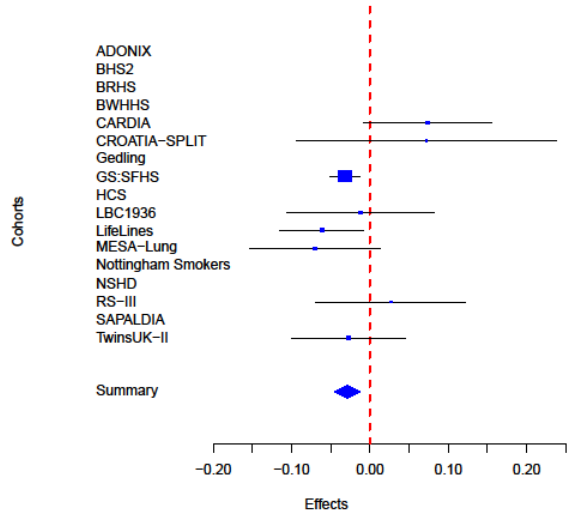

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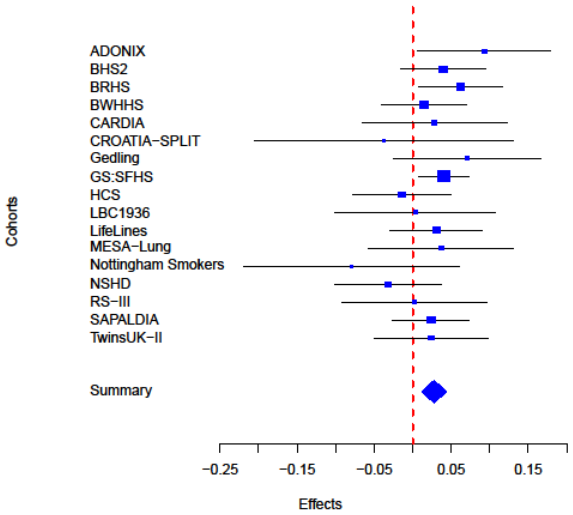

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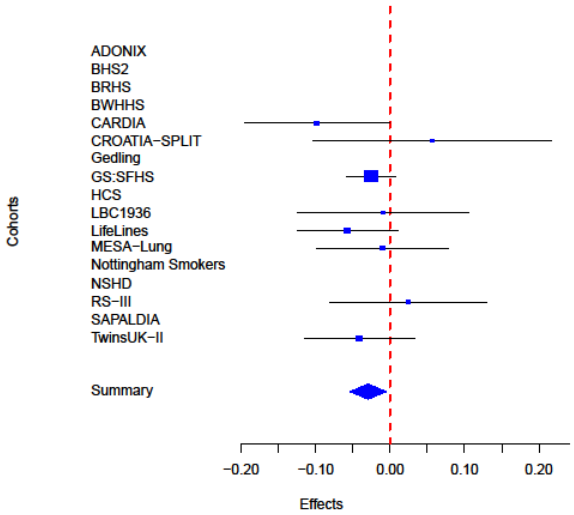

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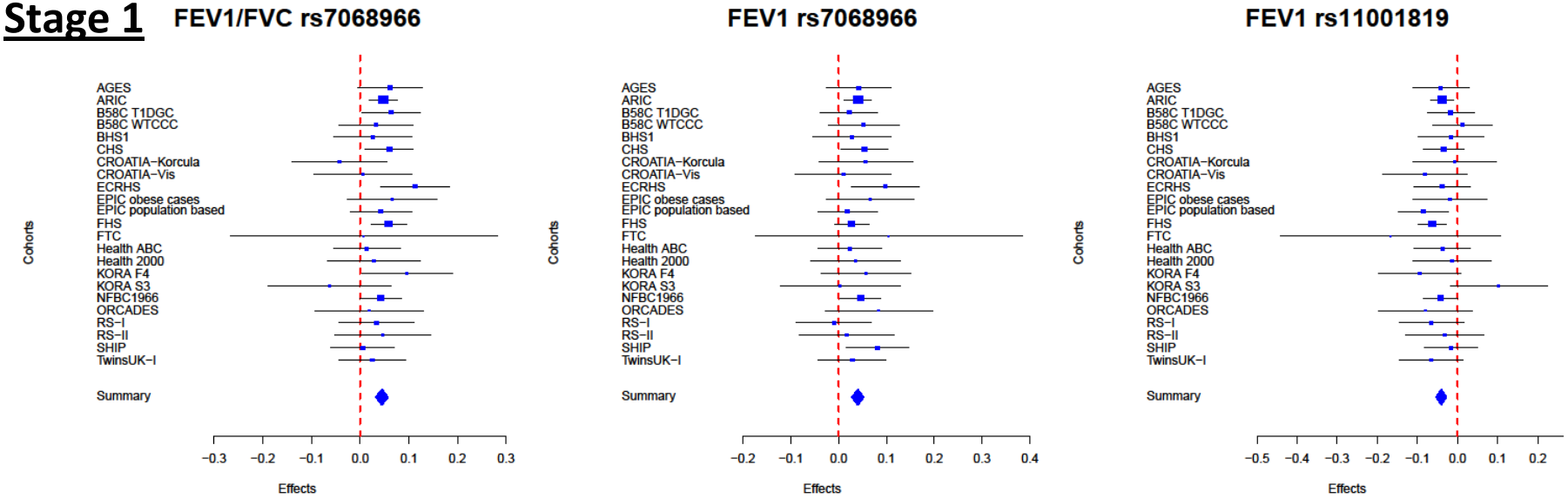

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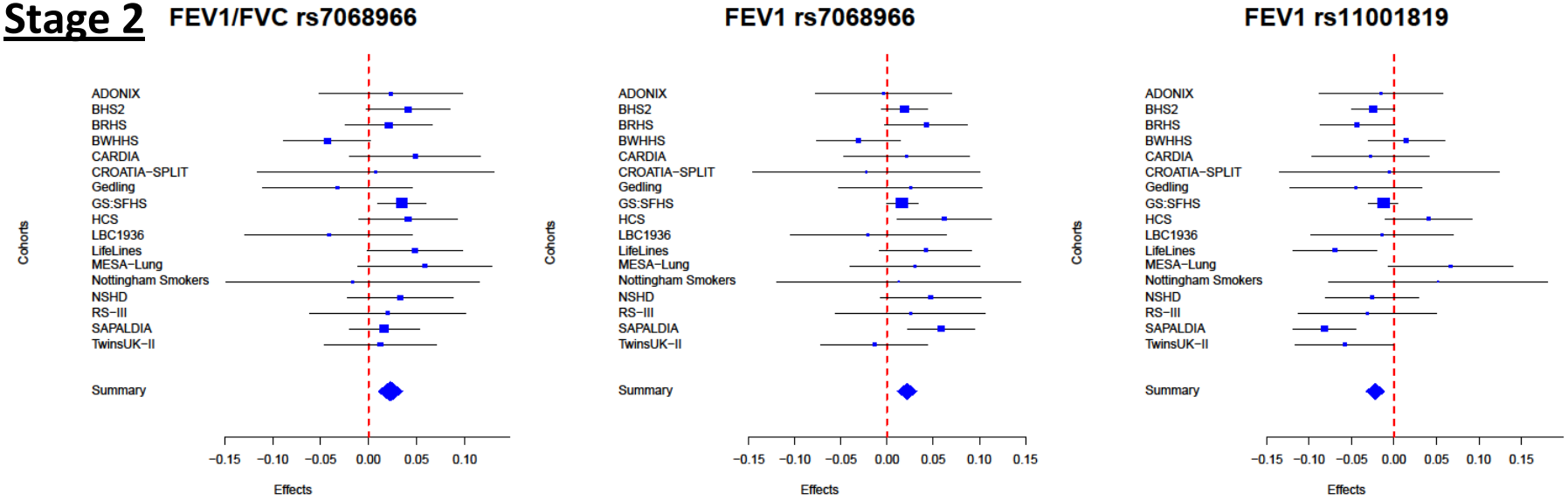

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Stage 1

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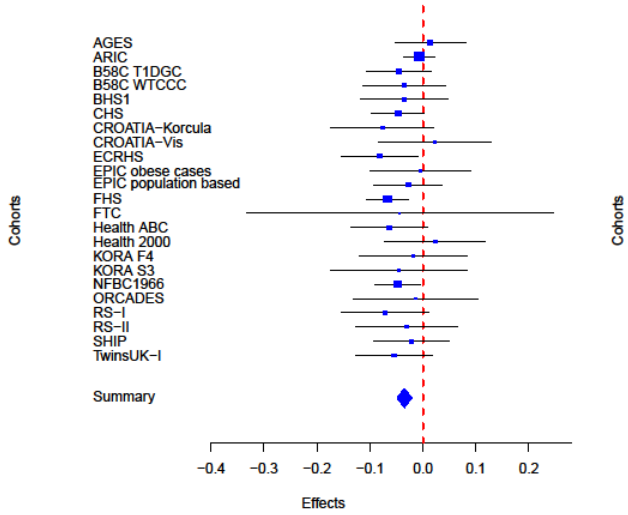
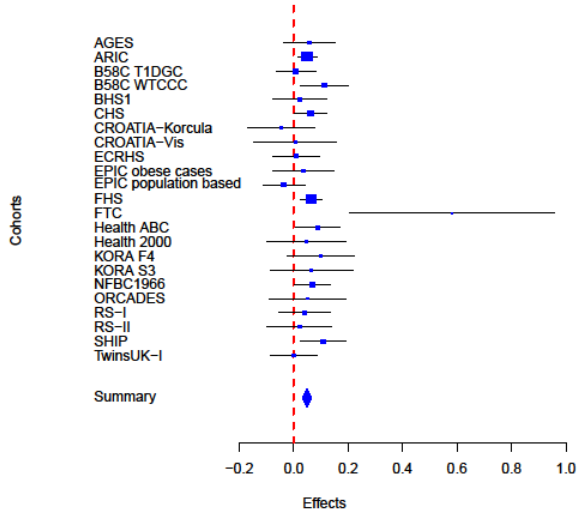


FEV1/FVC rs1036429



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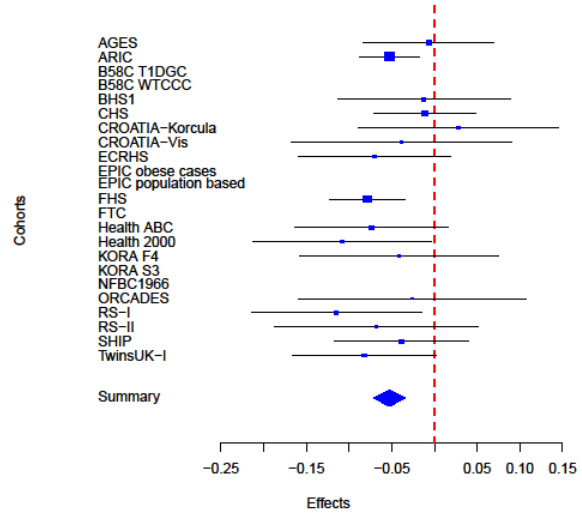

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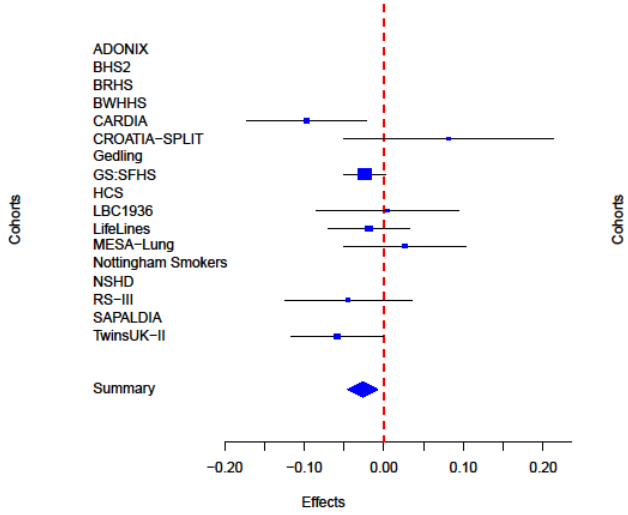

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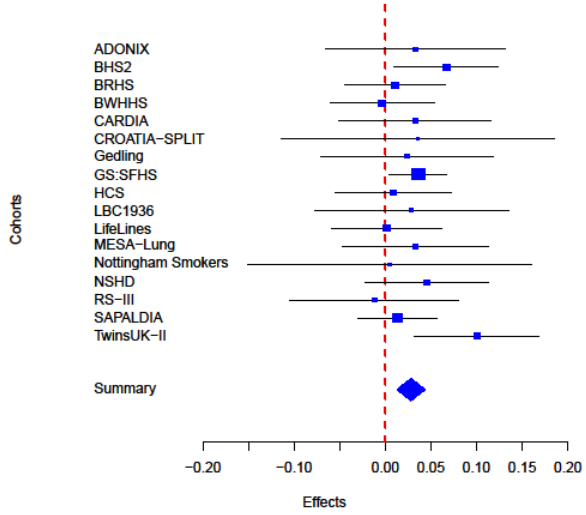

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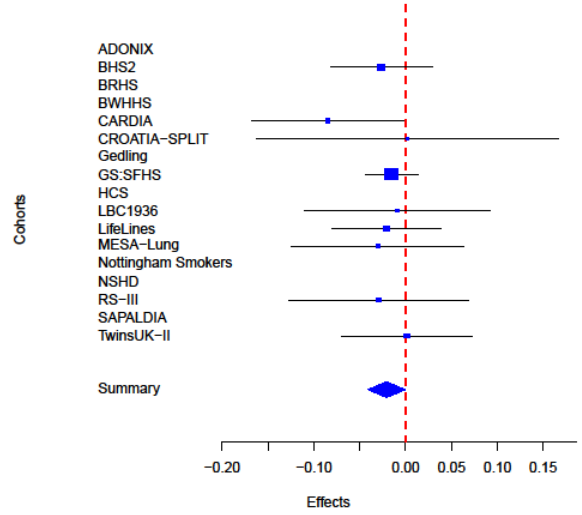

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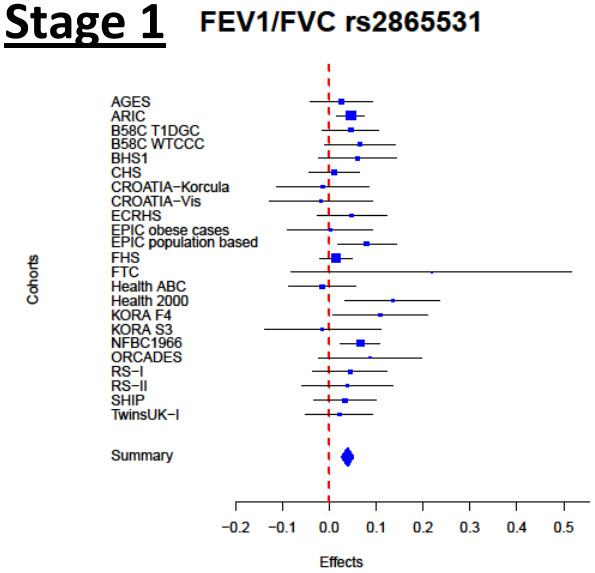
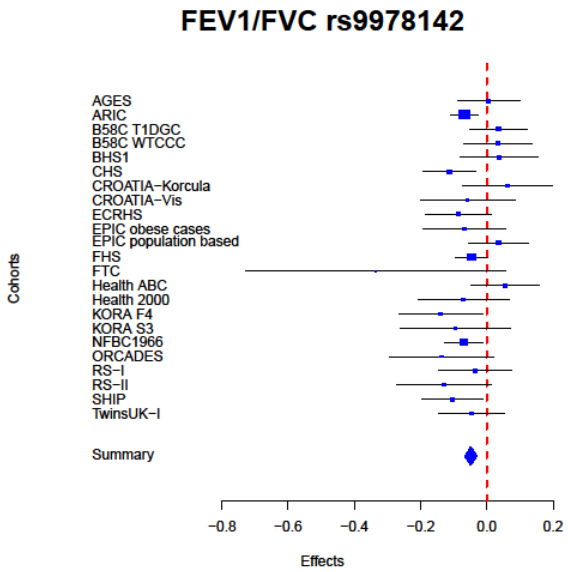
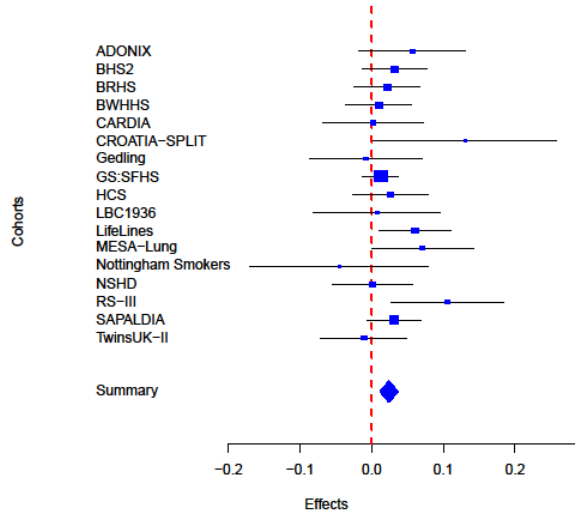
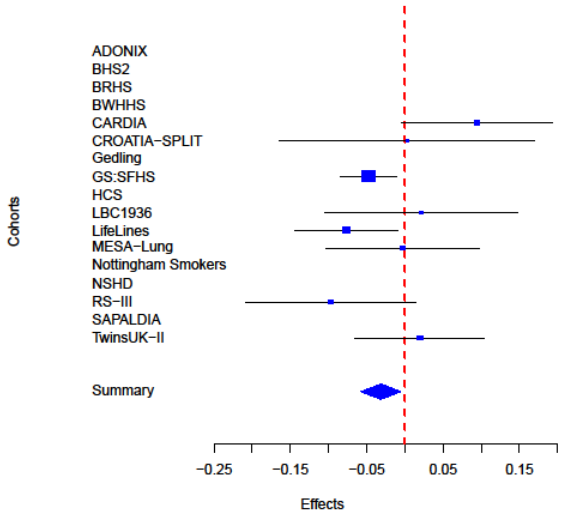
Stage 1





Stage 2





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Supplementary Tables

Supplementary Table 1 Sample population characteristics and genotyping platform details for each study.

A) Sample population characteristics for each study. Characteristics are shown for studies analyzed in Stage 1 (GWAS meta-analysis), Stage 2 (follow-up). Stage 1 studies: AGES, Age, Gene/Environment Susceptibility; ARIC, Atherosclerosis Risk in Communities; B58C-T1DGC, British 1958 Birth Cohort–Type 1 Diabetes Genetics Consortium; B58C-WTCCC, British 1958 Birth Cohort–Wellcome Trust Case Control Consortium; BHS1, Busselton Health Study 1; CHS, Cardiovascular Health Study; the CROATIA- Korcula study; the CROATIA-Vis study; ECRHS, the European Community Respiratory Health Survey; EPIC obese cases, European Prospective Investigation into Cancer and Nutrition, Obese Cases; EPIC population based, European Prospective Investigation into Cancer and Nutrition Cohort; FHS, Framingham Heart Study; FTC, Finnish Twin Cohort incorporating FinnTwin16 and FITSA; H2000, Finnish Health 2000 survey; Health ABC, Health, Aging, and Body Composition; KORA F4, Cooperative Health Research in the Region of Augsburg; KORA S3, Cooperative Health Research in the Region of Augsburg; NFBC1966, Northern Finland Birth Cohort of 1966; ORCADES, Orkney Complex Disease Study; RS-I and RS-II, Rotterdam Study; SHIP, Study of Health in Pomerania; the TwinsUK-I study. Stage 2 studies: ADONIX, Adult-Onset Asthma and Nitric Oxide; BHS2, Busselton Health Study 2; BRHS, British Regional Heart Study; BWHHS, British Women's Heart and Health Study; CARDIA, Coronary Artery Risk Development in Young Adults; the CROATIA-Split study; the Gedling study; GS:SFHS, Generation Scotland: Scottish Family Health Study; LBC1936, Lothian Birth Cohort 1936; the LifeLines study; MESA-Lung, Multi-Ethnic Study of Atherosclerosis; HCS, Hertfordshire Cohort Study; the Nottingham Smokers study; NSHD, Medical Research Council National Survey of Health and Development (also known as the British 1946 Birth Cohort); RS-III, Rotterdam Study; SAPALDIA, Swiss study on Air Pollution and Lung Disease in adults; the TwinsUK-II study. * Total number of individuals with both genotype and phenotype data and which were included in the analyses described in this paper.

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Study	*N* Total	*N* male	*N* female	Age range (y) at FEV_1/FVC measurement	Mean age, y (s.d.)	Mean FEV_1, L (s.d.)	Mean FVC, L (s.d.)	Mean FEV_1/FVC (s.d.)	*N* never-smokers	*N* ever-smokers	Genomic inflation factor (λ) FEV_1		Genomic inflation factor (λ) FEV_1/FVC	
Stage 1: GWAS											Ever-smokers	Never-smokers	Ever-smokers	Never-smokers
AGES	1689	686	1003	66-95	76.19 (5.63)	2.13(0.69)	2.86(0.85)	0.74(0.11)	803	886	1.009	1.012	1.003	1.003
ARIC	9078	4279	4799	44-66	54.27 (5.70)	2.94 (0.78)	3.99 (0.98)	0.74 (0.08)	3620	5458	1.034	1.007	1.019	1.019
B58C T1DGC	2343	1131	1212	44–45	44.5 (0)	3.31 (0.78)	4.19 (0.96)	0.79 (0.08)	692	1651	1.009	0.999	1.023	1.009
B58C WTCCC	1372	691	681	44–45	44.5 (0)	2.93 (0.75)	4.18 (0.96)	0.79 (0.08)	394	978	0.999	0.996	1.007	0.99
BHS1	1168	455	713	17-91	52.98 (17.07)	2.81 (0.97)	3.68 (0.11)	0.76 (0.09)	653	515	1.02	1.034	1.02	1.015
CHS	3140	1226	1914	65-95	72.3 (5.4)	2.12 (0.66)	3.00 (0.87)	0.71 (0.11)	1543	1597	1.035	1.021	1.02	1.033
CROATIA-Korcula	825	300	525	18–90	55.5 (13.5)	2.84 (0.81)	3.37 (0.93)	0.84 (0.09)	397	428	1.039	1.014	0.999	1.041
CROATIA-Vis	769	323	446	18–88	56.3 (15.3)	3.39 (1.22)	4.38 (1.43)	0.77 (0.09)	328	441	1.019	1.002	1.066	1.027
ECRHS	1594	784	810	19-48	33.90 (7.17)	3.78(0.82)	4.59 (1.03)	0.83 (0.07)	699	895	1.018	1.014	1.005	1.024
EPIC obese cases	1104	476	628	39–76	59.1 (8.8)	2.35 (0.69)	2.84 (0.87)	0.82 (0.17)	489	615	1.005	1.02	1.02	1.014
EPIC population based	2336	1100	1236	39–77	59.2 (9.0)	2.50 (0.72)	3.04 (0.90)	0.85 (0.16)	1061	1275	1.013	1.008	1.002	1.018
FHS	7911	3650	4261	19-92	52.2 (14.6)	3.03 (0.94)	4.02 (1.14)	0.75 (0.08)	3556	4355	1.02	1.032	1.007	1.026
FTC	134	13	121	23–76	57.4 (19.3)	2.69 (0.94)	2.93 (0.61)	0.79 (0.09)	104	30	1.054	1.011	1.005	1.003
Health ABC	1472	786	686	70-79	73.7 (2.8)	2.31 (0.66)	3.11 (0.81)	0.74 (0.08)	641	831	0.997	1.001	0.998	1.012
Health 2000	821	394	427	30-75	50.47(10.91)	3.29 (0.90)	4.16 (1.07)	0.79 (0.07)	249	572	1.001	1.023	1.007	1
KORA F4	904	426	478	42-61	53.82(4.39)	3.25 (0.79)	4.20 (0.97)	0.77 (0.06)	344	560	1.051	1.013	1.032	1.017
KORA S3	555	261	294	29–73	47.6 (9.0)	3.43 (0.78)	4.18 (0.99)	0.83 (0.07)	266	289	1.014	1.019	1.012	1.029

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NFBC1966	4556	2182	2374	31–31	31.0 (0)	3.96 (0.79)	4.73 (0.99)	0.84 (0.06)	1648	2908	1.022	1.011	1.023	1.004
ORCADES	692	322	370	19–93	54.9 (15.3)	2.88 (0.84)	3.58 (0.98)	0.80 (0.09)	404	288	1.014	1.046	1.015	1.051
RS-I	1224	556	668	65-97	74.5 (5.6)	2.31 (0.73)	3.16 (0.92)	0.73 (0.08)	361	863	1.029	1.023	1.026	1.017
RS-II	852	381	471	58-88	67.2 (6.3)	2.71 (0.78)	3.61 (1.08)	0.76 (0.09)	287	565	1.027	1.006	1.009	1.016
SHIP	1777	870	907	25–85	52.3 (13.7)	3.28 (0.89)	3.87 (1.03)	0.87 (0.06)	773	1004	1	0.996	1.016	0.991
TwinsUK-I	1885	0	1,885	18–79	48.4 (12.2)	2.73 (0.56)	3.40 (0.61)	0.80 (0.08)	943	942	0.998	1.012	1.009	1.005
Stage 1 sample size	48201													
Stage 2: follow-up														
ADONIX	1410	660	750	25-75	49.08 (13.54)	3.34 (0.86)	4.24(1.02)	0.79 (0.07)	792	618				
BHS2	3038	1368	1670	18-97	50.0 (16.7)	3.05 (0.951)	3.97 (1.15)	0.78 (0.08)	1633	1405				
BRHS	3862	3862	0	58-80	68.72 (5.48)	2.58 (0.69)	3.38 (0.84)	0.77 (0.17)	1121	2741				
BWHHS	3635	0	3635	59-80	68.83 (5.49)	1.98 (0.52)	2.82 (0.76)	0.71 (0.09)	2055	1580				
CARDIA	1626	768	858	17-32	25.6 (3.33)	3.68 (0.81)	4.70 (1.00)	0.82 (0.06)	932	694				
CROATIA-SPLIT	491	209	282	18-85	49.07 (14.60)	3.19 (0.91)	3.80 (1.06)	0.84 (0.08)	239	252				
Gedling	1266	633	633	27-80	56.14 (12.29)	2.85 (0.85)	3.68 (1.01)	0.77 (0.07)	634	632				
GS:SFHS	10399	4304	6095	18-93	46.37 (14.61)	3.11 (0.87)	4.05 (1.02)	0.77 (0.09)	5674	4725				
HCS	2848	1509	1339	59-73	66.14 (2.84)	2.44 (0.68)	3.42 (0.92)	0.72 (0.09)	1318	1530				
LBC1936	991	501	490	67-71	69.55 (0.84)	2.38 (0.67)	3.04 (0.87)	0.79 (0.10)	437	554				
LifeLines	3078	1232	1846	21-88	54.94 (9.75)	3.15 (0.81)	4.21 (1,01)	0.75 (0.08)	1075	2003				
MESA-Lung	1469	737	732	48-90	66.1 (9.7)	2.57 (0.76)	3.44 (0.99)	0.73 (0.09)	636	833				

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Nottingham Smokers	521	236	285	36-89	59.60 (10.48)	1.10 (0.95)	3.02 (1.05)	0.64 (0.16)	0	521				
NSHD	2511	1258	1253	53	53	2.79 (0.70)	3.50 (0.90)	0.80 (0.09)	1045	1466				
RS-III	1247	549	698	46-89	56.59 (5.58)	3.15 (0.85)	4.06 (1.14)	0.78 (0.09)	425	822				
SAPALDIA	5646	2753	2893	18-62	42.0 (11.4)	3.58 (0.84)	4.53 (1.04)	0.79 (0.07)	2653	2993				
TwinsUK-II	2373	0	2373	17-85	53.5(14.3)	2.62(0.61)	3.27(0.65)	0.80 (0.08)	1230	1143				
Stage 2 sample size	46411													
Total sample size	94612													

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B) Stage1 study, genotyping, imputation and genotype-phenotype data. Genotyping platforms, filters applied to SNPs and individuals (if any) before imputation, imputation software and genotype-phenotype association software are given. Studies: Age, Gene/Environment Susceptibility (AGES), Atherosclerosis Risk in Communities (ARIC), British 1958 Birth Cohort–Type 1 Diabetes Genetics Consortium (B58C T1DGC), British 1958 70Birth Cohort–Wellcome Trust Case Control Consortium (B58C WTCCC), Busselton Health Study 1(BHS1), Cardiovascular Health Study (CHS), CROATIA- Korcula, CROATIA-Vis, European Community Respiratory Health Survey (ECRHS), European Prospective Investigation into Cancer and Nutrition-obese Cases (EPIC obese cases), European Prospective Investigation into Cancer and Nutrition-cohort (EPIC population based), Framingham Heart Study (FHS), Finnish Twin Cohort incorporating FinnTwin16 and FITSA (FTC), Finnish Health 2000 survey (Health 2000), Health, Aging, and Body Composition (Health ABC), Cooperative Health Research in the Region of Augsburg (KORA F4), Cooperative Health Research in the Region of Augsburg (KORA S3), Northern Finland Birth Cohort of 1966 (NFBC1966), Orkney Complex Disease Study (ORCADES), Rotterdam Studies (RS-I and RS-II), Study of Health in Pomerania (SHIP) and TwinsUK-I. Abbreviations: GWAS= Genome-Wide Association Study, imp'n=imputation, HWE= Hardy Weinberg Equilibrium, MAF= minor allele frequency.
MACH and IMPUTE are two software implementations that share similar underlying population genetic models[3], and BIMBAM has been shown to perform similarly to MACH and IMPUTE in contrast with other imputation methods[4,5].

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Study name	GWAS platform	Calling algorithm	Individual call rate filter applied (before imp'n)	SNP call rate filter applied before imp'n	SNP HWE filter applied (before imp'n)	SNP MAF filter applied (before imp'n)	Other filter	No of SNPs after filtering (before imp'n)	Imp'n software and version	NCBI; HapMap CEU version for imp'n	Genotype-phenotype association software and version
AGES	Illumina Hu370CNV	BeadStudio	0.97	0.90	1e10-6	0.01	remove AT/GC SNPs	208340	MACH 1.0.16	36;21a	ProbABEL 0.1
ARIC	Affymetrix 6.0	Birdseed	0.95	0.95	1e10-6	0.01	no chromosomal location	669,450	MACH 1.0.16	36;22	ProbABEL 0.1-3
B58C T1DGC	Illumina 550K	ILLUMINUS	0.98	No	No	No	No	520010	MACH 1.0.13	35;21	ProbABEL 0.0-5b
B58C WTCCC	Affymetrix 500K	CHIAMO	0.98	No	No	No	No	490033	IMPUTE 0.2.0	35;21	SNPTEST 1.1.3
BHS1	Illumina 610-Quad	BeadStudio	0.97	0.99 for SNPS with MAF<1%, 0.95 for all other SNPs	5.7e10-7	0.01	No	549294	MACH 1.0.16	36	Mach2Qtl 1.0.8
CHS	Illumina 370 CNV	BeadStudio	0.95	0.97	1e10-5	heterozygote frequency >0	reproducibility errors<2	306,655	BimBam 0.99	36	R
CROATIA-Korcula	Illumina HumanHap 370cnv	Beadstudio	0.98 (for SNP of call rate >=0.98,MAF>=0.02,HWE>=E-10)	0.98	1e10-6	0.01	No	307728	MACH 1.0.15	36;22	GenABEL 1.4.2 , ProbABEL
CROATIA-Vis	Illumina HumanHap 300 v1	Beadstudio	0.97 (for SNP of call rate >=0.98,MAF>=0.02,HWE>=E-10)	0.98	1e10-6	0.01	No	305068	MACH 1.0.15	36;22	GenABEL 1.4.2, ProbABEL

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ECRHS (population based sample from first survey)	Illumina Quad 610k	GenCall	None	None	None	None	None	582892	MACH 1.0	36;22	ProbABEL 0.0-9
EPIC obese cases	Affymetrix 500K	BRLMM	0.94	0.90	1e10-6	0.01	No	397438	IMPUTE 0.3.1	35;21	SNPTEST 1.1.5
EPIC population-based	Affymetrix 500K	BRLMM	0.94	0.90	1e10-6	0.01	No	397438	IMPUTE 0.3.1	35;21	SNPTEST 1.1.5
FHS	Affy 500K + 50K Gene focused	Bayesian robust linear modeling using Mahalanobis distance (BRLMM)	0.97	0.97	1e10-6	0.01	MISHAP p<10-9, mendelian errors>100	378163	MACH 1.0.15	36;22	GWAF
FTC	Illumina 317K	BeadStudio	0.95	0.90	1e10-5	0.01	No	315987	MACH 1.0.16	36;22	PLINK 1.06
Health 2000	Illumina 610K	Illuminus	0.95	0.95	1e10-6	0.01	MDS-plot outliers removed (non-European ancestry)	555388	MACH 1.0	36;22	ProbABEL
Health ABC	Illumina Human 1M-Duo	BeadStudio 3.3.7	0.97	0.95	1e10-6	0.01	No sex mismatch, and cryptic relatedness	914,263	MACH 1.0.16.a	36;22	R version 2.9.2
KORA F4	Affymetrix 6.0	Birdseed2	0.93	No	No	No	No	909622	IMPUTE 0.4.2	36;22	SNPTEST 1.1.5
KORA S3	Affymetrix 500K	BRLMM	0.93	No	No	No	No	490033	MACH 1.0.9	35;21	MACH2QTL 1.0.4
NFBC1966	Illumina HumanCNV370-	Beadstudio	none	0.95	1e10-4	0.01	No	328007	IMPUTE v1.0	35; 21	SNPTEST 1.1.5

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	Duo										
ORCADES	Illumina HumanHap 300 v2	Beadstudio	0.98 (for SNP of call rate >=0.98,MAF>=0.02,HWE>=E-10)	0.98	1e10-6	0.01	No	306207	MACH 1.0.15	36;22	GenABEL 1.4.2, ProbABEL
RS-I	Illumina HapMap 550K	BeadStudio	0.98	0.98	1e10-6	0.01	excess autosomal heterozygosity, sex mismatch or outlying identity-by-state clustering estimates	512,349	MACH 1.0.15	36;22	MACH2QTL as implemented in GRIMP
RS-II	Illumina 550K + 610 Quad	GenomeStudio	0.98	0.98	1e10-6	0.01	excess autosomal heterozygosity, sex mismatch or outlying identity-by-state clustering estimates	537,405	MACH 1.0.16	36;22	MACH2QTL as implemented in GRIMP
SHIP	Affymetrix 6.0	BirdseedV2	0.92	No	No	No	QC callrate > 0.86 each Chip	869224	IMPUTE 0.5.0	36;22	SNPTEST 1.1.5
TwinsUK-I	Illumina 317K	Beadstudio	0.95	0.95 if MAF>0.05; <0.99 if 0.01<=MAF<0.05	5.7e10-7	0.01	unexpected relatedness based on pi_hat	296293	IMPUTE 0.5.0	36;22	GenABEL 1.4.2

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Supplementary Table 2 Literature search results for genes overlapping or proximal to novel lung function lead SNP and genes which contain a SNP with r^2>0.3 with lead SNP.

We systematically searched the scientific literature as catalogued by PubMed and refined our results using the PubMatrix text mining interface[6]. Additionally, we complemented our association findings by searching the Genetic Association Database—a comprehensive repository of published human genetic association studies[7]. Primers used for mRNA expression profiling are also included for each locus.

Lead SNP, Chr: position, chromosomal band	**Genes containing SNP with r^2>0.3 with sentinel SNP (HapMap release 22 CEU, functional annotation obtained using GeneCruiser).**	**Description of genes in region and biological plausibility**	**Animal model with lung function or pulmonary phenotype**	**Lookup in NHGRI GWAS table by sentinel SNP +/- 500kb and r^2>0.3. (P<5x10^{-8} in reported GWAS study)**
rs2284746 chr1: 17179262 1p36.13	**rs2284746**; ***MFAP2*** intron, sentinel. *rs6657613*; ***ATP13A2*** intron, r^2=0.84. *rs2871775*; ***SDHB*** intron, r^2=0.66. *rs2016693*; ***PADI2*** intron, r^2=0.43. *rs7513616*; ***CROCC*** intron, r^2=0.42.	***MFAP2***: Microfibrillar-associated protein 2 is a major antigen of elastin-associated microfibrils[8] and a candidate for involvement in the etiology of inherited connective tissue diseases. ***ATP13A2*** encodes a member of the P5 subfamily of ATPases which transports inorganic cations as well as other substrates. Mutations in ATP13A2 are associated with a form of Parkinson's Disease (PARK9, Kufor-Rakeb syndrome)[9]. ***SDHB*** is a component of the succinate dehydrogenase complex (II) of the respiratory chain and sporadic and familial mutations in this gene result in paragangliomas and pheochromocytoma[10]. ***PADI2*** encodes a peptidyl arginine deiminase which catalyses the post-translational deimination of proteins by converting arginine residues into citrullines in the presence of calcium ions. PADI2 protein levels are increased in bronchial mucosa and bronchoalveolar lavage cells of smokers[11]. ***CROCC*** encodes rootletin, a component of the rootlet at the proximal end of a cilium[12]. **mRNA expression profiling primers** (*MFAP2*) MFAP2-E8F(TCTGTGTTCGTACAGTGTGTGC), MFAP2-E9R(ACAGAGAGGCCTGGGATACTC) Expected product size: 398bp	*Crocc*-null mice develop photoreceptor degeneration and a lymphocytic lung infiltration consistent with impaired mucociliary clearance[13].	Sentinel SNP rs2284746 also associated with human height[14] (P=4x10^{-29}).
rs993925 chr1: 216926691 1q41	Sentinel SNP is 242.1kb downstream of *TGFB2* and 487.1kb upstream of *LYPLAL1* (no SNPs with r^2>0.3 with sentinel SNP in either gene).	This association signal is distal to *TGFB2*, transforming growth factor beta 2. TGFB2 is a member of a family of cytokines TGFB1-3 with a diverse repertoire of functions including regulating; cell proliferation, adhesion, migration and differentiation mediated via TGFB receptor 1 and 2 activation and smad signalling. TGFB2 has been suggested as a pro-fibrotic cytokine modulating epithelial repair mechanisms and extracellular matrix homeostasis including collagen deposition[15]**.** TGFB2 expression levels have been shown to be elevated in respiratory disease *e.g.* in bronchial epithelium in asthma[16]. **mRNA expression profiling primers** (*TGFB2*)	*Tgfb2-/-* mice have multiple cardiac defects, and dilated conducting airways with collapsed terminal bronchioles postnatally[17]. Tgfb2 contributes to airway remodeling and eosinophil recruitment in	none

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		TGFB2F(CGATCCGCGGGCAGATCCTG), TGFB2R(TGGAGGTGCCATCAATACCTGCA) Expected product size: 741bp	OVA-induced asthma model[18]	
rs12477314 chr2: 239542085 2q37.3	rs12477314 is 92.7kb downstream of *HDAC4* and 29.2kb upstream of *FLJ43879*.	***HDAC4*** (histone deacetylase 4) is a member of a family of proteins with enzymatic activity that removes acetylation from histone surrounding DNA thus influencing transcription factor access to the DNA. This deacetylase activity is thought to repress gene transcription. Reduced HDAC activity has been reported in lung tissue from subjects with COPD and this activity correlated with disease severity and inflammatory cytokine expression although HDAC2, 5 and HDAC8 differential expression levels were thought to mediate this observation[19]. Ongoing approaches to recover HDAC activity show potential for therapeutic intervention in COPD[20] **mRNA expression profiling primers** (*HDAC4*) HDAC4-E23F(CATGTGTTTCTGCCTTGCTG), HDAC4-E26R(GTCTGTCCCGTGTTCCCTGT) Expected product size: 523bp	*Hdac4*-null mice die soon after birth, displaying significant skeletal defects and growth retardation that impair mobility and breathing[21].	none
rs1529672 chr3: 25495586 3p24.2	**rs1529672**; ***RARB*** intron, sentinel.	***RARB*** codes for retinoic acid receptor beta, a nuclear receptor responsive to retinoic acid, a vitamin A derivative. This receptor also controls cell proliferation and differentiation. Retinoic acid has been implicated in embryonic lung branching morphogenesis[22]. Epigenetic regulation of the RARB gene promoter has been linked to various cancers including non-small cell lung cancer[23]. **mRNA expression profiling primers** (*RARB*) RARB-E3F(GATGCCAATACTGTCGACTCC), RARB-E6R(CAGAGGACCAAATCCAGCAT) Expected product size: 500bp	*Rarb*-null mice exhibit premature alveolar septation[24].	none
rs1344555 chr3: 170782913 3q26.2	**rs1344555**; ***EVI1*** intron, sentinel	***EVI1***, ecotropic viral integration site 1 codes for a zinc finger transcription factor and evidence suggests a proto-oncogenic role in proliferation in acute myeloid leukaemia[25,26]. The role of EVI1 in the lung is unclear at this time although increases in copy number have been reported in human squamous cell lung cancer[27]. Component of MECOM (*MDS1* and *EVI1* complex locus). **mRNA expression profiling primers** (*EVI1*) EVI1F(TGACCTGGAAACAACCTCGGGC), EVI1R(GCATTGGGAGGCGCCCTGAA) Expected product size: 951bp	*Evi1* is abundantly expressed in the bronchial epithelium of the developing mouse embryo[28].	none
rs153916 chr5: 95062456 5q15	rs153916 is 17.9kb upstream of ***SPATA9*** and 30.1kb upstream of **RHOBTB3**. *rs34895*; ***SPATA9*** intron, r^2=0.65.	Little is known regarding ***SPATA9***, spermatogenesis associated 9. However, this family of proteins were initially identified as mediators of spermatogenesis. Additional functions have now been identified for these proteins *e.g.* SPATA2 has been suggested to have a role in pancreatic development and β-cell proliferation[29]. ***RHOBTB3*** encodes a Rho GTPase which is required for protein transport from endosomes to the trans Golgi network. **mRNA expression profiling primers** (*SPATA9*) SPATAF2(CGAGCAACATTAATTCGTGGAT), SPATAR2(CACCTTCAGCAAACATAGGCT) Expected product size: 406bp	none	none
rs6903823 chr6:	**rs6903823**; ***ZKSCAN3*** intron, sentinel. *rs6912584*; ***ZNF323*** intron, r^2=0.95.	***ZKSCAN3***, zinc finger protein with KRAB and SCAN domains 3 is a transcription factor that has recently been identified as a regulator of many downstream targets including genes involved	none	SNP rs4324798 (r^2=0.42 with

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28430275 6p22.1	*rs7766356*; ***ZSCAN23*** 3' UTR, r^2=0.80. *rs7774981*; ***ZSCAN12*** 3'UTR, r^2=0.66. *rs13215054*; ***GPX6*** intron, r^2=0.60. *rs6901575*; ***PGBD1*** intron, r^2=0.51. *rs13205911*; ***ZNF192*** 3'UTR, r^2=0.50. *rs17763089*; ***HIST1H1B*** exon (synonymous), r^2=0.47. *rs200981;* ***HIST1H2AL*** exon (synonymous), r^2=0.42. *rs1150726*; ***ZNF187*** intron, r^2=0.40. *rs203878*; ***ZNF165*** 5'UTR, r^2=0.37. *rs1654774*; ***ZSCAN16*** intron, r^2=0.34. rs7206; ***ZNF193*** 3'UTR, r^2=0.33. *rs17720293*; ***ZKSCAN4*** intron, r^2=0.31. <u>Non-synonymous SNPs (gene, r^2 >0.3 with sentinel):</u> rs13201753 (*ZKSCAN3*, r^2=0.51). rs1997660 (*PGBD1*, r^2=0.49). rs2232423 (*ZSCAN12*, r^2=0.38). rs6456811 and rs3800325 (*PGBD1*, r^2=0.34). rs853684 (*ZNF323*, r^2=0.33).	in; cell growth/cell cycle/signal transduction *e.g.* VEGF, FGF23, cyclin D1, extracellular matrix and proteolysis *e.g.* MMP26, integrin beta 4 and transcription regulators *e.g.* ELF3[30]. Importantly, these functions have been linked to tumour growth[30] and proliferation in multiple myeloma[31]. ***ZNF323*** (zinc finger 323) is a member of the subfamily of C2H2 Kruppel-like zinc finger transcription factors. Preliminary mRNA expression data for *ZNF323* suggests a potential role in multiple organ embryogenesis including the lung[32]. ***ZNF192* (*ZKSCAN8*), *ZNF187* (*ZSCAN26*), *ZNF165* (*ZSCAN7*), *ZNF193*(*ZSCAN9*), *ZSCAN23*, *ZSCAN12*** and ***ZSCAN16*** encode zinc finger and SCAN domain-containing proteins. ***GPX6*** encodes a glutathione peroxidase. ***PGBD1*** piggyBac transposable element derived 1 is within part of a haplotype linked to high CD8+ T-lymphocyte numbers and Hereditary Hemochromatosis[33]. ***HIST1H1B*** and ***HIST1H2AL*** encode members of the H1 histone protein family, basic nuclear proteins which form the nucleosome which wraps and compacts the DNA into chromatin and may play a role in transcription regulation, DNA repair, DNA replication and chromosomal stability. ***ZKSCAN4*** encodes a zinc finger protein with KRAB and SCAN domains which may inhibit glucocorticoid receptor-mediated transactivation[34]. **eQTL result:** ***ZFP57*** encodes a zinc finger protein with a KRAB domain with a role in methylation associated with imprinting[35]. Mutations in this gene have been implicated in transient neonatal diabetes[36]. ***ZSCAN12* (*ZNF96*)** is described above. **mRNA expression profiling primers** (*ZKSCAN3*) ZKSCAN3F(GCGCCGCAGGTTTCAGGTGTT), ZKSCAN3R(CTGCTGTGTCCATTCAGGGGTGA) Expected product size: 300bp		rs6903823) associated with lung cancer[37] (P=2x10^{-8}).
<u>rs2857595</u> Chr6: 31676448 6p21.33	Sentinel SNP is 7.7kb upstream of ***NCR3*** (no SNP in NCR3 with r^2>0.3 with sentinel SNP), 14.6kb upstream of ***AIF1***. *rs3093975*; ***BAT1*** intron, r^2=0.95. *rs1800629*; ***TNFA*** promoter region (upstream), r^2=0.86. *rs3130614*; ***MICB*** intron, r^2=0.67. *rs7750641*; ***TCF19*** exon (non-synonymous), r^2=0.54. *rs2853975*; ***MICA*** intron, r^2=0.52. *rs3130557*; ***PSORS1C1(SEEK1)*** intron, r^2=0.50. *rs2233980*; ***C6orf15*** exon (synonymous), r^2=0.50. *rs1041981*; ***LTA*** exon (non-synonymous), r^2=0.47. *rs2071592*; ***NFKBIL1*** intron, r^2=0.47. *rs2071594*; ***ATP6V1G2*** 3'UTR, r^2=0.46.	***NCR3***, natural cytotoxity triggering receptor 3, blocking antibodies *in vitro* have demonstrated that NCR3 is required for efficient cytotoxicity responses by natural killer cells against normal cells and tumours[38]. AIF1, allograft inflammatory factor 1, is induced by chemokines and interferon and is involved in the regulation of vascular smooth muscle growth. AIF1 has been implicated in the pulmonary vasculopathy that characterizes systemic sclerosis[39,40]. ***TNFA***: rs1800629 (-308G/A) in the promoter region of TNFA (r^2 0.86) has previously been associated with asthma susceptibility in European ancestry subjects[41]. rs1800629 (-308G/A) been associated with lung function in COPD cases[42], but candidate gene studies reporting its association to COPD susceptibility have not provided consistent and conclusive evidence[43] and suggest publication bias. ***BAT1-BAT5*** are HLA-B associated transcripts. ***MICA*** and ***MICB*** encode the MHC class I chain-related proteins A and B[44]. These proteins are stress-induced and ligands for the activation of the cytolytic response of NK cell receptors. They are similar to MHC class I molecules but do not associate with beta-2-microglobulin or bind peptides. Polymorphisms in MICB have been associated with airflow obstruction in asthmatics[45]. ***TCF19*** encodes transcription factor 19. ***PSORS1C1*(*SEEK1*)** is a psoriasis susceptibility candidate gene[46] and overlaps *CDSN***.** The	*Tnfa* overexpression in mice results in increased lung volume, loss of small airspaces and thickened pleural septa[60]. *Lta* knockout mice have increased airway inflammation and remodelling, and elicit a severe Th1 response when challenged by allergens[61] *Cfb*-null mice infected with *P. aeruginosa* pneumonia exhibit increased mortality[62]	SNP rs3117582 (r^2=0.38 with rs2857595) associated with lung cancer[37,57,63] (strongest P=5x10^{-12}). SNP rs3099844 (r^2=0.67 with rs2857595) associated with neonatal lupus[64] (P=5x10^{-10}). SNP rs3131379 (r^2=0.34 with rs2857595)

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	rs3132450; ***BAT2(PRRC2A)*** intron, r^2=0.38. *rs3117582*; ***APOM*** intron, r^2=0.38. *rs9267531*; ***CSNK2B*** intron, r^2=0.38. *rs3131383*; ***CLIC1*** 5'UTR, r^2=0.34. *rs3131379*; **MSH5** intron, r^2=0.34. *rs915652*; ***VARS*** intron, r^2=0.34. *rs3130679*; ***C6orf48*** 3'UTR, r^2=0.34. *rs3132550*; ***CDSN*** intron, r^2=0.31. *rs3130628*; ***BAT3(BAG6)*** intron, r^2=0.30. *rs3130618*; ***BAT4(GPANK1)*** exon (non-synonymous), r^2=0.30. *rs1270942*; **CFB** intron, r^2=0.30. *rs389884*; **STK19** intron, r^2=0.30. <u>Non-synonymous SNPs (gene, r^2 >0.3 with sentinel):</u> rs7750641 (*TCF19*, r^2=0.54). rs1041981 (*LTA*, r^2=0.47). rs2233974 (*C6orf15*, r^2=0.38). rs3130618 (*BAT4*, r^2=0.30).	function of PSORS1C1 is unknown. ***CDSN*** encodes a protein found in corneodesmosomes, structures found within human epidermis and other cornified squamous epithelia. ***C6orf15*** **(*STG*)** No function is known for this gene in humans but the strongest signal of association in this region for a study of follicular lymphoma overlapped this gene[47]. ***LTA*** encodes lymphotoxin alpha, a cytokine produced by lymphocytes and a member of the tumour necrosis factor family. This gene has been associated with leprosy[48] and psoriatic arthritis[49]. ***NFKBIL1*** encodes a putative inhibitor of the NFκB complex which has a role in DNA transcription regulation and has shown association with rheumatoid arthritis[50] and may confer susceptibility to chronic thromboembolic-induced pulmonary hyptertension[51]. ***ATP6V1G2*** encodes a component of vacuolar ATPase (V-ATPase), a multisubunit enzyme that mediates acidification of intracellular compartments of eukaryotic cells. ***APOM*** encodes apolipoprotein M which may play a role in high density lipid metabolism[52]. ***CSNK2B*** encodes the beta subunit of casein kinase II which is believed to play a role in a wide range of cellular processes[53] including Wnt/beta-catenin signalling[54]. ***CLIC1*** encodes chloride intracellular channel 1 which may play a role in the maintenance of intracellular membranes[55]. ***MSH5*** encode a MutS-homologous protein with roles in meiotic and mitotic DNA recombination[56]. Common variants in the MSH5 locus have been associated with risk of lung cancer[57]. ***VARS*** encodes valyl tRNA synthetase which binds the tRNA with valine for translation. Other aminoacyl tRNA synthetases have been associated with disease including neurodegeneration[58]. ***C6orf48*** Function unknown. ***CFB*** encodes complement factor B, a component of the alternative pathway of complement activation. Complement factor B is cleaved into Ba and Bb with Bb being a serine protease that associates with C3b to form the alternative pathway C3 convertase. Polymorphisms in this gene have been associated with a reduced risk of age-related macular degeneration[59]. ***STK19*** encodes serine/threonine kinase 19 and may be involved in transcription regulation. **eQTL results:** ***HLA-DRB1*** and ***HLA-DQA1*** encode HLA beta and alpha chain class II paralogues, respectively, that play a key role in the immune system by presenting peptides derived from extracellular proteins. **mRNA expression profiling primers** (*NCR3*) NCR3-E2F(ATGCCAGCCAAGGGAGACT), NCR3-E4R(ACAGCCAGAAGAGGGTATGTGT) Expected product size: 577bp		associated with SLE[65] (P=2x10^{-52}).
<u>rs2798641</u> chr6: 109374743 6q21	**rs2798641*; ARMC2*** intron, sentinel.	***ARMC2***, armadillo repeat containing 2 is a member of a protein family containing a repeating motif of ~42 amino acids consisting of three alpha helices. Protein family members have been identified as having roles in many diverse protein functions including; cell signalling, protein degradation and cytoskeleton functions[66]. At this time little is known regarding the function of ARMC2. **mRNA expression profiling primers** (*ARMC2*) ARMC2F(GTGCTGCTTGCACACAACTTCAT), ARMC2R(TTCCATTGCCGTGCAGAGCTGG)	none	none

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		Expected product size: 578bp		
rs7068966 chr10: 12317998 10p13	**rs7068966**; ***CDC123*** intron, sentinel. *rs7072888*; ***NUDT5*** intron, r^2=0.37.	***CDC123***, cell division cycle 123 homolog shows high homology across species and has been shown to be a critical control protein modulating Eukaryotic initiation factor 2 in times of cell stress *e.g.* nutrition and growth in *Saccharomyces cerevisiae*[67]. ***NUDT5*** Human NUDT5 (hNUDT5) is an ADP-ribose (ADPR) pyrophosphatase (ADPRase) that plays important roles in controlling the intracellular levels of ADPR and preventing non-enzymatic ADP-ribosylation of proteins by hydrolyzing ADPR to AMP and ribose 5'-phosphate[68]. **eQTL results** *OSBPL1A* (located on chromosome 18) encodes an oxysterol-binding protein. **mRNA expression profiling primers** (*CDC123*) CDC123-E1F(CGAGGCGTTACCATCAAGA), CDC123-E8R(ATTCACACCATTTTCGGAGAAC) Expected product size: 460bp	none	none
rs11001819 chr10: 77985230 10q22.3	**rs11001819; *c10orf11*** intron, sentinel *rs7078013*; ***KCNMA1*** intron, r^2=0.54.	***C10orf11*** Individuals with a rare deletion that disrupts C10orf11 exhibit cognitive defects[69]. ***KCNMA1*** encodes the potassium large conductance calcium-activated channel, subfamily M, alpha member 1 (also known as BKCa), is present on airway smooth muscle cells and pulmonary endothelium and its activation may lead to bronchial relaxation[70] and pulmonary arterial vasodilation[71]. **mRNA expression profiling primers** (*C10orf11*): C10orf11-E2F(GGAGGAACTCATCTTGGACAAC), C10orf11-E6RB(TCCCATAGTAAACGTAGCGACA) Expected product size: 473bp	none	none
rs11172113 chr12: 55813550 12q13.3	**rs11172113**; ***LRP1*** intron, sentinel *rs167769*; ***STAT6*** intron, r^2=0.36	***LRP1***, low density lipoprotein receptor-related protein 1 is a member of a family of receptors involved in cholesterol homeostasis[72]. However, this receptor interacts with a diverse number of ligands *e.g.* ApoE, MMP-2, MMP-9, uPA-uPAR pathway components, amyloid precursor protein, and mediates the cellular processes related to these proteins including cell signalling and migration[73]. Several of these ligands have been implicated via differential expression in disease progression in COPD including MMP-9, uPA and uPAR[74]. ***STAT6*** encodes a signal transducer and activator of transcription 6, interleukin-4 induced protein and may play a role in allergic inflammation[75] and pathways leading to pulmonary fibrosis[76]. **mRNA expression profiling primers** (*LRP1*) LRP1F(AACCGGTACTACCTGCGCAAGC), LRP1R(TGGCTAGCCGTGCAGTTGGACA) Expected product size: 911bp	*Stat6*-null mice are protected from allergen-induced airway inflammation and eosinophilia[77]. Pharmacologic inhibition of *Stat6* ameliorates ovalbumin-induced bronchial constriction in mice[78].	none
rs1036429 chr12: 94795559 12q22	**rs1036429**; ***CCDC38*** intron, sentinel. *rs4762633*; ***SNRPF*** intron, r^2=0.96.	***CCDC38***, coiled-coil domain containing 38 is a member of a diverse protein family that contain two or more alpha helical domains that twist around each other forming a supercoil. These proteins are involved in a diverse array of functions and includes; skeletal proteins *e.g.* vimentin and motor proteins *e.g.* myosin[79]. At this time little is known regarding the function of CCDC38. ***SNRPF*** Small nuclear ribonucleoprotein F. The presence of anti-RNP antibodies has been associated with increased progression to pulmonary damage in individuals with Systemic Lupus Erythematosus[80].	none	none

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		mRNA expression profiling primers (*CCDC38*): CCDC38-E12F(AGAGAGCTGGAAGAGCAGAATC), CCDC38-E15R(TAGCCTTTCCTGTTGGTGTCTT) Expected product size: 498bp **mRNA expression profiling primers** (*SNRPF*): SNRPFF(CGGTACCTGCTGTAGTCACGA),SNRPFR(CTTCACCCAGATGTCCAGACA) Expected product size: 262bp		
rs12447804 chr16: 56632783 16q13	**rs12447804; *MMP15*** intron, sentinel. Non-synonymous SNPs (gene, r^2 >0.3 with sentinel): rs3743563 (*MMP15*, r^2=1).	***MMP15***, matrix metalloproteinase 15 (also called membrane type matrix metalloproteinase 2, MT2-MMP) is a member of a large protease family with diverse functional roles via protease activity and specificity including; tissue remodelling, wound healing, angiogenesis, and tumor invasion. MMP15 expression has been shown to be elevated in primary lung adenocarcinoma[81] and MMP15 has demonstrated anti- apoptosis properties[82]. MMP15 substrates include Pro-MMP-2, gelatin, fibronectin and laminin[83]. **mRNA expression profiling primers** (*MMP15*) MMP15-E1F(CTGCTCCTGGTGCTTCTGG), MMP15-E4R(AGGTCAGTGCTGGAGAAGGTC) Expected product size: 650bp	*Mmp15* expression is increased in the lungs of mice exposed to particulate matter[84].	none
rs2865531 chr16: 73947817 16q23.1	**rs2865531; *CFDP1*** intron, sentinel *rs12933281*; ***TMEM170A*** intron, r^2=0.97. *rs3115960*; ***CHST6*** intron, r^2=0.76.	***CFDP1*** encodes Craniofacial Development Protein 1. ***TMEM170A*** unknown. ***CHST6*** encodes carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 6. Mutations in this gene have been associated with macular corneal dystrophy. **mRNA expression profiling primers** (*CFDP1*) CFDP1E1F(TGCGGTCTTGTGAGTTTGAC), CFDP1E4R(GCTCTTCTGCTTTTACCAACAA) Expected product size: 500bp	*Cfdp1* is highly expressed in developing mouse lung[85]	none
rs9978142 chr21: 34574109 21q22.11	rs9978142 is 84.1kb upstream of ***KCNE2*** and 90kb downstream of ***C21orf82***.	***KCNE2***, potassium channel, voltage-gated, ISK-related subfamily, member 2 has been associated with thyroid dysfunction using KCNE2-/- mice which exhibited; hypothyroidism, dwarfism, alopecia, goitre and cardiac abnormalities[86]. The authors concluded that the KCNQ1-KCNE2 TSH-stimulated thyrocyte K+ channel was crucial for normal thyroid I– accumulation[86]. KCNQ1-KCNE2 K+ channels may modulate transepithelial anion secretion in Calu3 airway epithelial cells[87]. ***C21orf82*** unknown **mRNA expression profiling primers** (*KCNE2*) KCNE2F(ATTGGCGCCAGAACACAACAGCT), KCNE2R(GACATTTTGAACCCAGCCGCACC) Expected product size: 292bp	none	SNP rs9982601 (r^2=0.68 with rs9978142) associated with myocardial infarction[88] (P=6x10^{-11}).

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Supplementary Table 3 Association of the 16 novel regions, and previously reported regions, with A) FEV_1 and FEV_1/FVC in children, B) tobacco addiction, C) height and D) lung cancer. The effect of SNPs previously associated with height on lung function are also shown (E).

A) Association of the 16 novel regions, and previously reported regions, with FEV_1 and FEV_1/FVC in children. Effects of the 16 novel SNPs, and effects of SNPs in regions previously reported as associated with lung function, on FEV_1 and FEV_1/FVC in children were looked up in ALSPAC (Avon Longitudinal Study of Parents and Children, N=5062, 50% males, age mean (s.d.)=8.6(0.3)) and in the Raine Study (N=1219, 52% males, age mean (s.d.)=8.1(0.3)). Effect sizes estimates for the children's cohorts were meta-analysed using inverse variance weighting. *P* values still significant after applying a Bonferroni correction for 16 tests ($P<0.003125$) are shown in bold. To enable a comparison of effect sizes between children and adults, effect sizes in the SpiroMeta-CHARGE Stage 2 dataset only (to avoid potential winners' curse bias) are given for the novel loci. Effect sizes in the SpiroMeta-CHARGE GWAS Stage 1 are provided for the previously reported regions.

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Chr.	Measure	SNP_ID(NCBI36 position), function	Coded allele	ALSPAC N=5062			Raine N=1219			ALSPAC+Raine meta-analysis			SpiroMeta-CHARGE Stage 2		
				Beta	Se	*P*	Beta	Se	*P*	Beta	Se	*P*	Beta	Se	*P*
Novel loci															
1	FEV_1/FVC	rs2284746 (17179262), *MFAP2*(intron)	G	0.005	0.028	8.58E-01	0.002	0.043	9.61E-01	0.004	0.023	8.60E-01	-0.038	0.007	2.640E-07
1	FEV_1	rs2284746 (17179262), *MFAP2*(intron)	G	-0.064	0.029	2.70E-02	0.096	0.042	2.30 E-02	-0.013	0.024	5.93E-01	0.006	0.007	3.701E-01
1	FEV_1/FVC	rs993925 (216926691), *TGFB2*(downstream)	T	0.052	0.029	7.30E-02	0.015	0.05	7.67E-01	0.043	0.025	8.90E-02	0.023	0.01	1.758E-02
1	FEV_1	rs993925 (216926691), *TGFB2*(downstream)	T	0.058	0.03	5.30E-02	-0.011	0.049	8.20E-01	0.039	0.026	1.26E-01	0.003	0.007	7.292E-01
2	FEV_1/FVC	rs12477314 (239542085), *HDAC4*(downstream)	T	0.093	0.035	8.00E-03	0.063	0.048	1.93E-01	0.083	0.028	4.00E-03	0.031	0.008	8.410E-05
2	FEV_1	rs12477314 (239542085), *HDAC4*(downstream)	T	0.025	0.036	4.87E-01	0.058	0.048	2.31E-01	0.037	0.029	2.03E-01	0.025	0.007	1.816E-04
3	FEV_1/FVC	rs1529672 (25495586), *RARB*(intron)	C	-0.078	0.036	3.00E-01	-0.034	0.053	5.24E-01	-0.064	0.03	3.10E-02	-0.038	0.009	1.160E-05
3	FEV_1	rs1529672 (25495586), *RARB*(intron)	C	0.044	0.037	2.34E-01	0.011	0.053	8.41E-01	0.033	0.03	2.76E-01	-0.011	0.007	9.328E-02
3	FEV_1/FVC	rs1344555 (170782913), *MECOM*(intron)	T	0.016	0.035	6.48E-01	-0.068	0.053	2.00E-01	-0.01	0.029	7.43E-01	-0.017	0.012	1.551E-01
3	FEV_1	rs1344555 (170782913), *MECOM*(intron)	T	-0.013	0.036	7.18E-01	-0.064	0.052	2.19E-01	-0.03	0.03	3.20E-01	-0.025	0.009	6.436E-03
5	FEV_1/FVC	rs153916 (95062456), *SPATA9*(upstream)	T	0.037	0.027	1.71E-01	0.019	0.04	6.31E-01	0.032	0.022	1.60E-01	-0.025	0.009	6.671E-03
5	FEV_1	rs153916 (95062456), *SPATA9*(upstream)	T	0.001	0.028	9.72E-01	0.05	0.04	2.19E-01	0.017	0.023	4.64E-01	0.004	0.007	6.220E-01
6	FEV_1/FVC	rs6903823 (28430275), *ZKSCAN3*(intron)/*ZNF323*(intron)	G	-0.037	0.032	2.48E-01	-0.131	0.049	7.00E-03	-0.065	0.027	1.40E-02	-0.013	0.011	2.337E-01
6	FEV_1	rs6903823 (28430275), *ZKSCAN3*(intron)/*ZNF323*(intron)	G	0.02	0.034	5.56E-01	-0.036	0.049	4.64E-01	0.002	0.028	9.51E-01	-0.029	0.008	4.750E-04
6	FEV_1/FVC	rs2857595 (31676448), *NCR3*(upstream)	G	0.044	0.034	1.96E-01	0.08	0.05	1.09E-01	0.055	0.028	4.90E-02	0.028	0.008	5.364E-04
6	FEV_1	rs2857595 (31676448), *NCR3*(upstream)	G	-0.013	0.035	7.10E-01	-0.076	0.05	1.30E-01	-0.034	0.029	2.41E-01	0.017	0.007	9.411E-03
6	FEV_1/FVC	rs2798641 (109374743), *ARMC2*(intron)	T	-0.102	0.036	5.00E-03	0.049	0.052	3.49E-01	-0.053	0.03	7.30E-02	-0.03	0.012	1.565E-02
6	FEV_1	rs2798641 (109374743), *ARMC2*(intron)	T	-0.115	0.037	2.00E-03	-0.062	0.052	2.33E-01	-0.097	0.03	**1.00E-03**	-0.009	0.01	3.351E-01
10	FEV_1/FVC	rs7068966 (12317998), *CDC123*(intron)	T	0.051	0.027	5.90E-02	-0.03	0.04	4.64E-01	0.026	0.022	2.45E-01	0.023	0.006	3.861E-04
10	FEV_1	rs7068966 (12317998), *CDC123*(intron)	T	0.041	0.029	1.57E-01	0.044	0.04	2.74E-01	0.042	0.024	7.40E-02	0.022	0.005	3.560E-05
10	FEV_1/FVC	rs11001819 (77985230), *C10orf11*(intron)	G	-0.048	0.028	8.60E-02	-0.018	0.041	6.62E-01	-0.038	0.023	9.70E-02	-0.006	0.006	3.174E-01
10	FEV_1	rs11001819 (77985230), *C10orf11(*intron)	G	-0.04	0.029	1.68E-01	0.003	0.041	9.45E-01	-0.026	0.024	2.78E-01	-0.022	0.005	3.100E-05
12	FEV_1/FVC	rs11172113 (55813550), *LRP1*(intron)	T	-0.011	0.028	6.94E-01	-0.054	0.041	1.87E-01	-0.025	0.023	2.85E-01	-0.026	0.01	5.829E-03
12	FEV_1	rs11172113 (55813550), *LRP1*(intron)	T	-0.039	0.029	1.79E-01	-0.032	0.041	4.34E-01	-0.037	0.024	1.21E-01	-0.003	0.007	6.940E-01
12	FEV_1/FVC	rs1036429 (94795559), *CCDC38*(intron)	T	0.066	0.034	5.20E-02	0.014	0.052	7.82E-01	0.05	0.028	7.60E-02	0.028	0.008	3.348E-04
12	FEV_1	rs1036429 (94795559), *CCDC38*(intron)	T	-0.015	0.036	6.77E-01	0.001	0.052	9.79E-01	-0.01	0.03	7.43E-01	0.004	0.006	5.381E-01
16	FEV_1/FVC	rs12447804 (56632783), *MMP15*(intron)	T	-0.06	0.033	6.90E-02	0.089	0.051	8.40E-02	-0.017	0.028	5.52E-01	-0.021	0.01	4.204E-02
16	FEV_1	rs12447804 (56632783), *MMP15*(intron)	T	-0.074	0.034	3.00E-02	-0.006	0.051	9.12E-01	-0.053	0.028	6.10E-02	0.004	0.007	5.705E-01

Contd.

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				ALSPAC N=5062			Raine N=1219			ALSPAC+Raine meta-analysis			SpiroMeta-CHARGE Stage 2		
Chr.	**Measure**	**SNP_ID(NCBI36 position), function**	**Coded allele**	**Beta**	**Se**	***P***	**Beta**	**Se**	***P***	**Beta**	**Se**	***P***	**Beta**	**Se**	***P***
16	FEV_1/FVC	rs2865531 (73947817), *CFDP1*(intron)	T	-0.016	0.028	5.68E-01	0.023	0.041	5.85E-01	-0.004	0.023	8.67E-01	0.024	0.006	1.940E-04
16	FEV_1	rs2865531 (73947817), *CFDP1*(intron)	T	-0.037	0.029	2.02E-01	-0.066	0.041	1.12E-01	-0.046	0.024	5.00E-02	0.011	0.005	3.888E-02
21	FEV_1/FVC	rs9978142 (34574109), *KCNE2*(upstream)	T	-0.031	0.04	4.38E-01	0.125	0.059	3.50E-02	0.018	0.033	5.90E-01	-0.031	0.013	1.749E-02
21	FEV_1	rs9978142 (34574109), *KCNE2*(upstream)	T	-0.035	0.042	4.05E-01	0.095	0.059	1.12E-01	0.008	0.034	8.13E-01	-0.015	0.01	1.353E-01
Previously reported regions															
2	FEV_1/FVC	rs2571445(218391399), *TNS* (ns)	G	0.033	0.028	2.39E-01	-0.037	0.042	3.74E-01	0.011	0.023	6.31E-01	0.033	0.007	4.460E-06
2	FEV_1	rs2571445(218391399), *TNS1*(ns)	G	0.05	0.029	8.47E-02	0.045	0.042	2.83E-01	0.048	0.024	4.25E-02	0.047	0.007	9.830E-11
2	FEV_1/FVC	rs10498230(229210747), *PID1*(downstream)	T	0.072	0.052	1.66E-01	-0.073	0.076	3.39E-01	0.026	0.043	5.44E-01	0.068	0.014	1.130E-06
2	FEV_1	rs10498230(229210747), *PID1*(downstream)	T	0.078	0.054	1.49E-01	0.054	0.076	4.81E-01	0.07	0.044	1.13E-01	0.03	0.014	3.601E-02
4	FEV_1/FVC	rs2045517(90089987), *FAM13A*(intron)	T	0.004	0.028	8.86E-01	-0.03	0.042	4.72E-01	-0.007	0.023	7.78E-01	-0.047	0.007	2.000E-11
4	FEV_1	rs2045517(90089987), *FAM13A*(intron)	T	-0.035	0.029	2.27E-01	-0.013	0.042	7.57E-01	-0.028	0.024	2.43E-01	-0.012	0.007	8.933E-02
4	FEV_1/FVC	rs7671167(90103002), *FAM13A*(intron)	T	0.02	0.027	4.59E-01	-0.016	0.041	6.96E-01	0.009	0.023	6.85E-01	-0.042	0.007	1.270E-09
4	FEV_1	rs7671167(90103002), *FAM13A*(intron)	T	-0.024	0.028	3.91E-01	-0.017	0.041	6.74E-01	-0.022	0.023	3.44E-01	-0.017	0.007	1.635E-02
4	FEV_1/FVC	rs10516526(106908353), *GSTCD*(intron)	G	0.158	0.055	4.07E-03	-0.007	0.081	9.35E-01	0.106	0.045	1.98E-02	0.039	0.014	6.167E-03
4	FEV_1	rs10516526(106908353), *GSTCD*(intron)	G	0.069	0.057	2.26E-01	0.169	0.081	3.66E-02	0.102	0.047	2.81E-02	0.108	0.014	4.750E-14
4	FEV_1/FVC	rs17331332(107027556), *NPNT*(upstream)	G	-0.132	0.054	1.45E-02	0.031	0.08	6.95E-01	-0.081	0.045	7.14E-02	-0.057	0.014	5.300E-05
4	FEV_1	rs17331332(107027556), *NPNT*(upstream)	G	-0.074	0.056	1.86E-01	-0.177	0.079	2.57E-02	-0.108	0.046	1.79E-02	-0.102	0.014	1.110E-12
4	FEV_1/FVC	rs6823809(107048244), *NPNT*(intron)	T	0.113	0.039	3.76E-03	0.101	0.101	3.16E-01	0.112	0.036	2.18E-03	0.056	0.011	2.200E-07
4	FEV_1	rs6823809(107048244), *NPNT*(intron)	T	0.043	0.041	2.94E-01	0.103	0.095	2.80E-01	0.052	0.038	1.64E-01	0.05	0.011	4.820E-06
4	FEV_1/FVC	rs1032296(145654138), *HHIP*(upstream)	T	-0.012	0.029	6.79E-01	0.013	0.043	7.56E-01	-0.004	0.024	8.68E-01	-0.05	0.007	3.420E-12
4	FEV_1	rs1032296(145654138), *HHIP*(upstream)	T	0.02	0.03	5.05E-01	-0.053	0.042	2.12E-01	-0.004	0.024	8.57E-01	-0.047	0.007	8.740E-11
4	FEV_1/FVC	rs11100860(145698589), *HHIP*(upstream)	G	0.016	0.029	5.81E-01	-0.02	0.041	6.25E-01	0.004	0.024	8.68E-01	0.064	0.007	6.810E-20
4	FEV_1	rs11100860(145698589), *HHIP*(upstream)	G	-0.015	0.03	6.17E-01	0.056	0.041	1.70E-01	0.01	0.024	6.82E-01	0.041	0.007	4.270E-09
5	FEV_1/FVC	rs11168048(147822546), *HTR4*(intron)	T	-0.072	0.029	1.30E-02	0.011	0.041	7.86E-01	-0.044	0.024	6.08E-02	-0.047	0.007	5.970E-11
5	FEV_1	rs11168048(147822546), *HTR4*(intron)	T	-0.003	0.03	9.20E-01	0.057	0.041	1.71E-01	0.018	0.024	4.70E-01	-0.046	0.007	2.430E-10
5	FEV_1/FVC	rs3995090(147826008), *HTR4*(intron)	C	0.074	0.028	8.22E-03	-0.001	0.04	9.88E-01	0.049	0.023	3.12E-02	0.046	0.007	1.040E-10
5	FEV_1	rs3995090(147826008), *HTR4*(intron)	C	0	0.029	1.00E+00	-0.042	0.04	2.98E-01	-0.014	0.023	5.41E-01	0.045	0.007	3.330E-10
5	FEV_1/FVC	rs1985524(147827981), *HTR4*(intron)	G	-0.083	0.028	3.03E-03	0.04	0.04	3.21E-01	-0.043	0.023	6.10E-02	-0.045	0.007	2.900E-10
5	FEV_1	rs1985524(147827981), *HTR4*(intron)	G	-0.004	0.029	8.90E-01	0.052	0.041	2.05E-01	0.015	0.024	5.35E-01	-0.048	0.007	3.060E-11

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				ALSPAC N=5062			Raine N=1219			ALSPAC+Raine meta-analysis			SpiroMeta-CHARGE Stage 2		
Chr.	**Measure**	**SNP_ID(NCBI36 position), function**	**Coded allele**	**Beta**	**Se**	***P***	**Beta**	**Se**	***P***	**Beta**	**Se**	***P***	**Beta**	**Se**	***P***
5	FEV_1/FVC	rs11134779(156869344), *ADAM19*(intron)	G	0.013	0.029	6.54E-01	-0.036	0.042	3.90E-01	-0.003	0.024	9.06E-01	-0.042	0.007	6.010E-09
5	FEV_1	rs11134779(156869344), *ADAM19*(intron)	G	-0.051	0.03	8.91E-02	0.039	0.042	3.60E-01	-0.021	0.024	3.93E-01	-0.027	0.007	2.396E-04
6	FEV_1/FVC	rs2070600(32259421), *AGER*(ns)	T	0.126	0.054	1.96E-02	0.192	0.081	1.83E-02	0.146	0.045	1.15E-03	0.126	0.016	9.070E-15
6	FEV_1	rs2070600(32259421), *AGER*(ns)	T	0.05	0.056	3.72E-01	0.089	0.081	2.73E-01	0.063	0.046	1.75E-01	0.025	0.016	1.271E-01
6	FEV_1/FVC	rs3817928(142792209), *GPR126*(intron)	G	0.106	0.035	2.46E-03	0.045	0.05	3.68E-01	0.086	0.029	2.75E-03	0.059	0.008	2.270E-12
6	FEV_1	rs3817928(142792209), *GPR126*(intron)	G	-0.033	0.036	3.59E-01	0.032	0.05	5.26E-01	-0.011	0.029	7.11E-01	0.023	0.009	8.625E-03
6	FEV_1/FVC	rs262129(142894837), *LOC153910*(unknown)	G	0.118	0.03	8.38E-05	0.054	0.044	2.23E-01	0.098	0.025	8.19E-05	0.056	0.008	2.910E-13
6	FEV_1	rs262129(142894837), *LOC153910*(unknown)	G	-0.021	0.032	5.12E-01	0.017	0.044	6.98E-01	-0.008	0.026	7.61E-01	0.031	0.008	5.440E-05
9	FEV_1/FVC	rs16909859(97244613), *PTCH1*(downstream)	G	0.057	0.05	2.54E-01	0.022	0.09	8.12E-01	0.049	0.044	2.66E-01	0.08	0.013	7.450E-10
9	FEV_1	rs16909859(97244613), *PTCH1*(downstream)	G	0.058	0.052	2.65E-01	-0.128	0.092	1.62E-01	0.013	0.045	7.80E-01	-0.014	0.013	2.933E-01
9	FEV_1/FVC	rs16909898(97270829), *PTCH1*(intron)	G	-0.089	0.048	6.37E-02	0.002	0.088	9.77E-01	-0.068	0.042	1.06E-01	-0.072	0.012	3.940E-09
9	FEV_1	rs16909898(97270829), *PTCH1*(intron)	G	-0.022	0.049	6.53E-01	0.098	0.089	2.67E-01	0.006	0.043	8.85E-01	0.015	0.012	2.211E-01
15	FEV_1/FVC	rs12899618(69432174), *THSD4*(intron)	G	0.045	0.039	2.49E-01	0.092	0.057	1.02E-01	0.06	0.032	6.03E-02	0.076	0.01	1.860E-15
15	FEV_1	rs12899618(69432174), *THSD4*(intron)	G	-0.024	0.041	5.58E-01	-0.029	0.057	6.10E-01	-0.026	0.033	4.39E-01	0.036	0.01	1.567E-04
15	FEV_1/FVC	rs8033889(69467134), *THSD4*(intron)	T	-0.051	0.034	1.34E-01	-0.104	0.051	4.09E-02	-0.067	0.028	1.70E-02	-0.072	0.008	2.030E-17
15	FEV_1	rs8033889(69467134), *THSD4*(intron)	T	0.031	0.035	3.76E-01	0.094	0.051	6.30E-02	0.051	0.029	7.41E-02	-0.044	0.009	3.010E-07
15	FEV_1/FVC	rs2568494(76528019), *IREB2*(intron)	G	0.014	0.029	6.29E-01	0.028	0.043	5.22E-01	0.018	0.024	4.48E-01	0.029	0.007	5.250E-05
15	FEV_1	rs2568494(76528019), *IREB2*(intron)	G	-0.023	0.03	4.43E-01	0.015	0.043	7.27E-01	-0.011	0.025	6.68E-01	0.023	0.007	1.635E-03
15	FEV_1/FVC	rs8034191(76593078), *CHRNA3/5*(intron)	T	0.026	0.029	3.70E-01	-0.01	0.042	8.13E-01	0.014	0.024	5.47E-01	0.032	0.007	9.650E-06
15	FEV_1	rs8034191(76593078), *CHRNA3/5*(intron)	T	-0.03	0.03	3.17E-01	0.007	0.042	8.67E-01	-0.017	0.024	4.75E-01	0.031	0.007	2.070E-05
15	FEV_1/FVC	rs2036527(76638670), *CHRNA5*(uptream)	G	0.038	0.03	2.05E-01	-0.015	0.047	7.57E-01	0.023	0.025	3.66E-01	0.032	0.007	1.190E-05
15	FEV_1	rs2036527(76638670), *CHRNA5*(uptream)	G	-0.015	0.031	6.28E-01	0.04	0.047	3.97E-01	0.002	0.026	9.51E-01	0.036	0.008	2.400E-06
15	FEV_1/FVC	rs8040868(76698236), *CHRNA3*(s)	T	0.039	0.028	1.64E-01	-0.027	0.042	5.19E-01	0.019	0.023	4.25E-01	0.04	0.008	1.140E-06
15	FEV_1	rs8040868(76698236), *CHRNA3*(s)	T	0.003	0.03	9.20E-01	0.041	0.042	3.21E-01	0.016	0.024	5.09E-01	0.039	0.008	2.980E-06

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B) Relation of 16 novel lung function loci, and previously reported loci, with tobacco addiction. Effects of the 16 novel SNPs associated with lung function on two smoking phenotypes (cigarettes per day and ever-smokers vs. never-smokers) were looked up in the Oxford-GlaxoSmithKline (Ox-GSK) study, a collaborative effort to investigate the genetic basis of smoking-related behavioral traits [89]. Results for the SpiroMeta-CHARGE joint meta-analysis of Stage 1 and Stage 2 for the lung function measure that showed stronger association are reported for the novel loci. Results for the SpiroMeta-CHARGE GWAS stage (stage 1) for the lung function measure that showed stronger association are reported for the previously reported loci.

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				Lung function (Stage 1 and Stage 2 meta-analysis)			Cigarettes per day			Ever vs. Never smoking		
Chr.	**SNP ID(NCBI36 position), function**	**Coded allele**	**Measure**	**Beta**	**Se**	***P***	**Beta**	**Se**	***P***	**Beta**	**Se**	***P***
Novel loci												
1	rs2284746 (17179262), *MFAP2*(intron)	G	FEV_1/FVC	-0.04	0.005	7.50E-16	0.004	0.01	6.85E-01	-0.015	0.018	3.99E-01
1	rs993925 (216926691), *TGFB2*(downstream)	T	FEV_1/FVC	0.034	0.006	1.16E-08	-0.007	0.011	5.12E-01	-0.027	0.019	1.53E-01
2	rs12477314 (239542085), *HDAC4*(downstream)	T	FEV_1/FVC	0.041	0.006	1.68E-12	-0.021	0.012	8.83E-02	0.014	0.022	5.20E-01
3	rs1529672 (25495586), *RARB*(intron)	C	FEV_1/FVC	-0.048	0.006	3.97E-14	-0.013	0.014	3.65E-01	0.024	0.025	3.38E-01
3	rs1344555 (170782913), *MECOM*(intron)	T	FEV_1	-0.034	0.006	2.65E-08	0.011	0.013	3.86E-01	0.01	0.022	6.51E-01
5	rs153916 (95062456), *SPATA9*(upstream)	T	FEV_1/FVC	-0.031	0.005	2.12E-08	-0.021	0.01	3.70E-02	0.02	0.018	2.72E-01
6	rs6903823 (28430275), *ZKSCAN3*(intron)/*ZNF323*(intron)	G	FEV_1	-0.037	0.006	2.18E-10	0.02	0.012	8.86E-02	-0.026	0.021	2.16E-01
6	rs2857595 (31676448), *NCR3*(upstream)	G	FEV_1/FVC	0.037	0.006	2.28E-10	-0.002	0.014	8.55E-01	-0.009	0.025	7.12E-01
6	rs2798641 (109374743), *ARMC2*(intron)	T	FEV_1/FVC	-0.041	0.007	8.35E-09	0.007	0.013	5.69E-01	-0.036	0.025	1.39E-01
10	rs7068966 (12317998), *CDC123*(intron)	T	FEV_1/FVC	0.033	0.005	6.13E-13	0.001	0.01	9.22E-01	0.02	0.018	2.74E-01
10	rs11001819 (77985230), *C10orf11*(intron)	G	FEV_1	-0.029	0.004	2.98E-12	-0.011	0.01	2.70E-01	0.015	0.018	4.05E-01
12	rs11172113 (55813550), *LRP1*(intron)	T	FEV_1/FVC	-0.032	0.006	1.24E-08	-0.006	0.01	5.41E-01	0.022	0.019	2.44E-01
12	rs1036429 (94795559), *CCDC38*(intron)	T	FEV_1/FVC	0.038	0.006	2.30E-11	0.006	0.012	6.35E-01	0.028	0.021	1.85E-01
16	rs12447804 (56632783), *MMP15*(intron)	T	FEV_1/FVC	-0.038	0.007	3.59E-08	-0.005	0.013	6.69E-01	-0.005	0.022	8.06E-01
16	rs2865531 (73947817), *CFDP1*(intron)	T	FEV_1/FVC	0.031	0.005	1.77E-11	0.019	0.01	5.30E-02	0.002	0.018	9.13E-01
21	rs9978142 (34574109), *KCNE2*(upstream)	T	FEV_1/FVC	-0.043	0.008	2.65E-08	0.007	0.013	5.84E-01	0.007	0.024	7.59E-01
Previously reported loci												
2	rs2571445(218391399), *TNS1*(ns)	G	FEV_1	0.047	0.007	9.83E-11	-0.011	0.011	3.09E-01	0.023	0.02	2.47E-01
2	rs10498230(229210747), *PID1*(downstream)	T	FEV_1/FVC	0.068	0.014	1.13E-06	-0.061	0.019	**1.62E-03**	-0.05	0.033	1.38E-01
4	rs2045517(90089987), *FAM13A* (intron)	T	FEV_1/FVC	-0.047	0.007	2.00E-11	-0.01	0.01	3.23E-01	0.004	0.018	8.40E-01
4	rs7671167(90103002), *FAM13A* (intron)	T	FEV_1/FVC	-0.042	0.007	1.27E-09	-0.013	0.01	1.91E-01	0.014	0.018	4.35E-01
4	rs10516526(106908353), *GSTCD*(intron)	G	FEV_1	0.108	0.014	4.75E-14	0.03	0.02	1.23E-01	0.018	0.034	6.08E-01
4	rs17331332(107027556), *NPNT* (upstream)	G	FEV_1	-0.102	0.014	1.11E-12	-0.037	0.019	5.25E-02	-0.031	0.033	3.51E-01
4	rs6823809(107048244), *NPNT*(intron)	T	FEV_1/FVC	0.056	0.011	2.20E-07	0.011	0.026	6.77E-01	-0.045	0.066	5.02E-01
4	rs1032296(145654138), *HHIP*(upstream)	T	FEV_1/FVC	-0.05	0.007	3.42E-12	0.007	0.01	4.97E-01	-0.002	0.018	9.01E-01
4	rs11100860(145698589), *HHIP*(upstream)	G	FEV_1/FVC	0.064	0.007	6.81E-20	-0.002	0.01	8.58E-01	0.001	0.017	9.32E-01

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				Lung function (Stage 1 and Stage 2 meta-analysis)			Cigarettes per day			Ever vs. Never smoking		
Chr.	**SNP ID(NCBI36 position), function**	**Coded allele**	**Measure**	**Beta**	**Se**	***P***	**Beta**	**Se**	***P***	**Beta**	**Se**	***P***
5	rs11168048(147822546), *HTR4*(intron)	T	FEV_1/FVC	-0.047	0.007	5.97E-11	0.003	0.01	7.34E-01	-0.012	0.018	5.04E-01
5	rs3995090(147826008), *HTR4*(intron)	C	FEV_1/FVC	0.046	0.007	1.04E-10	-0.002	0.01	8.69E-01	0.014	0.018	4.25E-01
5	rs1985524(147827981), *HTR4*(intron)	G	FEV_1	-0.048	0.007	3.06E-11	0	0.01	9.97E-01	-0.027	0.018	1.32E-01
5	rs11134779(156869344), *ADAM19*(intron)	G	FEV_1/FVC	-0.042	0.007	6.01E-09	-0.015	0.01	1.43E-01	0.012	0.019	5.27E-01
6	rs2070600(32259421), *AGER*(ns)	T	FEV_1/FVC	0.126	0.016	9.07E-15	0.033	0.026	1.98E-01	0.056	0.044	2.03E-01
6	rs3817928(142792209), *GPR126*(intron)	G	FEV_1/FVC	0.059	0.008	2.27E-12	-0.004	0.012	7.16E-01	0.005	0.021	8.10E-01
6	rs262129(142894837), *LOC153910*(unknown)	G	FEV_1/FVC	0.056	0.008	2.91E-13	0.005	0.011	6.56E-01	0.019	0.02	3.39E-01
9	rs16909859(97244613), *PTCH1*(downstream)	G	FEV_1/FVC	0.08	0.013	7.45E-10	-0.005	0.02	7.81E-01	-0.012	0.033	7.09E-01
9	rs16909898(97270829), *PTCH1*(intron)	G	FEV_1/FVC	-0.072	0.012	3.94E-09	0.024	0.018	1.91E-01	0.019	0.031	5.45E-01
15	rs12899618(69432174), *THSD4*(intron)	G	FEV_1/FVC	0.076	0.01	1.86E-15	-0.013	0.014	3.36E-01	-0.012	0.024	6.31E-01
15	rs8033889(69467134), *THSD4*(intron)	T	FEV_1/FVC	-0.072	0.008	2.03E-17	-0.004	0.012	7.57E-01	-0.02	0.022	3.59E-01
15	rs2568494(76528019), *IREB2*(intron)	G	FEV_1/FVC	0.029	0.007	5.25E-05	-0.082	0.01	**2.15E-15**	-0.016	0.018	3.62E-01
15	rs8034191(76593078), *CHRNA3/5*(intron)	T	FEV_1/FVC	0.032	0.007	9.65E-06	-0.09	0.011	**1.59E-17**	-0.02	0.018	2.75E-01
15	rs2036527(76638670), *CHRNA5*(uptream)	G	FEV_1	0.036	0.008	2.40E-06	-0.091	0.011	**6.34E-18**	-0.016	0.018	3.86E-01
15	rs8040868(76698236), *CHRNA3*(coding-synon)	T	FEV_1/FVC	0.04	0.008	1.14E-06	-0.09	0.011	**2.53E-17**	-0.023	0.019	2.26E-01

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C) Relation of16 novel lung function loci, and previously reported loci, with height. Effects of the 16 novel SNPs, and previously reported SNPs, associated with lung function on height were looked up in the GIANT dataset[90]. Directions of effect for height have been flipped to refer to the same coded allele as lung function. Both effect sizes for lung and for height can be interpreted as proportion of a standard deviation. *P* values still significant after applying a Bonferroni correction for 16 tests (*P*<0.003125) are shown in bold. Results for the SpiroMeta-CHARGE Stage 1 and Stage 2 meta-analysis for the lung function measure that showed stronger association are reported for the novel loci. Results from the GWAS Stage 1 for the lung function measure that showed stronger association are reported for the previously reported loci. A column indicating whether the effect of each SNP on height is on the same direction as the effect on lung is included. Abbreviations: ns=nonsynonymous, s= synonymous.

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Chr.	SNP ID(NCBI36 position), function	Coded allele	Measure	Lung function (Stage 1+ Stage 2 meta-analysis)			Height (GIANT consortium)			Relationship of direction of effect on height to direction of effect on lung function
				Beta	Se	*P*	Beta	Se	*P*	
Novel loci										
1	rs2284746 (17179262), *MFAP2*(intron)	G	FEV_1/FVC	-0.04	0.005	7.50E-16	0.0354	0.0045	**5.638E-15**	different
1	rs993925 (216926691), *TGFB2*(downstream)	T	FEV_1/FVC	0.034	0.006	1.16E-08	0.0105	0.005	3.605E-02	same
2	rs12477314 (239542085), *HDAC4*(downstream)	T	FEV_1/FVC	0.041	0.006	1.68E-12	-0.0029	0.0057	6.124E-01	different
3	rs1529672 (25495586), *RARB*(intron)	C	FEV_1/FVC	-0.048	0.006	3.97E-14	0.0012	0.0063	8.494E-01	different
3	rs1344555 (170782913), *MECOM*(intron)	T	FEV_1	-0.034	0.006	2.65E-08	-0.0145	0.0056	9.681E-03	same
5	rs153916 (95062456), *SPATA9*(upstream)	T	FEV_1/FVC	-0.031	0.005	2.12E-08	0.0027	0.0045	5.513E-01	different
6	rs6903823 (28430275), *ZKSCAN3*(intron)/*ZNF323*(intron)	G	FEV_1	-0.037	0.006	2.18E-10	-0.0017	0.0056	7.617E-01	same
6	rs2857595 (31676448), *NCR3*(upstream)	G	FEV_1/FVC	0.037	0.006	2.28E-10	-0.0148	0.006	1.306E-02	different
6	rs2798641 (109374743), *ARMC2*(intron)	T	FEV_1/FVC	-0.041	0.007	8.35E-09	-0.0042	0.0058	4.723E-01	same
10	rs7068966 (12317998), *CDC123*(intron)	T	FEV_1/FVC	0.033	0.005	6.13E-13	0.0078	0.0045	8.521E-02	same
10	rs11001819 (77985230), *C10orf11*(intron)	G	FEV_1	-0.029	0.004	2.98E-12	0.0024	0.0045	5.964E-01	different
12	rs11172113 (55813550), *LRP1*(intron)	T	FEV_1/FVC	-0.032	0.006	1.24E-08	0.003	0.0047	5.189E-01	different
12	rs1036429 (94795559), *CCDC38*(intron)	T	FEV_1/FVC	0.038	0.006	2.30E-11	-0.0053	0.0056	3.444E-01	different
16	rs12447804 (56632783), *MMP15*(intron)	T	FEV_1/FVC	-0.038	0.007	3.59E-08	0.0077	0.0075	3.054E-01	different
16	rs2865531 (73947817), *CFDP1*(intron)	T	FEV_1/FVC	0.031	0.005	1.77E-11	-0.0129	0.0045	4.418E-03	different
21	rs9978142 (34574109), *KCNE2*(upstream)	T	FEV_1/FVC	-0.043	0.008	2.65E-08	-0.0122	0.0062	4.914E-02	same
Previously reported loci										
2	rs2571445 (218391399), *TNS1*(ns)	G	FEV_1	0.047	0.007	9.83E-11	-0.0032	0.0047	4.914E-01	different
2	rs10498230 (229210747), *PID1*(downstream)	T	FEV_1/FVC	0.068	0.014	1.13E-06	-0.0111	0.0087	2.023E-01	different
4	rs2045517 (90089987), *FAM13A*(intron)	T	FEV_1/FVC	-0.047	0.007	2.00E-11	0.0058	0.0045	2.006E-01	different
4	rs7671167 (90103002), *FAM13A*(intron)	T	FEV_1/FVC	-0.042	0.007	1.27E-09	0.0072	0.0045	1.121E-01	different
4	rs10516526 (106908353), *GSTCD*(intron)	G	FEV_1	0.108	0.014	4.75E-14	0.0032	0.0092	7.275E-01	same
4	rs17331332 (107027556), *NPNT*(upstream)	G	FEV_1	-0.102	0.014	1.11E-12	-0.002	0.0093	8.298E-01	same
4	rs6823809 (107048244), *NPNT*(intron)	T	FEV_1/FVC	0.056	0.011	2.20E-07	-0.0001	0.0072	9.888E-01	different
4	rs1032296 (145654138), *HHIP*(upstream)	T	FEV_1/FVC	-0.05	0.007	3.42E-12	-0.0152	0.0047	1.082E-03	same
4	rs11100860 (145698589), *HHIP*(upstream)	G	FEV_1/FVC	0.064	0.007	6.81E-20	0.0151	0.0045	8.618E-04	same

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				Lung function (Stage 1+ Stage 2 meta-analysis)			Height (GIANT consortium)			Relationship of direction of effect on height to direction of effect on lung function
Chr.	**SNP ID(NCBI36 position), function**	**Coded allele**	**Measure**	**Beta**	**Se**	***P***	**Beta**	**Se**	***P***	
5	rs11168048 (147822546), *HTR4*(intron)	T	FEV_1/FVC	-0.047	0.007	5.97E-11	-0.0133	0.0049	6.524E-03	same
5	rs3995090 (147826008), *HTR4*(intron)	C	FEV_1/FVC	0.046	0.007	1.04E-10	0.0143	0.0049	3.448E-03	same
5	rs1985524 (147827981), *HTR4*(intron)	G	FEV_1	-0.048	0.007	3.06E-11	-0.015	0.0049	2.156E-03	same
5	rs11134779 (156869344), *ADAM19*(intron)	G	FEV_1/FVC	-0.042	0.007	6.01E-09	-0.0092	0.0047	4.791E-02	same
6	rs2070600 (32259421), *AGER*(ns)	T	FEV_1/FVC	0.126	0.016	9.07E-15	0.0094	0.0114	4.116E-01	same
6	rs3817928 (142792209), *GPR126*(intron)	G	FEV_1/FVC	0.059	0.008	2.27E-12	-0.0368	0.0055	1.967E-11	different
6	rs262129 (142894837), *LOC153910*(unknown)	G	FEV_1/FVC	0.056	0.008	2.91E-13	-0.0443	0.005	9.173E-19	different
9	rs16909859 (97244613), *PTCH*1(downstream)	G	FEV_1/FVC	0.08	0.013	7.45E-10	-0.0266	0.0082	1.226E-03	different
9	rs16909898 (97270829), *PTCH1*(intron)	G	FEV_1/FVC	-0.072	0.012	3.94E-09	0.0313	0.0078	5.392E-05	different
15	rs12899618 (69432174), *THSD4*(intron)	G	FEV_1/FVC	0.076	0.01	1.86E-15	-0.0075	0.0061	2.175E-01	different
15	rs8033889 (69467134), *THSD4*(intron)	T	FEV_1/FVC	-0.072	0.008	2.03E-17	0.0015	0.0054	7.798E-01	different
15	rs2568494 (76528019), *IREB2*(intron)	G	FEV_1/FVC	0.029	0.007	5.25E-05	0.0021	0.0047	6.516E-01	same
15	rs8034191 (76593078), *CHRNA3/5*(intron)	T	FEV_1/FVC	0.032	0.007	9.65E-06	-0.0002	0.0047	9.657E-01	different
15	rs2036527 (76638670), *CHRNA5*(uptream)	G	FEV_1	0.036	0.008	2.40E-06	-0.0005	0.0048	9.165E-01	different
15	rs8040868 (76698236), *CHRNA3*(s)	T	FEV_1/FVC	0.04	0.008	1.14E-06	-0.006	0.0064	3.515E-01	different

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D) Relation of 16 novel lung function loci, and previously reported loci, with lung cancer. Effects of the 16 novel SNPs, and previously reported SNPs, associated with lung function on lung cancer were assessed in the International Lung Cancer Consortium (ILCCO) GWAS meta-analysis[37]. Directions of effect for lung cancer have been flipped to refer to the same coded allele as lung function. *P* values still significant after applying a Bonferroni correction for 16 tests (*P*<0.003125) are shown in bold. The ILCCO GWAS meta-analysis only had genotyped data, for this reason proxy SNPs were given when the top SNP was not included in their data. Leading SNP, region name and r^2 between leading SNP and proxy SNP are also provided. Results for the SpiroMeta-CHARGE Stage 1 and Stage 2 meta-analysis are reported for the SNPs that were followed up in Stage 2 and were included in the lung cancer dataset (rs1529672, rs2857595, rs2798641, rs11001819, rs11172113, rs1036429) and results from the GWAS Stage 1 only are provided for the other loci, for the lung function measure that showed stronger association.

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Chr.	Proxy SNP ID (NCBI36 position), function	Leading SNP (region name), r^2 with proxy	Coded allele	Lung function				Lung cancer		
				Measure	Beta	Se	*P*	Beta	Se	*P*
Novel loci										
1	rs761423 (17174259), *MFAP2* (intron)	rs2284746 (*MFAP2*), 0.63	T	FEV_1/FVC	0.038	0.007	8.72E-08	0.033	0.017	6.24E-02
1	rs2871775 (17218492), *SDHB* (intron)	rs2284746 (*MFAP2*), 0.66	G	FEV_1/FVC	-0.040	0.007	9.08E-09	-0.015	0.017	3.81E-01
2	rs4591362 (239542675), *HDAC4*(downstream)	rs12477314 (*HDAC4*), 0.94	G	FEV_1/FVC	-0.049	0.009	8.29E-09	-0.020	0.021	3.49E-01
3	rs1529672 (25495586), *RARB* (intron)	rs1529672 (*RARB*), 1	C	FEV_1/FVC	-0.048	0.006	3.97E-14	-0.013	0.027	6.33E-01
3	rs2056777 (25515395), *RARB* (intron)	rs1529672 (*RARB*), 0.77	T	FEV_1/FVC	-0.050	0.009	5.31E-08	-0.011	0.027	6.80E-01
3	rs1362772 (170739927), *MECOM*(intron)	rs1344555 (*MECOM*), 1	T	FEV_1	-0.040	0.009	3.24E-06	-0.010	0.022	6.63E-01
3	rs7642776 (170753972), *MECOM*(intron)	rs1344555 (*MECOM*), 0.94	G	FEV_1	0.038	0.008	5.38E-06	0.013	0.021	5.37E-01
5	rs2548125 (95037182), *SPATA9* (intron)	rs153916 (*SPATA9*), 0.61	G	FEV_1/FVC	-0.029	0.007	3.50E-05	-0.012	0.018	5.08E-01
6	rs209181 (28900456), *LOC401242* (downstream)	rs6903823 (*ZKSCAN3/ZNF323*), 0.69	G	FEV_1	0.035	0.012	2.25E-03	-0.106	0.026	**3.41E-05**
6	rs3099844 (31556955), *HCG26* (downstream)	rs2857595 (*NCR3*), 0.67	C	FEV_1	0.058	0.011	1.92E-07	-0.141	0.027	**2.21E-07**
6	rs2857595 (31676448), *NCR3*(upstream)	rs2857595 (*NCR3*), 1	G	FEV_1/FVC	0.037	0.006	2.28E-10	-0.051	0.022	1.91E-02
6	rs1475055 (109350925), *ARMC2* (intron)	rs2798641 (*ARMC2*), 0.73	T	FEV_1/FVC	0.027	0.008	7.67E-04	-0.011	0.020	5.87E-01
6	rs2798641 (109374743), *ARMC2* (intron)	rs2798641 (*ARMC2*), 1	T	FEV_1/FVC	-0.041	0.007	8.35E-09	0.006	0.022	7.72E-01
10	rs1317549 (12285320), *CDC123* (intron)	rs7068966 (*CDC123*), 0.68	T	FEV_1/FVC	-0.038	0.007	8.95E-08	0.013	0.018	4.78E-01
10	rs4478891 (12307660), *CDC123* (intron)	rs7068966 (*CDC123*), 0.85	G	FEV_1/FVC	0.043	0.007	8.71E-10	-0.005	0.018	7.61E-01
10	rs2130800 (77944824), *C10orf11* (intron)	rs11001819 (*C10orf11*), 0.73	T	FEV_1	0.038	0.007	5.45E-08	0.031	0.017	7.80E-02
10	rs11001819 (77985230), *C10orf11* (intron)	rs11001819 (*C10orf11*), 1	G	FEV_1	-0.029	0.004	2.98E-12	-0.051	0.020	1.21E-02
10	rs2637260 (77990352), *C10orf11* (downstream)	rs11001819 (*C10orf11*), 0.72	T	FEV_1	0.035	0.007	7.38E-07	0.024	0.017	1.72E-01
12	rs11172113 (55813550), *LRP1* (intron)	rs11172113 (*LRP1*), 1	T	FEV_1/FVC	-0.032	0.006	1.24E-08	-0.010	0.018	5.84E-01
12	rs1466535 (55820737), *LRP1* (intron)	rs11172113 (*LRP1*), 0.72	G	FEV_1/FVC	-0.025	0.007	5.76E-04	0.004	0.018	8.45E-01
12	rs7307510 (94761701), *SNRPF* (upstream)	rs1036429 (*CCDC38*), 0.96	T	FEV_1/FVC	0.049	0.009	3.49E-08	0.009	0.023	6.82E-01
12	rs1036429 (94795559), *CCDC38* (intron)	rs1036429 (*CCDC38*), 1	T	FEV_1/FVC	0.038	0.006	2.30E-11	0.011	0.022	6.06E-01
16	rs2304488 (56631711), *MMP15* (intron)	rs12447804 (*MMP15*), 0.88	G	FEV_1/FVC	-0.040	0.008	9.45E-07	0.019	0.021	3.62E-01
16	rs12597233 (56657709), *MMP15* (downstream)	rs12447804 (*MMP15*), 0.87	G	FEV_1/FVC	0.038	0.008	4.80E-06	-0.012	0.022	5.85E-01
16	rs4243111 (73878328), *CFDP1*(downstream)	rs2865531 (*CFDP1*), 0.93	T	FEV_1/FVC	-0.037	0.007	1.52E-07	-0.036	0.018	4.22E-02
16	rs1424013 (74053487), *TMEM170* (intron)	rs2865531 (*CFDP1*), 0.82	T	FEV_1/FVC	0.033	0.007	3.92E-06	0.046	0.018	1.00E-02
21	rs973754 (34555400), *C21orf82* (downstream)	rs9978142 (*KCNE2*), 0.81	G	FEV_1/FVC	-0.043	0.010	2.09E-05	-0.010	0.025	6.78E-01
Previously reported regions										
2	rs1035672 (218383444), *TNS1* (intron)	rs2571445 (*TNS1*), 0.96	G	FEV_1	-0.046	0.007	3.03E-10	-0.020	0.018	2.66E-01

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Chr.	Proxy SNP ID (NCBI36 position), function	Leading SNP (region name), r^2 with proxy	Coded allele	Lung function				Lung cancer		
				Measure	Beta	Se	*P*	Beta	Se	*P*
2	rs2571445 (218391399), *TNS1* (non synonymous)	rs2571445 (*TNS1*), 1	G	FEV_1	0.047	0.007	9.83E-11	0.016	0.018	3.72E-01
4	rs2869967 (90088355), *FAM13A* (intron)	rs2045517 (*FAM13A*), 1	T	FEV_1/FVC	0.047	0.007	2.08E-11	0.026	0.018	1.36E-01
4	rs6849143 (90147512), *FAM13A* (intron)	rs2045517 (*FAM13A*), 0.75	T	FEV_1/FVC	-0.038	0.007	5.99E-08	-0.020	0.018	2.51E-01
4	rs11727735 (106851319), *GSTCD* (intron)	rs10516526 (*GSTCD*), 1	G	FEV_1	0.105	0.014	1.65E-13	-0.029	0.036	4.19E-01
4	rs10516526 (106908353), *GSTCD* (intron)	rs10516526 (*GSTCD*), 1	G	FEV_1	0.108	0.014	4.75E-14	-0.029	0.036	4.31E-01
4	rs1828591 (145700230), *HHIP* (upstream)	rs11100860 (*HHIP*), 1	G	FEV_1/FVC	0.063	0.007	1.44E-19	-0.005	0.018	7.82E-01
4	rs1512288 (145710731), *HHIP* (upstream)	rs11100860 (*HHIP*), 1	G	FEV_1/FVC	-0.062	0.007	3.46E-19	0.000	0.018	9.89E-01
5	rs2277027 (156864954), *ADAM19* (intron)	rs11134779 (*ADAM19*), 1	C	FEV_1/FVC	-0.042	0.007	6.65E-09	0.007	0.018	6.93E-01
5	rs1422795 (156868942), *ADAM19* (non synonymous)	rs11134779 (*ADAM19*), 1	T	FEV_1/FVC	0.041	0.007	1.05E-08	-0.007	0.018	7.11E-01
6	rs2070600 (32259421), *AGER* (non synonymous)	rs2070600 (*AGER*), 1	T	FEV_1/FVC	0.126	0.016	9.07E-15	-0.004	0.044	9.27E-01
6	rs2854050 (32293583), *NOTCH4* (intron)	rs2070600 (*AGER*), 1	G	FEV_1/FVC	-0.083	0.016	9.34E-08	0.022	0.040	5.80E-01
6	rs6570507 (142721265), *GPR126* (intron)	rs262129 (*GPR126*), 0.72	G	FEV_1/FVC	-0.051	0.008	2.25E-11	0.006	0.019	7.49E-01
6	rs11155242 (142733242), *GPR126* (non synonymous)	rs3817928 (*GPR126*), 1	C	FEV_1/FVC	0.055	0.009	1.88E-10	0.003	0.022	8.99E-01
6	rs3748069 (142809326), *GPR126* (downstream)	rs262129 (*GPR126*), 0.84	G	FEV_1/FVC	0.053	0.008	2.02E-12	-0.007	0.019	7.01E-01
6	rs7776356 (142818722), *GPR126* (downstream)	rs3817928 (*GPR126*), 1	G	FEV_1/FVC	0.059	0.008	4.16E-12	-0.001	0.021	9.69E-01
9	rs10512249 (97296130), *PTCH1* (intron)	rs16909859 (*PTCH1*), 0.84	G	FEV_1/FVC	0.066	0.012	1.54E-08	-0.067	0.029	1.90E-02
15	rs1913768 (69436598), *THSD4* (intron)	rs8033889 (*THSD4*), 0.673	G	FEV_1/FVC	0.075	0.009	2.77E-15	-0.014	0.024	5.49E-01
15	rs8033889 (69467134), *THSD4* (intron)	rs8033889 (*THSD4*), 1	T	FEV_1/FVC	-0.072	0.008	2.03E-17	0.014	0.025	5.85E-01
15	rs8034191 (76593078), *AGPHD1* (intron)	rs8040868 (*CHRNA3*), 0.70	T	FEV_1/FVC	0.032	0.007	9.65E-06	-0.258	0.018	2.19E-46
15	rs1051730 (76681394), *CHRNA3* (synonymous)	rs8040868 (*CHRNA3*), 0.76	G	FEV_1/FVC	0.032	0.007	1.46E-05	-0.273	0.018	1.91E-51

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E) Association of published height SNPs with FEV_1 and FEV_1/FVC. Effects sizes and *P* values for the 180 loci that reached genome-wide significance ($P < 5x10^{-8}$) in the combined Stage1 and 2 analysis of height reported by the GIANT consortium[90] are shown, together with the effect sizes, standard errors and *P* values for FEV_1 and FEV_1/FVC in the SpiroMeta-CHARGE GWAS dataset. Directions of effect for height have been flipped to refer to the same coded allele as lung function. Both effect sizes for lung and for height can be interpreted as proportion of a standard deviation. *P* values still significant after applying a Bonferroni correction for 180 tests ($P < 2.8x10^{-4}$) are shown in bold. Columns indicating whether the effect of each SNP on height is on the same direction as the effect on lung are included.

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Chr.	SNP ID(NCBI36 position), Nearest_OMIM_height_gene	Coded allele	Height		FEV_1				FEV_1/FVC			
			Beta	*P*	Beta	Se	*P*	Direction of effect for FEV_1 relative to height	Beta	Se	*P*	Direction of effect for FEV_1/FVC relative to height
1	rs425277(2059032), *PRKCZ*	T	0.022	2.10E-08	0.004	0.008	5.88E-01	same	-0.007	0.008	3.68E-01	different
1	rs2284746(17179262), *MFAP2*	G	0.04	3.90E-29	0.008	0.007	2.78E-01	same	-0.042	0.007	**2.47E-09**	different
1	rs1738475(23409478), *HTR1D*	G	-0.025	3.00E-12	-0.002	0.007	7.73E-01	same	-0.004	0.007	5.76E-01	same
1	rs4601530(24916698), *CLIC4*	T	-0.028	2.20E-12	0.03	0.008	**1.47E-04**	different	0.019	0.008	1.32E-02	different
1	rs7532866(26614131), *LIN28*	G	-0.021	3.40E-08	-0.017	0.008	2.19E-02	same	-0.001	0.007	8.94E-01	same
1	rs2154319(41518357), *SCMH1*	T	-0.03	1.80E-12	-0.008	0.009	3.57E-01	same	-0.003	0.008	6.80E-01	same
1	rs17391694(78396214), *GIPC2*	T	0.042	1.70E-11	0.013	0.013	3.16E-01	same	0.007	0.012	5.90E-01	same
1	rs6699417(88896031), *PKN2*	T	0.021	5.00E-09	0.001	0.007	8.44E-01	same	-0.011	0.007	1.04E-01	different
1	rs10874746(93096559), *RPL5*	T	-0.024	6.70E-11	0.005	0.007	4.69E-01	different	0.015	0.007	3.10E-02	different
1	rs9428104(118657110), *SPAG17*	G	0.041	5.60E-23	-0.013	0.008	1.26E-01	different	0.015	0.008	6.91E-02	same
1	rs11205277(148159496), *SF3B4*	G	0.046	4.80E-32	-0.021	0.008	9.16E-03	different	-0.011	0.008	1.76E-01	different
1	rs17346452(170319910), *DNM3*	T	-0.04	1.40E-23	-0.014	0.008	7.77E-02	same	0.002	0.008	8.09E-01	different
1	rs1325598(175058872), *PAPPA2*	G	0.022	1.10E-09	-0.008	0.007	2.76E-01	different	-0.003	0.007	6.59E-01	different
1	rs1046934(182290152), *TSEN15*	C	0.044	2.10E-31	-0.001	0.007	8.97E-01	different	0.01	0.007	1.75E-01	same
1	rs10863936(210304421), *DTL*	G	0.021	1.90E-09	-0.003	0.007	6.47E-01	different	-0.011	0.007	1.11E-01	different
1	rs6684205(216676325), *TGFB2*	G	0.028	1.50E-12	0.002	0.008	7.94E-01	same	-0.007	0.008	3.75E-01	different
1	rs11118346(217810342), *LYPLAL1*	T	-0.025	1.90E-12	0.008	0.007	2.61E-01	different	0.004	0.007	5.67E-01	different
1	rs10799445(225978506), *JMJD4*	C	-0.032	2.40E-13	0.001	0.008	9.45E-01	different	-0.005	0.008	5.67E-01	same
2	rs4665736(25041103), *DNAJC27*	T	0.029	7.30E-16	-0.008	0.007	2.67E-01	different	-0.012	0.007	9.28E-02	different
2	rs6714546(33214929), *LTBP1*	G	0.026	1.60E-09	0.004	0.008	6.48E-01	same	0.002	0.008	8.24E-01	same
2	rs17511102(37814117), *CDC42EP3*	T	0.06	1.60E-18	0.004	0.014	7.88E-01	same	0.015	0.013	2.69E-01	same
2	rs2341459(44621706), *C2orf34*	T	0.025	7.90E-10	-0.006	0.008	4.53E-01	different	-0.003	0.008	7.13E-01	different
2	rs12474201(46774789), *SOCS5*	G	-0.028	2.60E-13	0.001	0.008	9.37E-01	different	0.003	0.007	6.68E-01	different
2	rs3791675(55964813), *EFEMP1*	T	-0.053	2.50E-35	-0.02	0.008	1.28E-02	same	0.025	0.008	1.88E-03	different
2	rs11684404(88705737), *EIF2AK3*	T	-0.028	9.90E-14	0.02	0.007	7.65E-03	different	0.002	0.007	8.34E-01	different
2	rs7567288(134151294), *NCKAP5*	T	-0.032	2.10E-12	0.008	0.009	3.75E-01	different	0.016	0.009	7.32E-02	different
2	rs7567851(178392966), *PDE11A*	G	-0.037	3.30E-08	-0.009	0.013	4.86E-01	same	0.019	0.013	1.47E-01	different

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			Beta	*P*	Beta	Se	*P*	Direction of effect for FEV_1 relative to height	Beta	Se	*P*	Direction of effect for FEV_1/FVC relative to height
2	rs1351164(217980143), *TNS1*	T	0.034	2.10E-14	-0.017	0.009	5.42E-02	different	-0.015	0.009	8.06E-02	different
2	rs12470505(219616613), *CCDC108/IHH*	T	0.041	8.90E-12	0.007	0.012	5.81E-01	same	-0.009	0.012	4.59E-01	different
2	rs2629046(224755988), *SERPINE2*	T	0.024	7.90E-12	-0.009	0.007	1.96E-01	different	-0.006	0.007	4.08E-01	different
2	rs2580816(232506210), *NPPC*	T	-0.045	5.80E-22	0.007	0.009	4.49E-01	different	-0.007	0.009	4.75E-01	same
2	rs12694997(241911659), *SEPT2*	G	0.024	1.20E-08	0.004	0.008	5.94E-01	same	-0.001	0.008	8.59E-01	different
3	rs2597513(13530836), *HDAC11*	T	-0.036	7.40E-10	0.014	0.012	2.45E-01	different	0.025	0.011	2.66E-02	different
3	rs13088462(51046753), *DOCK3*	T	-0.052	3.80E-10	-0.011	0.016	5.18E-01	same	-0.026	0.016	1.07E-01	same
3	rs2336725(53093779), *RTF1*	T	-0.027	9.70E-13	0.002	0.007	7.52E-01	different	0.009	0.007	2.41E-01	different
3	rs9835332(56642722), *C3orf63*	G	0.026	5.30E-13	0.005	0.007	4.41E-01	same	0.006	0.007	3.99E-01	same
3	rs17806888(67499012), *SUCLG2*	T	0.036	2.10E-09	-0.018	0.011	1.16E-01	different	-0.02	0.011	8.55E-02	different
3	rs9863706(72520103), *RYBP*	T	-0.031	4.10E-13	-0.011	0.009	2.00E-01	same	0.002	0.008	8.02E-01	different
3	rs6439167(130533446), *C3orf47*	T	-0.034	8.90E-15	-0.014	0.009	9.99E-02	same	0	0.008	9.68E-01	different
3	rs9844666(137456906), *PCCB*	G	0.024	3.50E-09	-0.01	0.008	2.04E-01	different	-0.001	0.008	9.08E-01	different
3	rs724016(142588260), *ZBTB38*	G	0.07	3.10E-86	-0.003	0.007	6.26E-01	different	0.002	0.007	7.52E-01	same
3	rs572169(173648421), *GHSR*	T	0.033	2.80E-18	0.011	0.008	1.64E-01	same	0.008	0.007	2.73E-01	same
3	rs720390(187031377), *IGF2BP2*	G	-0.029	1.90E-14	0.004	0.007	5.75E-01	different	0.013	0.007	7.13E-02	different
4	rs2247341(1671115), *SLBP/FGFR3*	G	-0.025	1.50E-11	0.017	0.007	1.99E-02	different	0.01	0.007	1.88E-01	different
4	rs6449353(17642586), *LCORL*	T	0.075	7.10E-46	0.013	0.01	2.07E-01	same	0.003	0.01	7.57E-01	same
4	rs17081935(57518233), *POLR2B*	T	0.03	3.70E-11	0.007	0.009	4.07E-01	same	0.015	0.009	7.98E-02	same
4	rs7697556(73734177), *ADAMTS3*	T	0.028	2.00E-14	-0.007	0.007	3.36E-01	different	0.007	0.007	3.32E-01	same
4	rs788867(82369030), *PRKG2/BMP3*	T	-0.043	8.90E-28	0.005	0.008	4.86E-01	different	0.002	0.008	8.03E-01	different
4	rs10010325(106325802), *TET2*	C	-0.024	3.90E-11	-0.009	0.007	2.16E-01	same	-0.014	0.007	4.05E-02	same
4	rs7689420(145787802), *HHIP*	T	-0.073	6.20E-51	-0.008	0.009	4.21E-01	same	-0.008	0.009	3.84E-01	same
4	rs955748(184452669), *WWC2*	G	0.023	4.40E-08	-0.003	0.008	7.19E-01	different	-0.011	0.008	1.54E-01	different
5	rs1173727(32866278), *NPR3*	T	0.034	1.60E-21	-0.009	0.007	1.82E-01	different	-0.002	0.007	7.23E-01	different
5	rs11958779(55037656), *SLC38A9*	G	0.027	1.80E-12	0.005	0.008	4.73E-01	same	-0.008	0.007	2.65E-01	different
5	rs10037512(88390431), *MEF2C*	T	0.032	2.00E-18	0.002	0.007	7.77E-01	same	0.003	0.007	7.19E-01	same

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			Beta	*P*	Beta	Se	*P*	Direction of effect for FEV_1 relative to height	Beta	Se	*P*	Direction of effect for FEV_1/FVC relative to height
5	rs13177718(108141243), *FER*	T	-0.04	3.00E-08	0.002	0.014	8.90E-01	different	0.021	0.014	1.33E-01	different
5	rs1582931(122685098), *CEP120*	G	0.023	1.50E-10	0.005	0.007	4.54E-01	same	0.002	0.007	7.95E-01	same
5	rs274546(131727766), *SLC22A5*	G	0.029	7.30E-16	-0.007	0.007	3.13E-01	different	0.001	0.007	8.87E-01	same
5	rs526896(134384604), *PITX1*	T	0.03	2.30E-13	0	0.008	9.51E-01	different	0.007	0.008	3.83E-01	same
5	rs4282339(168188818), *SLIT3*	G	0.036	6.60E-16	0.003	0.009	7.55E-01	same	0.006	0.009	4.97E-01	same
5	rs12153391(171136043), *FBXW11*	C	0.03	3.60E-12	-0.001	0.008	8.96E-01	different	-0.007	0.008	3.99E-01	different
5	rs889014(172916720), *BOD1*	T	-0.03	9.40E-16	0.008	0.007	2.83E-01	different	0.004	0.007	5.72E-01	different
5	rs422421(176449932), *FGFR4/NSD1*	T	-0.031	1.10E-12	0.005	0.009	5.76E-01	different	0.018	0.008	3.90E-02	different
5	rs6879260(179663620), *GFPT2*	T	-0.022	1.60E-09	0.003	0.007	7.20E-01	different	-0.014	0.007	5.38E-02	same
6	rs3812163(7670759), *BMP6*	T	0.036	1.20E-23	-0.026	0.007	**2.14E-04**	different	-0.001	0.007	9.33E-01	different
6	rs1047014(19949472), *ID4*	T	-0.032	1.80E-13	0.005	0.009	5.44E-01	different	-0.011	0.008	1.78E-01	same
6	rs806794(26308656), *Histone cluster*	G	-0.052	1.20E-39	0.006	0.008	4.67E-01	different	-0.013	0.008	9.67E-02	same
6	rs3129109(29192211), *OR2J3*	T	-0.032	2.40E-17	-0.01	0.007	1.61E-01	same	0.001	0.007	8.49E-01	different
6	rs2256183(31488508), *MICA*	G	-0.04	7.80E-29	0.007	0.007	3.11E-01	different	0.01	0.007	1.46E-01	different
6	rs6457620(32771977), *HLA* locus	G	0.029	2.10E-16	-0.002	0.007	7.58E-01	different	-0.025	0.007	2.92E-04	different
6	rs2780226(34307070), *HMGA1*	T	-0.076	8.10E-28	-0.015	0.014	2.63E-01	same	0.023	0.014	8.63E-02	different
6	rs6457821(35510783), *PPARD/FANCE*	C	0.104	2.10E-12	-0.007	0.029	7.96E-01	different	0.058	0.028	3.97E-02	same
6	rs9472414(45054484), *SUPT3H/RUNX2*	T	0.026	1.80E-09	-0.002	0.008	7.97E-01	different	0.003	0.008	7.01E-01	same
6	rs9360921(76322362), *SENP6*	T	-0.042	2.60E-13	0.015	0.011	1.81E-01	different	0.011	0.011	3.36E-01	different
6	rs310405(81857081), *FAM46A*	G	-0.026	2.20E-13	-0.007	0.007	3.14E-01	same	-0.012	0.007	9.00E-02	same
6	rs7759938(105485647), *LIN28B*	T	-0.045	8.30E-31	0.016	0.008	3.93E-02	different	-0.006	0.008	4.26E-01	same
6	rs1046943(109890634), *ZBTB24*	G	-0.02	2.50E-08	-0.012	0.007	8.88E-02	same	0	0.007	9.46E-01	different
6	rs961764(117628849), *VGLL2*	G	0.024	1.30E-11	-0.003	0.007	6.42E-01	different	0.009	0.007	2.23E-01	same
6	rs1490384(126892853), *C6orf173*	T	0.034	3.90E-21	0.022	0.007	2.07E-03	same	-0.002	0.007	7.46E-01	different
6	rs6569648(130390812), *L3MBTL3*	T	-0.04	1.10E-21	-0.002	0.008	8.41E-01	same	0.013	0.008	1.13E-01	different
6	rs7763064(142838982), *GPR126*	G	0.048	1.10E-33	-0.03	0.008	**1.33E-04**	different	-0.052	0.008	**6.80E-12**	different
6	rs543650(152152636), *ESR1*	T	-0.034	1.20E-17	0.002	0.008	7.58E-01	different	0.002	0.008	8.44E-01	different

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			Beta	*P*	Beta	Se	*P*	Direction of effect for FEV_1 relative to height	Beta	Se	*P*	Direction of effect for FEV_1/FVC relative to height
6	rs9456307(158849430), *TULP4*	T	0.048	2.20E-09	0.001	0.016	9.38E-01	same	-0.007	0.016	6.76E-01	different
7	rs798489(2768329), *GNA12*	T	-0.048	1.90E-33	0.006	0.008	4.72E-01	different	-0.002	0.008	7.93E-01	same
7	rs4470914(19583047), *TWISTNB*	T	0.029	9.20E-10	-0.008	0.01	4.25E-01	different	-0.014	0.009	1.39E-01	different
7	rs12534093(23469499), *IGF2BP3*	T	0.034	2.00E-14	0.008	0.008	3.46E-01	same	-0.003	0.008	7.43E-01	different
7	rs1708299(28156471), *JAZF1*	G	-0.04	5.80E-25	0.014	0.008	6.07E-02	different	0.002	0.008	8.31E-01	different
7	rs6959212(38094851), *STARD3NL*	T	-0.024	1.60E-09	0.003	0.008	7.21E-01	different	0.002	0.008	7.68E-01	different
7	rs42235(92086012), *CDK6*	T	0.057	7.70E-47	0	0.008	9.50E-01	different	-0.007	0.008	3.52E-01	different
7	rs822552(148281567), *PDIA4*	G	0.025	2.60E-08	-0.023	0.009	8.01E-03	different	-0.003	0.009	7.28E-01	different
7	rs2110001(150147955), *TMEM176A*	G	0.031	3.30E-13	0.019	0.008	1.86E-02	same	0.007	0.008	4.03E-01	same
8	rs1013209(24172249), *ADAM28*	T	-0.025	1.60E-09	0.021	0.008	1.03E-02	different	-0.002	0.008	8.37E-01	same
8	rs7460090(57356717), *SDR16C5*	T	0.058	8.20E-27	0.012	0.011	2.52E-01	same	-0.003	0.01	8.07E-01	different
8	rs6473015(78341040), *PEX2*	C	0.029	6.90E-13	0.011	0.008	1.72E-01	same	-0.002	0.008	8.42E-01	different
8	rs6470764(130794847), *GSDMC*	T	-0.05	1.70E-28	-0.004	0.009	6.39E-01	same	-0.002	0.009	8.34E-01	same
8	rs12680655(135706519), *ZFAT*	G	-0.028	1.60E-14	0.016	0.007	2.15E-02	different	0.014	0.007	4.40E-02	different
9	rs7864648(16358732), *BNC2*	T	0.022	2.10E-08	0	0.008	9.87E-01	different	0.004	0.008	6.30E-01	same
9	rs11144688(77732106), *PCSK5*	G	0.049	9.60E-12	0.001	0.015	9.29E-01	same	0.009	0.015	5.31E-01	same
9	rs7853377(85742025), *C9orf64*	G	0.024	4.50E-08	0.007	0.009	4.29E-01	same	0.008	0.009	3.38E-01	same
9	rs8181166(88306448), *ZCCHC6*	G	-0.026	2.70E-12	0.014	0.007	5.36E-02	different	0.003	0.007	6.68E-01	different
9	rs2778031(90025546), *SPIN1*	T	0.031	9.00E-13	0.005	0.008	5.62E-01	same	0.01	0.008	2.16E-01	same
9	rs9969804(94468941), *IPPK*	C	-0.03	7.70E-17	0.003	0.007	6.58E-01	different	0.015	0.007	3.15E-02	different
9	rs1257763(95933766), *PTPDC1*	G	-0.069	9.90E-10	-0.003	0.022	8.98E-01	same	-0.005	0.022	8.13E-01	same
9	rs473902(97296056), *PTCH1/FANCC*	T	0.065	2.30E-17	-0.012	0.016	4.26E-01	different	-0.024	0.015	1.16E-01	different
9	rs7027110(108638867), *ZNF462*	G	-0.031	2.30E-13	0.024	0.008	3.80E-03	different	0.01	0.008	2.35E-01	different
9	rs1468758(112846903), *LPAR1*	T	-0.026	1.40E-09	-0.004	0.008	6.21E-01	same	-0.006	0.008	4.26E-01	same
9	rs751543(118162163), *PAPPA*	T	0.026	6.50E-10	-0.005	0.008	5.47E-01	different	-0.003	0.008	7.14E-01	different
9	rs7466269(132453905), *FUBP3*	G	-0.032	2.60E-17	-0.012	0.007	1.11E-01	same	-0.02	0.007	6.62E-03	same
9	rs7849585(138251691), *QSOX2*	T	0.029	4.70E-14	0.014	0.008	7.84E-02	same	-0.002	0.008	8.08E-01	different

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			Beta	*P*	Beta	Se	*P*	Direction of effect for FEV_1 relative to height	Beta	Se	*P*	Direction of effect for FEV_1/FVC relative to height
10	rs7909670(12958770), *CCDC3*	T	-0.021	3.20E-09	0.002	0.007	7.78E-01	different	-0.001	0.007	8.76E-01	same
10	rs2145998(80791702), *PPIF*	T	0.026	3.60E-13	0	0.007	9.72E-01	different	0.006	0.007	3.59E-01	same
10	rs11599750(101795432), *CPN1*	T	-0.028	1.60E-13	-0.01	0.007	1.55E-01	same	-0.012	0.007	9.58E-02	same
11	rs2237886(2767307), *KCNQ1*	T	0.046	2.20E-13	-0.005	0.012	7.13E-01	different	-0.008	0.012	5.31E-01	different
11	rs7926971(12654616), *TEAD1*	G	0.023	4.40E-10	-0.017	0.007	1.41E-02	different	0.006	0.007	3.59E-01	same
11	rs1330(17272605), *NUCB2*	T	0.022	4.90E-09	-0.007	0.008	3.32E-01	different	0.003	0.007	7.11E-01	same
11	rs10838801(48054856), *PTPRJ/SLC39A13*	G	0.027	3.50E-12	-0.01	0.008	1.94E-01	different	-0.008	0.008	2.87E-01	different
11	rs1814175(49515748), *FOLH1*	T	0.022	1.60E-08	-0.006	0.008	4.80E-01	different	0.002	0.008	8.07E-01	same
11	rs5017948(51270794), *OR4A5*	T	-0.027	3.10E-08	-0.002	0.01	8.63E-01	same	0	0.009	9.70E-01	different
11	rs3782089(65093395), *SSSCA1*	T	-0.058	3.60E-13	-0.019	0.016	2.45E-01	same	0.009	0.016	5.74E-01	different
11	rs7112925(66582736), *RHOD*	T	-0.023	9.00E-10	0.003	0.007	7.14E-01	different	-0.001	0.007	8.98E-01	same
11	rs634552(74959700), *SERPINH1*	T	0.039	3.50E-13	-0.024	0.01	2.15E-02	different	-0.007	0.01	4.72E-01	different
11	rs494459(118079885), *TREH*	T	0.02	1.70E-08	0.003	0.007	6.23E-01	same	-0.003	0.007	6.39E-01	different
11	rs654723(128091365), *FLI1*	C	-0.025	3.60E-11	0.003	0.007	6.98E-01	different	0.002	0.007	7.78E-01	different
12	rs2856321(11747040), *ETV6*	G	0.029	4.50E-15	-0.008	0.007	2.50E-01	different	-0.013	0.007	6.49E-02	different
12	rs10770705(20748734), *SLCO1C1*	C	-0.033	8.00E-18	0.014	0.008	6.45E-02	different	0.004	0.007	6.38E-01	different
12	rs2638953(28425682), *CCDC91*	G	-0.032	6.70E-17	0.018	0.007	1.70E-02	different	-0.003	0.007	6.80E-01	same
12	rs2066807(55026949), *STAT2*	G	0.054	1.00E-13	0.018	0.014	2.07E-01	same	-0.001	0.014	9.16E-01	different
12	rs1351394(64638093), *HMGA2*	T	0.06	1.70E-65	0.012	0.007	8.47E-02	same	0.016	0.007	2.12E-02	same
12	rs10748128(68113925), *FRS2*	T	0.038	2.10E-20	-0.009	0.008	2.63E-01	different	-0.005	0.008	5.37E-01	different
12	rs11107116(92502635), *SOCS2*	T	0.052	1.40E-34	0.008	0.008	3.14E-01	same	-0.006	0.008	4.67E-01	different
12	rs7971536(100897919), *CCDC53/GNPTAB*	T	0.028	8.20E-14	0.012	0.007	9.22E-02	same	0.003	0.007	7.20E-01	same
12	rs11830103(122389499), *SBNO1*	G	0.035	3.90E-15	-0.01	0.009	2.67E-01	different	-0.015	0.009	7.90E-02	different
13	rs7332115(32045548), *PDS5B/BRCA2*	T	-0.023	5.50E-10	-0.006	0.007	4.16E-01	same	0.007	0.007	3.49E-01	different
13	rs3118905(50003335), *DLEU7*	G	0.056	1.10E-45	-0.024	0.008	2.40E-03	different	-0.004	0.008	6.44E-01	different
13	rs7319045(90822575), *GPC5*	G	-0.025	1.20E-11	-0.01	0.007	1.70E-01	same	-0.012	0.007	1.09E-01	same
14	rs1950500(23900690), *NFATC4*	T	0.034	2.20E-18	-0.011	0.008	1.62E-01	different	-0.004	0.008	6.24E-01	different

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Chr.	SNP ID(NCBI36 position), Nearest_OMIM_height_gene	Coded allele	Height		FEV_1				FEV_1/FVC			
			Beta	*P*	Beta	Se	*P*	Direction of effect for FEV_1 relative to height	Beta	Se	*P*	Direction of effect for FEV_1/FVC relative to height
14	rs2093210(60027032), *SIX6*	T	-0.032	6.20E-17	-0.007	0.008	3.77E-01	same	0.011	0.008	1.30E-01	different
14	rs1570106(67882868), *RAD51L1*	T	-0.026	8.10E-09	-0.018	0.009	4.56E-02	same	-0.021	0.009	1.46E-02	same
14	rs862034(74060499), *LTBP2*	G	0.028	7.30E-14	-0.013	0.007	8.64E-02	different	-0.003	0.007	6.97E-01	different
14	rs7155279(91555634), *TRIP11*	T	-0.024	1.40E-10	0.019	0.007	1.01E-02	different	0.008	0.007	2.81E-01	different
15	rs16964211(49317787), *CYP19A1*	G	0.05	1.70E-09	0.012	0.016	4.66E-01	same	-0.009	0.016	5.85E-01	different
15	rs7178424(60167551), *C2CD4A*	T	-0.021	5.60E-09	-0.012	0.007	8.08E-02	same	-0.007	0.007	2.93E-01	same
15	rs10152591(67835211), *TLE3*	C	-0.041	2.70E-10	-0.002	0.013	8.45E-01	same	-0.002	0.012	8.65E-01	same
15	rs12902421(69948457), *MYO9A*	T	-0.062	2.90E-08	0.01	0.023	6.75E-01	different	0.026	0.023	2.51E-01	different
15	rs5742915(72123686), *PML*	T	-0.031	1.00E-15	0.002	0.008	8.21E-01	different	0.017	0.008	2.85E-02	different
15	rs11259936(82371586), *ADAMTSL3*	C	0.044	1.70E-35	0.009	0.007	1.90E-01	same	0.021	0.007	2.77E-03	same
15	rs16942341(87189909), *ACAN*	T	-0.13	3.80E-27	0.004	0.024	8.80E-01	different	-0.002	0.023	9.38E-01	same
15	rs2871865(97012419), *IGF1R*	G	-0.057	2.90E-21	-0.004	0.012	7.61E-01	same	0.017	0.012	1.35E-01	different
15	rs4965598(98577137), *ADAMTS17*	T	-0.028	4.30E-13	-0.003	0.008	7.15E-01	same	0.015	0.007	4.02E-02	different
16	rs11648796(732191), *NARFL*	G	0.034	1.20E-13	-0.01	0.01	3.22E-01	different	0.002	0.01	8.69E-01	same
16	rs26868(2189377), *CASKIN1*	T	-0.034	9.00E-17	0.004	0.008	6.11E-01	different	0	0.008	9.87E-01	different
16	rs1659127(14295806), *MKL2*	G	-0.027	1.10E-11	-0.008	0.008	3.08E-01	same	0.005	0.008	5.47E-01	different
16	rs8052560(87304743), *CTU2/GALNS*	C	-0.029	3.30E-08	0.002	0.011	8.43E-01	different	-0.001	0.011	9.52E-01	same
17	rs4640244(21224816), *KCNJ12*	G	-0.024	2.30E-08	-0.004	0.008	6.03E-01	same	0.003	0.008	7.20E-01	different
17	rs3110496(24941897), *ANKRD13B*	G	0.022	7.30E-09	-0.006	0.008	4.54E-01	different	-0.012	0.007	1.05E-01	different
17	rs3764419(26188149), *ATAD5/RNF135*	C	0.035	1.80E-21	-0.016	0.007	2.56E-02	different	0.002	0.007	8.21E-01	same
17	rs17780086(27367395), *LRRC37B*	G	-0.028	2.60E-08	-0.002	0.01	8.22E-01	same	-0.025	0.01	1.31E-02	same
17	rs1043515(34175722), *PIP4K2B*	G	0.023	2.90E-10	-0.005	0.007	4.46E-01	different	-0.027	0.007	**1.22E-04**	different
17	rs4986172(40571807), *ACBD4*	T	-0.032	2.30E-16	-0.009	0.008	2.55E-01	same	-0.008	0.007	2.76E-01	same
17	rs2072153(44745013), *ZNF652*	G	-0.021	3.50E-08	-0.002	0.008	7.84E-01	same	-0.007	0.007	3.54E-01	same
17	rs4605213(46599746), *NME2*	G	-0.021	2.70E-08	0.013	0.008	9.69E-02	different	-0.002	0.007	8.19E-01	same
17	rs227724(52133816), *NOG*	T	0.03	7.40E-15	-0.001	0.007	8.41E-01	different	-0.001	0.007	8.74E-01	different
17	rs2079795(56851431), *TBX2*	T	0.04	2.10E-24	-0.023	0.008	2.78E-03	different	-0.006	0.008	4.24E-01	different

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Chr.	SNP ID(NCBI36 position), Nearest_OMIM_height_gene	Coded allele	Height		FEV_1				FEV_1/FVC			
			Beta	*P*	Beta	Se	*P*	Direction of effect for FEV_1 relative to height	Beta	Se	*P*	Direction of effect for FEV_1/FVC relative to height
17	rs2665838(59320197), *CSH1/GH1*	G	0.042	5.10E-25	0.006	0.008	4.31E-01	same	0	0.008	9.82E-01	different
17	rs11867479(65601802), *KCNJ16/KCNJ2*	T	0.025	1.50E-10	-0.007	0.008	3.65E-01	different	0.006	0.008	4.25E-01	same
18	rs4800452(18981609), *CABLES1*	T	0.051	4.20E-30	-0.023	0.009	7.84E-03	different	0	0.009	9.98E-01	different
18	rs9967417(45213498), *DYM*	G	0.038	9.30E-25	-0.004	0.007	6.04E-01	different	-0.002	0.007	7.65E-01	different
18	rs17782313(56002077), *MC4R*	T	-0.028	3.80E-11	-0.016	0.008	5.22E-02	same	0	0.008	9.59E-01	different
19	rs12982744(2128193), *DOT1L*	G	0.03	3.40E-16	-0.01	0.007	1.80E-01	different	-0.002	0.007	7.38E-01	different
19	rs7507204(3379834), *NFIC*	G	-0.036	4.30E-16	-0.006	0.009	5.22E-01	same	-0.007	0.009	3.90E-01	same
19	rs891088(7135762), *INSR*	G	0.029	2.40E-12	0	0.008	9.59E-01	different	0.002	0.008	8.30E-01	same
19	rs4072910(8550031), *ADAMTS10*	G	0.031	3.60E-13	0.002	0.009	8.23E-01	same	-0.003	0.009	6.93E-01	different
19	rs2279008(17144303), *MYO9B*	T	0.025	2.50E-08	-0.004	0.009	6.89E-01	different	0.004	0.009	6.61E-01	same
19	rs17318596(46628935), *ATP5SL*	G	-0.032	5.00E-16	0.006	0.008	4.39E-01	different	0.003	0.008	6.73E-01	different
20	rs1741344(4049800), *SMOX*	T	-0.023	3.30E-09	0.012	0.007	1.09E-01	different	0	0.007	9.82E-01	different
20	rs2145272(6574218), *BMP2*	G	0.039	2.10E-24	-0.018	0.007	1.84E-02	different	0.016	0.007	2.60E-02	same
20	rs7274811(31796842), *ZNF341*	T	-0.041	5.90E-22	-0.003	0.008	7.03E-01	same	-0.004	0.008	5.87E-01	same
20	rs143384(33489170), *GDF5*	G	0.063	1.00E-58	0.004	0.008	1.54E-01	same	0.018	0.008	1.45E-02	same
20	rs237743(47336426), *ZNFX1*	G	-0.041	1.30E-20	0.008	0.007	3.65E-01	different	0.008	0.008	3.41E-01	different
21	rs2834442(34612656), *KCNE2*	T	-0.026	5.10E-12	-0.002	0.007	1.82E-01	same	-0.024	0.007	9.36E-04	same
22	rs4821083(31386341), *SYN3*	T	0.031	3.10E-10	0.03	0.008	1.93E-01	same	-0.014	0.01	1.54E-01	different

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Supplementary Table 4 Associations in never-smokers and ever-smokers in the Stage 1 and 2 data, and tests for interaction with smoking.

Each of the SNPs included in the table showed genome-wide significant association ($P<5x10^{-8}$) with either FEV_1 or FEV_1/FVC in the Stage 1 and 2 data. The stratum-specific estimates are shown for Stage 1 (GWAS), Stage 2 and Stage 1 + 2 data for the trait with the strongest association. *P* values for the interaction between ever-smokers and never-smokers in the combined Stage 1 + 2 meta-analysis are shown.

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Chr.	SNP_ID (NCBI36 position), function	Measure	Stage 1						Stage 2						Stage 1 + Stage 2 meta-analysis				Interaction
			Ever-smokers			Never-smokers			Ever-smokers			Never-smokers			Ever-smokers		Never-smokers		
			Beta	Se	*P*	Beta	Se	*P*	Beta	Se	*P*	Beta	Se	*P*	Beta	Se	Beta	Se	*P*
1	rs2284746 (17179262), *MFAP2* (intron)	FEV_1/FVC	-0.046	0.009	5.82E-07	-0.036	0.010	3.43E-04	-0.039	0.010	1.04E-04	-0.037	0.011	7.02E-04	-0.043	0.007	-0.036	0.007	5.12E-01
1	rs993925 (216926691), *TGFB2* (downstream)	FEV_1/FVC	0.047	0.010	4.85E-06	0.032	0.011	4.59E-03	0.031	0.014	2.29E-02	0.016	0.014	2.43E-01	0.041	0.008	0.026	0.009	1.91E-01
2	rs12477314 (239542085), *HDAC4* (downstream)	FEV_1/FVC	0.054	0.012	3.58E-06	0.049	0.013	1.14E-04	0.042	0.011	1.90E-04	0.019	0.011	9.56E-02	0.048	0.008	0.032	0.008	1.88E-01
3	rs1529672 (25495586), *RARB* (intron)	FEV_1/FVC	-0.072	0.013	1.64E-08	-0.044	0.014	1.97E-03	-0.047	0.012	7.44E-05	-0.025	0.012	3.80E-02	-0.059	0.009	-0.033	0.009	4.29E-02
3	rs1344555 (170782913), *MECOM* (intron)	FEV_1	-0.053	0.012	5.13E-06	-0.029	0.012	2.05E-02	-0.022	0.013	8.79E-02	-0.029	0.012	1.57E-02	-0.040	0.009	-0.029	0.009	3.81E-01
5	rs153916 (95062456), *SPATA9* (upstream)	FEV_1/FVC	-0.041	0.009	6.39E-06	-0.022	0.010	2.81E-02	-0.022	0.013	9.55E-02	-0.028	0.013	3.31E-02	-0.035	0.008	-0.024	0.008	3.28E-01
6	rs6903823 (28430275), *ZKSCAN3* (intron)/ *ZNF323* (intron)	FEV_1	-0.043	0.012	3.30E-04	-0.051	0.012	4.20E-05	-0.033	0.012	5.79E-03	-0.027	0.011	1.63E-02	-0.038	0.008	-0.037	0.008	9.64E-01
6	rs2857595 (31676448), *NCR3* (upstream)	FEV_1/FVC	0.053	0.012	9.43E-06	0.045	0.013	7.01E-04	0.035	0.011	1.91E-03	0.020	0.012	7.59E-02	0.043	0.008	0.031	0.009	3.11E-01
6	rs2798641 (109374743), *ARMC2* (intron)	FEV_1/FVC	-0.056	0.012	2.97E-06	-0.036	0.013	6.55E-03	-0.038	0.017	2.70E-02	-0.020	0.017	2.45E-01	-0.050	0.010	-0.030	0.010	1.67E-01

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Chr.	**SNP_ID (NCBI36 position), function**	**Measure**	**Stage 1**						**Stage 2**						**Stage 1 + Stage 2 meta-analysis**				**Interaction**
			Ever-smokers			**Never-smokers**			**Ever-smokers**			**Never-smokers**			**Ever-smokers**		**Never-smokers**		
			Beta	**Se**	***P***	**Beta**	**Se**	***P***	**Beta**	**Se**	***P***	**Beta**	**Se**	***P***	**Beta**	**Se**	**Beta**	**Se**	***P***
10	rs7068966 (12317998), *CDC123* (intron)	FEV_1/FVC	0.053	0.009	4.55E-09	0.034	0.010	7.48E-04	0.029	0.009	1.31E-03	0.016	0.009	7.72E-02	0.041	0.006	0.024	0.007	7.15E-02
10	rs11001819 (77985230), *C10orf11* (intron)	FEV_1	-0.036	0.010	1.61E-04	-0.047	0.010	2.99E-06	-0.020	0.008	9.85E-03	-0.023	0.007	1.23E-03	-0.026	0.006	-0.031	0.006	5.56E-01
12	rs11172113 (55813550), *LRP1* (intron)	FEV_1/FVC	-0.036	0.010	1.66E-04	-0.034	0.010	1.01E-03	-0.033	0.013	1.31E-02	-0.020	0.013	1.40E-01	-0.035	0.008	-0.029	0.008	5.97E-01
12	rs1036429 (94795559), *CCDC38* (intron)	FEV_1/FVC	0.049	0.011	1.76E-05	0.050	0.012	6.28E-05	0.039	0.011	3.91E-04	0.019	0.011	8.77E-02	0.044	0.008	0.033	0.008	3.45E-01
16	rs12447804 (56632783), *MMP15* (intron)	FEV_1/FVC	-0.058	0.013	7.47E-06	-0.047	0.014	6.79E-04	-0.029	0.014	4.77E-02	-0.011	0.014	4.31E-01	-0.045	0.010	-0.030	0.010	2.71E-01
16	rs2865531 (73947817), *CFDP1* (intron)	FEV_1/FVC	0.034	0.009	2.23E-04	0.045	0.010	9.48E-06	0.033	0.009	2.19E-04	0.014	0.009	1.20E-01	0.034	0.006	0.028	0.007	5.42E-01
21	rs9978142 (34574109), *KCNE2* (upstream)	FEV_1/FVC	-0.055	0.013	1.61E-05	-0.040	0.014	5.06E-03	-0.046	0.019	1.34E-02	-0.018	0.019	3.25E-01	-0.052	0.011	-0.032	0.011	1.94E-01

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Supplementary Table 5 Lung function associations (FEV_1 and FEV_1/FVC) in Stage 1 for all previously reported loci (A) and all SNPs taken forward to follow-up in Stage 2 (B).

A) Effects in the SpiroMeta-CHARGE dataset of loci previously reported to be associated with FEV_1, FEV_1/FVC, or COPD[1,2,91-94] providing that they also showed association with lung function, are shown for both lung function measures. Details of the selection of these SNPs are shown in the **Online Methods**. *P* values below $5x10^{-8}$ for FEV_1 and FEV_1/FVC are shown in bold. The sample sizes (*N*) shown are the effective sample sizes. Effective sample size within each study is the product of sample size and imputation quality metric. For each locus, the most significant SNP for either FEV_1 or FEV_1/FVC (as indicated in the third column) in the SpiroMeta-CHARGE dataset (SpiroMeta-CHARGE in 2nd column) is also included. Abbreviations: ns=nonsynonymous, s= synonymous.
Previous studies which report these loci are Cho *et al.* (2010)[91], DeMeo *et al.* (2009)[94], Hancock *et al.* (2010)[1], Pillai *et al.* (2009)[92], Repapi *et al.* (2010)[2] and Wilk *et al.* (2009)[93].

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Chr.	Paper reported	Measure	SNP ID (NCBI36 position), function	Region name	Coded allele	FEV_1		FEV_1/FVC		N
						Beta (Se)	*P*	Beta (Se)	*P*	
2	Repapi *et al.*	FEV_1	rs2571445(218391399), *TNS1*(ns)	*TNS1*	G	0.047 (0.007)	**9.83E-11**	0.033 (0.007)	4.46E-06	45839
2	Hancock *et al.*	FEV_1/FVC	rs10498230(229210747), *PID1*(downstream)	*PID1*	T	0.03 (0.014)	3.60E-02	0.068 (0.014)	1.13E-06	44957
4	Hancock *et al.*	FEV_1/FVC	rs2869967(90088355), *FAM13A*	*FAM13A*	T	0.012 (0.007)	9.38E-02	0.047 (0.007)	**2.08E-11**	47710
4	SpiroMeta-CHARGE	FEV_1/FVC	rs2045517(90089987), *FAM13A* (intron)	*FAM13A*	T	-0.012 (0.007)	8.93E-02	-0.047 (0.007)	**2.00E-11**	47675
4	Cho *et al.*	COPD	rs7671167(90103002), *FAM13A*	*FAM13A*	T	-0.017 (0.007)	1.64E-02	-0.042 (0.007)	**1.27E-09**	47723
4	Repapi *et al.*	FEV_1	rs10516526(106908353), *GSTCD*(intron)	*GSTCD-NPNT*	G	0.108 (0.014)	**4.75E-14**	0.039 (0.014)	6.17E-03	47970
4	Hancock *et al.*	FEV_1	rs17331332(107027556), *NPNT* (upstream)	*GSTCD-NPNT*	G	-0.102 (0.014)	1.11E-12	-0.057 (0.014)	5.30E-05	39503
4	SpiroMeta-CHARGE	FEV_1/FVC	rs6823809(107048244), *NPNT*(intron)	*GSTCD-NPNT*	T	0.050 (0.011)	4.82E-06	0.056 (0.011)	2.20E-07	23656
4	SpiroMeta-CHARGE	FEV_1	rs1032296(145654138), *HHIP*(upstream)	*HHIP*	T	-0.047 (0.007)	8.74E-11	-0.050 (0.007)	**3.42E-12**	45318
4	Repapi *et al.*	FEV_1/FVC	rs12504628(145655774), *HHIP*	*HHIP*	T	-0.044 (0.007)	**1.03E-09**	-0.063 (0.007)	**5.54E-19**	46204
4	Wilk *et al.*	FEV_1/FVC	rs11100860(145698589), *HHIP*(upstream)	*HHIP*	G	0.041 (0.007)	**4.27E-09**	0.064 (0.007)	**6.81E-20**	47876
4	Hancock *et al.*	FEV_1/FVC	rs1980057(145705188), *HHIP*	*HHIP*	T	0.042 (0.007)	**4.07E-09**	0.063 (0.007)	**1.06E-19**	47865
5	Hancock *et al.*	FEV_1/FVC	rs11168048(147822546), *HTR4*(intron)	*HTR4*	T	-0.046 (0.007)	**2.43E-10**	-0.047 (0.007)	**5.97E-11**	44976
5	Repapi *et al.*	FEV_1	rs3995090(147826008), *HTR4*	*HTR4*	C	0.045 (0.007)	**3.33E-10**	0.046 (0.007)	**1.04E-10**	47607
5	SpiroMeta-CHARGE	FEV_1	rs1985524(147827981), *HTR4*	*HTR4*	G	-0.048 (0.007)	**3.06E-11**	-0.045 (0.007)	**2.90E-10**	45623
5	Hancock *et al.*	FEV_1/FVC	rs2277027(156864954), *ADAM19*	*ADAM19*	C	-0.026 (0.007)	3.10E-04	-0.042 (0.007)	**6.65E-09**	48023
5	SpiroMeta-CHARGE	FEV_1/FVC	rs11134779(156869344), *ADAM19*(intron)	*ADAM19*	G	-0.027 (0.007)	2.40E-04	-0.042 (0.007)	**6.01E-09**	48075
6	Hancock *et al.* and Repapi *et al.*	FEV_1/FVC	rs2070600(32259421), *AGER*(ns)	*AGER*	T	0.025 (0.016)	1.27E-01	0.126 (0.016)	**9.07E-15**	46314
6	Repapi *et al.*	FEV_1/FVC	rs2395730(39892343), *DAAM2* (intron)	*DAAM2*	C	-0.004 (0.007)	5.95E-01	0.022 (0.007)	1.39E-03	47256
6	SpiroMeta-CHARGE	FEV_1/FVC	rs11756622(39898021), *DAAM2* (intron)	*DAAM2*	T	0.047 (0.019)	1.23E-02	0.064 (0.019)	5.48E-04	28276

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Chr.	Paper reported	Measure	SNP ID (NCBI36 position), function	Region name	Coded allele	FEV_1		FEV_1/FVC		N
						Beta (Se)	*P*	Beta (Se)	*P*	
6	Hancock *et al.*	FEV_1/FVC	rs3817928(142792209), *GPR126*	*GPR126-LOC153910*	G	0.023 (0.009)	8.63E-03	0.059 (0.008)	**2.27E-12**	46730
6	SpiroMeta-CHARGE	FEV_1/FVC	rs262129(142894837), *LOC153910*(unknown)	*GPR126-LOC153910*	G	0.031 (0.008)	5.44E-05	0.056 (0.008)	**2.91E-13**	47014
9	SpiroMeta-CHARGE	FEV_1/FVC	rs16909859(97244613), *PTCH1*(downstream)	*PTCH1*	G	-0.014 (0.013)	2.93E-01	0.08 (0.013)	**7.45E-10**	43353
9	Hancock *et al.*	FEV_1/FVC	rs16909898(97270829), *PTCH1*	*PTCH1*	G	0.015 (0.012)	2.21E-01	-0.072 (0.012)	**3.94E-09**	42486
15	Repapi *et al.*	FEV_1/FVC	rs12899618(69432174), *THSD4*	*THSD4*	G	0.036 (0.01)	1.57E-04	0.076 (0.01)	**1.86E-15**	46657
15	SpiroMeta-CHARGE	FEV_1/FVC	rs8033889(69467134), *THSD4* (intron)	*THSD4*	T	-0.044 (0.009)	3.01E-07	-0.072 (0.008)	**2.03E-17**	46995
15	DeMeo *et al* (2009)	COPD	rs2568494(76528019), *IREB2*(intron)	*CHRNA3-CHRNA5-IREB2-LOC123688*	G	0.023 (0.007)	1.64E-03	0.029 (0.007)	5.25E-05	47919
15	Pillai *et al.* (2009)	COPD	rs8034191(76593078), *LOC123688*	*CHRNA3-CHRNA5-IREB2-LOC123688*	T	0.031 (0.007)	2.07E-05	0.032 (0.007)	9.65E-06	47954
15	SpiroMeta-CHARGE	FEV_1	rs2036527(76638670), *CHRNA5*(uptream)	*CHRNA3-CHRNA5-IREB2-LOC123688*	G	0.036 (0.008)	2.40E-06	0.032 (0.007)	1.19E-05	45038
15	SpiroMeta-CHARGE	FEV_1/FVC	rs8040868(76698236), *CHRNA3*(s)	*CHRNA3-CHRNA5-IREB2-LOC123688*	T	0.039 (0.008)	2.98E-06	0.04 (0.008)	1.14E-06	35121

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B) Tests for association with lung function for all SNPs followed up in Stage 2. 34 SNPs which showed novel evidence of association ($P < 3x10^{-6}$) were followed up for both lung function measures in Stage 2. The sample sizes (*N*) shown are the effective sample sizes for Stage 1, Stage 2 and the joint analysis of Stage 1 and 2. Effective sample size within each study is the product of sample size and imputation quality metric. $P< 5x10^{-8}$ for Stage 1 and 2 are shown in bold. Abbreviations: ns=nonsynonymous, s= synonymous. For the *CHRNA3/5* and *MMP15* regions, the lead SNP had an effective sample size ≥70 but <80% and so a proxy SNP was also included. For the *CHRNA3/5*, *MICB/NCR3* and *CDC123* regions, there were different top SNPs for FEV_1 and FEV_1/FVC and so both lead SNPs were taken forward.

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Chr.	Measure	SNP_ID (NCBI36 position), function	Coded allele	Stage 1			Stage 2			Stage 1 + Stage 2 meta-analysis		
				Beta (Se)	*P*	N	Beta (Se)	*P*	N	Beta (Se)	*P*	N
1	FEV_1/FVC	rs2284746 (17179262), *MFAP2*(intron)	G	-0.042 (0.007)	2.47E-09	45944	-0.038 (0.007)	2.64E-07	35310	-0.04 (0.005)	**7.50E-16**	81254
1	FEV_1	rs2284746 (17179262), *MFAP2*(intron)	G	0.008 (0.007)	2.78E-01	45944	0.006 (0.007)	3.70E-01	35310	0.007 (0.005)	1.48E-01	81254
1	FEV_1/FVC	rs993925 (216926691), *TGFB2*(downstream)	T	0.04 (0.007)	2.54E-07	42402	0.023 (0.01)	1.76E-02	21162	0.034 (0.006)	**1.16E-08**	63564
1	FEV_1	rs993925 (216926691), *TGFB2*(downstream)	T	0.025 (0.007)	1.51E-03	42402	0.003 (0.007)	7.29E-01	21162	0.014 (0.005)	8.71E-03	63564
2	FEV_1/FVC	rs2544527 (15843619), *DDX1*(downstream)	T	-0.04 (0.007)	1.08E-07	45352	0 (0.01)	9.75E-01	21115	-0.026 (0.006)	8.73E-06	66467
2	FEV_1	rs2544527 (15843619), *DDX1*(downstream)	T	-0.024 (0.007)	1.55E-03	45352	-0.017 (0.007)	1.95E-02	21115	-0.021 (0.005)	5.53E-05	66467
2	FEV_1/FVC	rs3769124 (239014101), *ASB1*(intron)	G	-0.038 (0.01)	1.95E-04	44924	-0.032 (0.02)	1.11E-01	10579	-0.036 (0.009)	2.83E-05	55503
2	FEV_1	rs3769124 (239014101), *ASB1*(intron)	G	-0.053 (0.01)	2.76E-07	44924	-0.023 (0.02)	2.44E-01	10579	-0.047 (0.009)	6.50E-08	55503
2	FEV_1/FVC	rs12477314 (239542085), *HDAC4*(downstream)	T	0.052 (0.008)	4.48E-09	45585	0.031 (0.008)	8.41E-05	45704	0.041 (0.006)	**1.68E-12**	91289
2	FEV_1	rs12477314 (239542085), *HDAC4*(downstream)	T	0.032 (0.008)	2.77E-04	45585	0.025 (0.007)	1.82E-04	45704	0.028 (0.005)	1.02E-07	91289
3	FEV_1/FVC	rs1529672 (25495586), *RARB*(intron)	C	-0.06 (0.009)	7.75E-10	40624	-0.038 (0.009)	1.16E-05	45386	-0.048 (0.006)	**3.97E-14**	86010
3	FEV_1	rs1529672 (25495586), *RARB*(intron)	C	-0.037 (0.009)	1.78E-04	40624	-0.011 (0.007)	9.33E-02	45386	-0.02 (0.006)	2.16E-04	86010
3	FEV_1/FVC	rs9310995 (32904119), *TRIM71*(intron)	T	0.017 (0.007)	1.70E-02	44835	-0.013 (0.009)	1.60E-01	21070	0.007 (0.006)	2.36E-01	65905
3	FEV_1	rs9310995 (32904119), *TRIM71*(intron)	T	0.035 (0.007)	1.28E-06	44835	0.009 (0.007)	2.00E-01	21070	0.023 (0.005)	3.60E-06	65905
3	FEV_1/FVC	rs1344555 (170782913), *MECOM*(intron)	T	-0.019 (0.008)	2.61E-02	46067	-0.017 (0.012)	1.55E-01	21104	-0.018 (0.007)	6.65E-03	67171
3	FEV_1	rs1344555 (170782913), *MECOM*(intron)	T	-0.042 (0.008)	1.91E-06	46067	-0.025 (0.009)	6.44E-03	21104	-0.034 (0.006)	**2.65E-08**	67171
4	FEV_1/FVC	rs1541374 (106267809), *TET2*(upstream)	T	-0.026 (0.007)	5.56E-04	45221	-0.014 (0.01)	1.72E-01	20516	-0.022 (0.006)	2.05E-04	65737
4	FEV_1	rs1541374 (106267809), *TET2*(upstream)	T	-0.036 (0.007)	2.43E-06	45221	-0.015 (0.007)	4.36E-02	20516	-0.026 (0.005)	5.80E-07	65737
5	FEV_1/FVC	rs1551943 (52230790), *ITGA1*(intron)	G	0.048 (0.008)	1.20E-08	43787	0.007 (0.008)	3.71E-01	45914	0.026 (0.006)	2.43E-06	89701
5	FEV_1	rs1551943 (52230790), *ITGA1*(intron)	G	0.022 (0.008)	9.93E-03	43787	-0.006 (0.006)	3.53E-01	45914	0.004 (0.005)	3.61E-01	89701
5	FEV_1/FVC	rs153916 (95062456), *SPATA9*(upstream)	T	-0.033 (0.007)	2.06E-06	47530	-0.025 (0.009)	6.67E-03	21428	-0.031 (0.005)	**2.12E-08**	68958
5	FEV_1	rs153916 (95062456), *SPATA9*(upstream)	T	-0.001 (0.007)	8.91E-01	47530	0.004 (0.007)	6.22E-01	21428	0.001 (0.005)	8.20E-01	68958
5	FEV_1/FVC	rs10067603 (131831767), *C5orf56*(downstream)	G	-0.04 (0.008)	1.60E-06	44134	-0.006 (0.011)	6.03E-01	21167	-0.028 (0.006)	1.46E-05	65301
5	FEV_1	rs10067603 (131831767), *C5orf56*(downstream)	G	-0.007 (0.008)	3.83E-01	44134	0.013 (0.008)	1.14E-01	21167	0.002 (0.006)	6.74E-01	65301
6	FEV_1/FVC	rs1928168 (22125717), *AK026189*(intron)	T	0.037 (0.007)	8.99E-08	47936	0.011 (0.009)	2.40E-01	21323	0.028 (0.005)	1.69E-07	69259
6	FEV_1	rs1928168 (22125717), *AK026189*(intron)	T	0.025 (0.007)	2.61E-04	47936	0.002 (0.007)	7.69E-01	21323	0.015 (0.005)	2.25E-03	69259
6	FEV_1/FVC	rs6903823 (28430275), *ZKSCAN3*(intron)/*ZNF323*(intron)	G	-0.027 (0.008)	2.28E-03	47057	-0.013 (0.011)	2.34E-01	21428	-0.021 (0.007)	1.19E-03	68485
6	FEV_1	rs6903823 (28430275), *ZKSCAN3*(intron)/*ZNF323*(intron)	G	-0.046 (0.008)	2.00E-07	47057	-0.029 (0.008)	4.75E-04	21428	-0.037 (0.006)	**2.18E-10**	68485

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Chr.	Measure	SNP_ID(NCBI36 position), function	Coded allele	Stage 1			Stage 2			Stage 1 + Stage 2 meta-analysis		
				Beta (Se)	*P*	N	Beta (Se)	*P*	N	Beta (Se)	*P*	N
6	FEV_1/FVC	rs3094548 (29463181), *OR12D2*(upstream)	G	-0.027 (0.008)	1.15E-03	42516	-0.015 (0.01)	1.37E-01	20733	-0.022 (0.006)	3.39E-04	63249
6	FEV_1	rs3094548 (29463181), *OR12D2*(upstream)	G	-0.042 (0.008)	4.11E-07	42516	-0.016 (0.008)	3.60E-02	20733	-0.029 (0.005)	1.45E-07	63249
6	FEV_1/FVC	rs2855812 (31580699), *MICB*(intron)	T	-0.034 (0.008)	5.11E-05	46921	-0.015 (0.011)	1.59E-01	21190	-0.027 (0.006)	2.45E-05	68111
6	FEV_1	rs2855812 (31580699), *MICB*(intron)	T	-0.045 (0.008)	8.57E-08	46921	-0.013 (0.008)	1.06E-01	21190	-0.03 (0.006)	1.80E-07	68111
6	FEV_1/FVC	rs2857595 (31676448), *NCR3*(upstream)	G	0.049 (0.009)	7.86E-08	45540	0.028 (0.008)	5.36E-04	45657	0.037 (0.006)	**2.28E-10**	91197
6	FEV_1	rs2857595 (31676448), *NCR3*(upstream)	G	0.04 (0.009)	1.46E-05	45540	0.017 (0.007)	9.41E-03	45657	0.025 (0.005)	1.30E-06	91197
6	FEV_1/FVC	rs2647044 (32775888), *HLA-DQB1*(upstream)	G	0.053 (0.011)	2.71E-06	44610	0.007 (0.022)	7.63E-01	8381	0.044 (0.01)	5.95E-06	52991
6	FEV_1	rs2647044 (32775888), *HLA-DQB1*(upstream)	G	0.031 (0.011)	6.71E-03	44610	0.009 (0.022)	6.71E-01	8381	0.027 (0.01)	5.62E-03	52991
6	FEV_1/FVC	rs2798641 (109374743), *ARMC2*(intron)	T	-0.047 (0.009)	2.81E-07	46369	-0.03 (0.012)	1.57E-02	20999	-0.041 (0.007)	**8.35E-09**	67368
6	FEV_1	rs2798641 (109374743), *ARMC2*(intron)	T	-0.046 (0.009)	5.39E-07	46369	-0.009 (0.01)	3.35E-01	20999	-0.03 (0.006)	4.69E-06	67368
6	FEV_1/FVC	rs3734729 (150612560), *PPP1R14C*(untranslated-3)	G	-0.045 (0.017)	8.71E-03	43680	-0.058 (0.023)	1.00E-02	20998	-0.05 (0.013)	1.93E-04	64678
6	FEV_1	rs3734729 (150612560), *PPP1R14C*(untranslated-3)	G	-0.085 (0.016)	1.08E-06	43680	-0.021 (0.017)	2.24E-01	20998	-0.055 (0.012)	4.48E-06	64678
10	FEV_1/FVC	rs1878798 (12283489), *CDC123*(intron)	G	0.042 (0.007)	3.48E-09	46164	0.024 (0.009)	1.15E-02	21086	0.035 (0.005)	**9.56E-11**	67250
10	FEV_1	rs1878798 (12283489), *CDC123*(intron)	G	0.042 (0.007)	3.11E-09	46164	0.015 (0.007)	3.65E-02	21086	0.029 (0.005)	**1.84E-09**	67250
10	FEV_1/FVC	rs7068966 (12317998), *CDC123*(intron)	T	0.045 (0.007)	1.28E-10	47085	0.023 (0.006)	3.86E-04	45892	0.033 (0.005)	**6.13E-13**	92977
10	FEV_1	rs7068966 (12317998), *CDC123*(intron)	T	0.04 (0.007)	1.19E-08	47085	0.022 (0.005)	3.56E-05	45892	0.029 (0.004)	**2.82E-12**	92977
10	FEV_1/FVC	rs11001819 (77985230), *C10orf11*(intron)	G	-0.019 (0.007)	6.50E-03	45546	-0.006 (0.006)	3.17E-01	45677	-0.012 (0.005)	7.58E-03	91223
10	FEV_1	rs11001819 (77985230), *C10orf11*(intron)	G	-0.041 (0.007)	1.42E-08	45546	-0.022 (0.005)	3.10E-05	45677	-0.029 (0.004)	**2.98E-12**	91223
12	FEV_1/FVC	rs4762767 (19757396), *AEBP2*(downstream)	G	-0.036 (0.007)	2.42E-06	48016	-0.008 (0.011)	4.47E-01	21324	-0.027 (0.006)	8.15E-06	69340
12	FEV_1	rs4762767 (19757396), *AEBP2*(downstream)	G	-0.028 (0.007)	3.85E-04	48016	-0.012 (0.008)	1.34E-01	21324	-0.021 (0.005)	1.52E-04	69340
12	FEV_1/FVC	rs11172113 (55813550), *LRP1*(intron)	T	-0.035 (0.007)	1.36E-06	45387	-0.026 (0.01)	5.83E-03	20256	-0.032 (0.006)	**1.24E-08**	65643
12	FEV_1	rs11172113 (55813550), *LRP1*(intron)	T	-0.021 (0.007)	3.55E-03	45387	-0.003 (0.007)	6.94E-01	20256	-0.013 (0.005)	1.19E-02	65643
12	FEV_1/FVC	rs1036429 (94795559), *CCDC38*(intron)	T	0.049 (0.008)	1.24E-08	47814	0.028 (0.008)	3.35E-04	46183	0.038 (0.006)	**2.30E-11**	93997
12	FEV_1	rs1036429 (94795559), *CCDC38*(intron)	T	0.01 (0.008)	2.67E-01	47814	0.004 (0.006)	5.38E-01	46183	0.006 (0.005)	2.26E-01	93997
15	FEV_1/FVC	rs2036527 (76638670), *CHRNA5*(uptream)	G	0.032 (0.007)	1.19E-05	45038	0 (0.01)	9.82E-01	20874	0.022 (0.006)	1.81E-04	65912
15	FEV_1	rs2036527 (76638670), *CHRNA5*(uptream)	G	0.036 (0.007)	2.40E-06	45038	0.015 (0.008)	5.44E-02	20874	0.026 (0.005)	6.90E-07	65912
15	FEV_1/FVC	rs12914385 (76685778), *CHRNA3*(intron)	T	-0.03 (0.007)	2.28E-05	47226	0.002 (0.01)	8.08E-01	21327	-0.019 (0.006)	5.17E-04	68553
15	FEV_1	rs12914385 (76685778), *CHRNA3*(intron)	T	-0.034 (0.007)	2.95E-06	47226	-0.015 (0.007)	4.10E-02	21327	-0.025 (0.005)	4.72E-07	68553
15	FEV_1/FVC	rs8040868 (76698236), *CHRNA3*(s)	T	0.04 (0.008)	1.14E-06	35121	-0.005 (0.01)	6.10E-01	21131	0.022 (0.006)	3.01E-04	56252
15	FEV_1	rs8040868 (76698236), *CHRNA3*(s)	T	0.039 (0.008)	2.98E-06	35121	0.012 (0.007)	9.86E-02	21131	0.025 (0.005)	4.06E-06	56252

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Chr.	Measure	SNP_ID(NCBI36 position), function	Coded allele	Stage 1			Stage 2			Stage 1 + Stage 2 meta-analysis		
				Beta (Se)	*P*	N	Beta (Se)	*P*	N	Beta (Se)	*P*	N
16	FEV_1/FVC	rs12447804 (56632783), *MMP15*(intron)	T	-0.053 (0.009)	7.12E-08	35123	-0.021 (0.01)	4.20E-02	23693	-0.038 (0.007)	**3.59E-08**	58816
16	FEV_1	rs12447804 (56632783), *MMP15*(intron)	T	-0.017 (0.009)	8.02E-02	35123	0.004 (0.007)	5.71E-01	23693	-0.004 (0.006)	4.73E-01	58816
16	FEV_1/FVC	rs3743563 (56636666), *MMP15*(missense)	G	0.043 (0.008)	1.80E-07	47179	0.013 (0.008)	1.22E-01	43190	0.028 (0.006)	6.76E-07	90369
16	FEV_1	rs3743563 (56636666), *MMP15*(missense)	G	0.015 (0.008)	8.52E-02	47179	-0.001 (0.007)	8.74E-01	43190	0.006 (0.005)	2.79E-01	90369
16	FEV_1/FVC	rs2865531 (73947817), *CFDP1*(intron)	T	0.039 (0.007)	2.30E-08	47594	0.024 (0.006)	1.94E-04	46286	0.031 (0.005)	**1.77E-11**	93880
16	FEV_1	rs2865531 (73947817), *CFDP1*(intron)	T	0.024 (0.007)	6.30E-04	47594	0.011 (0.005)	3.89E-02	46286	0.016 (0.004)	1.09E-04	93880
16	FEV_1/FVC	rs12716852 (76746239), *WWOX*(intron)	G	0.011 (0.007)	1.24E-01	47510	-0.004 (0.009)	6.85E-01	21228	0.006 (0.005)	2.81E-01	68738
16	FEV_1	rs12716852 (76746239), *WWOX*(intron)	G	0.036 (0.007)	3.45E-07	47510	0.013 (0.007)	7.11E-02	21228	0.025 (0.005)	1.92E-07	68738
21	FEV_1/FVC	rs9978142 (34574109), *KCNE2*(upstream)	T	-0.048 (0.009)	8.23E-07	44577	-0.031 (0.013)	1.75E-02	20693	-0.043 (0.008)	**2.65E-08**	65270
21	FEV_1	rs9978142 (34574109), *KCNE2*(upstream)	T	-0.012 (0.009)	2.47E-01	44577	-0.015 (0.01)	1.35E-01	20693	-0.013 (0.007)	5.57E-02	65270

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Supplementary Table 6 Estimated number of undiscovered variants and proportion of variance explained.

Effect sizes and standard errors estimated using non-discovery data are shown for genome-wide significant loci in SpiroMeta-CHARGE Stage 1 or Stage1 + 2 data. Sample sizes (N) are effective sample sizes for the non-discovery data. Estimates of discovery power for the 26 loci associated with lung function, estimates of the number of variants with similar effect sizes, and the proportion of the variance for FEV_1 and FEV_1/FVC that each individual discovered variant explains are shown. The total r^2 accounted for by discovered and putative undiscovered variants in combination is calculated as the sum of the products of r^2 multiplied by the number of estimated variants.

Chr.	SNP ID (NCBI36 position), function	FEV_1 excluding winners' curse bias		FEV_1/FVC excluding winners' curse bias		N	Power	Estimated variants	R2 (%) FEV_1	R2 (%) FEV_1/FVC
		Beta	Se	Beta	Se					
1	rs2284746(17179262), *MFAP2*(intron)	0.006	0.007	-0.038	0.007	35371[n2]	0.707	1.4	0.002	0.072
1	rs993925(216926691), *TGFB2*(downstream)	0.003	0.007	0.023	0.01	21414[n2]	0.214	4.7	0	0.024
2	rs2571445(218391399), *TNS1*(ns)	0.041	0.009	0.034	0.009	29130[s]	0.863	1.2	0.082	0.055
2	rs12477314(239542085), *HDAC4*(downstream)	0.025	0.007	0.031	0.008	45821[n2]	0.341	2.9	0.02	0.031
3	rs1529672(25495586), RARB(intron)	-0.011	0.007	-0.038	0.009	45466[n2]	0.376	2.7	0.003	0.041
3	rs1344555(170782913), *MECOM*(intron)	-0.025	0.009	-0.017	0.012	21313[n2]	0.207	4.8	0.021	0.01
4	rs2045517(90089987), *FAM13A* (intron)	-0.006	0.009	-0.037	0.009	25736[c]	0.654	1.5	0.002	0.067
4	rs10516526(106908353), *GSTCD*(intron)	0.07	0.034	0.035	0.033	7587[sc]	0.627	1.6	0.062	0.016
4	rs11100860(145698589), *HHIP*(upstream)	0.042	0.008	0.058	0.007	40202[f]	0.996	1	0.085	0.163
5	rs153916(95062456), *SPATA9*(upstream)	0.004	0.007	-0.025	0.009	21647[n2]	0.252	4	0.001	0.031
5	rs1985524(147827981), *HTR4*	-0.047	0.017	-0.052	0.017	7204[sc]	0.961	1	0.107	0.134
5	rs11134779(156869344), *ADAM19*(intron)	-0.03	0.01	-0.023	0.01	25917[c]	0.495	2	0.04	0.024
6	rs6903823(28430275), *ZKSCAN3*(intron)/*ZNF323*(intron)	-0.029	0.008	-0.013	0.011	21489[n2]	0.248	4	0.031	0.006
6	rs2857595(31676448), *NCR3*(upstream)	0.017	0.007	0.028	0.008	46107[n2]	0.129	7.8	0.009	0.025
6	rs2070600(32259421), *AGER*(ns)	0.012	0.04	0.093	0.04	7226[sc]	0.695	1.4	0.001	0.084
6	rs2798641(109374743), *ARMC2*(intron)	-0.009	0.01	-0.03	0.012	21173[n2]	0.214	4.7	0.002	0.026
6	rs262129(142894837), *LOC153910*(unknown)	0.014	0.01	0.045	0.01	25317[c]	0.319	3.1	0.008	0.081
9	rs16909859(97244613), *PTCH1*(downstream)	-0.021	0.018	0.062	0.017	22923[c]	0.539	1.9	0.006	0.058
10	rs7068966(12317998), *CDC123*(intron)	0.022	0.005	0.023	0.006	46067[n2]	0.209	4.8	0.024	0.026
10	rs11001819(77985230), *C10orf11*(intron)	-0.022	0.005	-0.006	0.006	45932[n2]	0.108	9.3	0.024	0.002
12	rs11172113(55813550), *LRP1*(intron)	-0.003	0.007	-0.026	0.01	20509[n2]	0.292	3.4	0	0.033
12	rs1036429(94795559), *CCDC38*(intron)	0.004	0.006	0.028	0.008	46311[n2]	0.204	4.9	0.001	0.026
15	rs8033889(69467134), *THSD4* (intron)	-0.039	0.011	-0.072	0.011	28974[s]	0.996	1	0.05	0.174
16	rs12447804(56632783), *MMP15*(intron)	0.004	0.007	-0.021	0.01	24398[n2]	0.059	16.8	0.001	0.015
16	rs2865531(73947817), *CFDP1*(intron)	0.011	0.005	0.024	0.006	46304[n2]	0.175	5.7	0.006	0.028
21	rs9978142(34574109), *KCNE2*(upstream)	-0.015	0.01	-0.031	0.013	20944[n2]	0.253	3.9	0.006	0.024

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Total variants		101.5		
Total % variance explained by estimated variants			1.355	3.016
Total % polygenic variance explained by estimated variants			3.388	7.538

[n2] no exclusions in SpiroMeta-CHARGE Stage 2

[s] excluding SpiroMeta consortium discovery GWAS of Repapi et al. (2010)

[c] excluding CHARGE consortium discovery GWAS of Hancock et al. (2010)

[sc] excluding SpiroMeta consortium discovery GWAS of Repapi et al. (2010) and CHARGE consortium discovery GWAS of Hancock et al. (2010)

[f] excluding FHS from SpiroMeta-CHARGE Stage 1

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Supplementary Note

PCR expression profiling

Peripheral blood mononuclear cells were isolated from whole blood using 6% (w/v) dextran and 42%–51% (v/v) Percoll gradients (Sigma). Ethical approval for the use of primary cells was obtained from the local ethics committees. Total RNA was extracted from samples using an RNeasy kit (Qiagen) as directed by the manufacturer. cDNA was generated from 1 µg of RNA template using random hexamers and a SuperScript kit (Invitrogen) as directed by the manufacturer. PCR assays were designed to cross intron-exon boundaries and where splice variation was known, in order to detect all variants. Primer sequences are given in **Supplementary Table 2.** All PCR was done using Platinum Taq High Fidelity (Invitrogen) with 100 ng of cDNA template in a 25-µl reaction. Cycling conditions were as follows: 94 °C for 3 min, 35 cycles of 94 °C for 45 s, 55 °C for 30 s, and 72 °C for 90 s. *GAPDH* gene was used as a positive control for the cDNA quality, and water (H_2O) as a negative control.

Linkage disequilibrium at 6p21.32-22.1 region of association with FEV1 and FEV1/FVC.

The novel signal of association with FEV_1/FVC at SNP rs2857595 (upstream of *NCR3*) is independent (r^2<0.01) of the previously reported association of rs2070600 (non-synonymous SNP in *AGER*).
The novel signal of association with FEV_1 at SNP rs6903823 (intron of *ZKSCAN3*/*ZNF323*) is also independent (r^2=0.01) of SNP rs2070600 (non-synonymous SNP in *AGER*) and is in low LD (r^2=0.31) with rs2857595 (novel signal upstream of *NCR3*) which show association with FEV_1/FVC.

Interaction analysis

The analysis carried out to test for Gene x Smoking interaction (**Supplementary Table 4**) was a Z-test comparing the effect of a given SNP in ever-smokers and in never-smokers.

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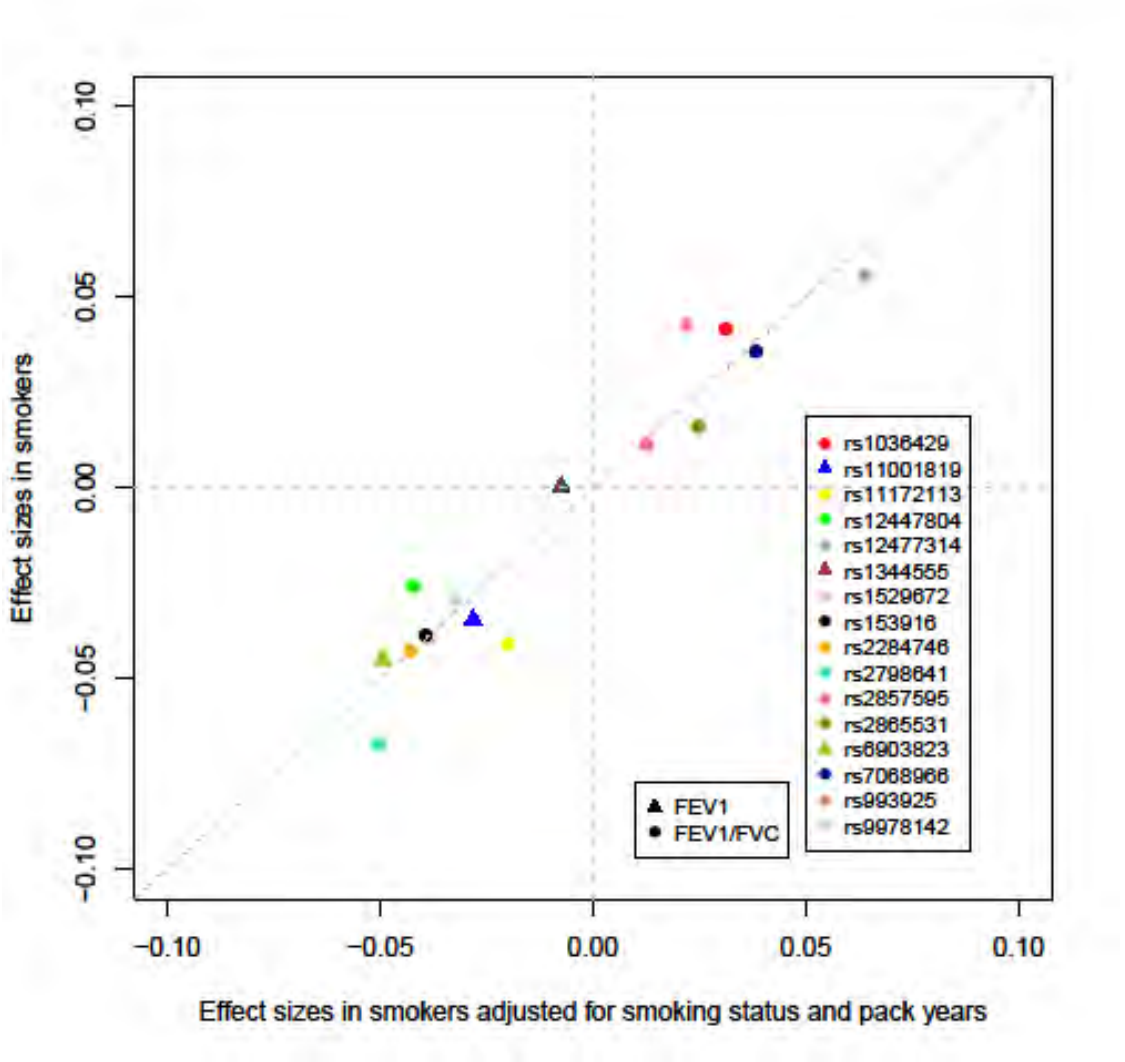
Effect of pack-years adjustment

To assess the sensitivity of the results to the amount of cigarettes smoked, an analysis was undertaken on ever-smokers adjusting for smoking status (current or ex smoker) and pack-years. The cohorts that were included in this analysis (BHS2, CARDIA, Gedling, HCS, LBC1936, LifeLines, MESA-Lung, Nottingham Smokers, NSHD, SAPALDIA and TwinsUK-II) were a subset of the follow-up studies that were chosen because of the availability of pack-years data. As represented below, effect size estimates for ever-smokers adjusted for smoking status and pack years and effect sizes for ever-smokers without any smoking adjustment were very similar across the novel loci.



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Estimation of the number of undiscovered variants and calculation of the proportion of variance explained

Our approach to estimate the number of independent variants associated with lung function measures that have similar effect sizes to the 26 variants reported here is based on the approach developed by Park *et al.*[95]. We estimated winners' curse bias free effect sizes, and obtained the number of undiscovered variants using the discovery power to detect the unbiased effect sizes.

To calculate the unbiased effect sizes for the 26 genome-wide significant ($P<5x10^{-8}$) variants we excluded discovery data for each variant. Effect size estimates for the 16 novel loci reported here were obtained using SpiroMeta-CHARGE Stage 2 data. The discovery data for *HHIP*[92,93] included the data from FHS, therefore we excluded this study in our estimation of effect size estimates. For the remaining 9 loci previously discovered, effect sizes were calculated excluding studies involved in discovery GWAS of Repapi *et al*. 2010, or discovery GWAS of Hancock *et al*. 2010, or discovery GWAS of any of them, as indicated in **Supplementary Table 6.**

To estimate the power for discovered associations we followed the approach used by the ICBP consortium for systolic and diastolic blood pressure[96].This approach takes into account that two phenotypes were analysed in parallel and it also takes into account uncertainty about true effect sizes of discovered variants. The discovery power is expressed as a function of the true effect sizes and it is then integrated with respect to a joint probability distribution for true effect sizes on FEV_1 and FEV_1/FVC. The unbiased estimates of effect sizes are used as the means for the true effect size distributions.

We followed Park *et al*. 2010 to obtain the proportion of variance explained by the inferred number of variants. First, the number of variants of a given effect size was obtained as the inverse of the power to detect them. Then, the proportion of variance explained by a variant of effect size β^2_i and allele frequency p_i was calculated as

$$\frac{2\, p_i(i-p_i)\, \beta^2_i}{V}$$

where V is the phenotypic variance. Finally, the proportion of variance explained by the inferred number of variants is obtained summing the product of the number of variants of a given effect size by the proportion of variance explained by one of them, over each of the 26 genome-wide significant ($P<5x10^{-8}$) variants. We assumed a heritability of 40%[97-100] to estimate the proportion of the additive polygenic variance of each trait.

The confidence interval for the total number of variants was obtained using bootstrapping, as in Park *et al*. 2010.

MAGENTA analysis

We tested whether the Stage 1 GWAS results were enriched for known biological pathways using MAGENTA v2[101]. Briefly, MAGENTA defines a *P* value for each gene that is the lowest SNP *P* value within 110kb upstream and 40kb downstream of the gene and is corrected for gene size, number of SNPs per gene and linkage disequilibrium within the region. For each gene set, the null hypothesis that there is a random distribution of gene association score ranks within the gene set is tested against the alternative hypothesis that there are more gene association score ranks above a given rank cut-off (75^{th} percentile cut-off is recommended for polygenic traits) compared to random sampling of 10,000 gene sets of identical size. For each gene set, a false discovery rate (FDR) is calculated as the fraction of all randomly sampled gene sets (10,000 x number of gene sets tested) that have more genes with *P* value below the cut off (75^{th} percentile) than in the gene set being tested, divided by the fraction of real gene sets that have more genes with *P* value below the cut off (75^{th} percentile) than in the gene set being tested.

Six databases of biological pathways were tested: including Ingenuity Pathway (June 2008, number of pathways n=92), KEGG (2010, n=186), PANTHER Molecular Function (January 2010, n=276), PANTHER Biological Processes (January 2010, n=254), PANTHER Pathways (January 2010, n=141) and Gene Ontology (April 2010, n=9542). Significance thresholds were Bonferroni corrected for each database.

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Genes which contain a SNP with r^2>0.3 with any of our sentinel SNPs were flagged in the analysis. Genes in the HLA region on chromosome 6 were included.

No gene sets were significant for FEV_1/FVC. Two gene sets were significant for FEV_1 after multiple testing correction for the number of gene sets tested within the database.

From the KEGG database, a Systemic Lupus Erythematosus (SLE) was significant (P=1x10^{-3}, FDR=0.03). This gene set contains 140 genes with an effective number of genes of 74 in this analysis. Flagged genes for this gene set were *TNF* and *HIST1H2AL*.

From the PANTHER Biological Processes database, the MHC-I mediated immunity pathway was significant (P=2x10^{-3}, FDR=0.019). This gene set contains 22 genes with an effective number of genes of 16 in this analysis. Flagged genes for this gene set were *MICA* and *MICB*.

GRAIL analysis

The previously described GRAIL[102] algorithm was used to mine PubMed abstracts (prior to 2006), the Gene Ontology database and the Novartis Gene Expression Analysis for evidence of functional connections between genes in the 27 regions associated with lung function. For each lung function locus, boundaries were defined for testing in GRAIL such that all genes containing a SNP with r^2>0.3 (see **Supplementary Table 2**) with the leading SNP in the region were included.

No genes were identified that were connected by the literature, Gene Ontology or Expression Atlas to genes in the other associated loci (P<0.01).

CNV analysis

All lead 16 SNPs plus all SNPs with r^2>0.8 with any lead SNP were checked for correlation with known CNVs. 192 SNP genotypes from HapMap release 24 were compared to 5238 GSV CNV genotypes[103] and 1319 McCarroll *et al*[104] CNV genotypes for the same CEU individuals. No SNP had r^2>0.3 with any of the CNVs tested.

eQTL analysis

Within each of the 16 novel regions, the lead SNPs and any SNPs with r^2>0.8 with the lead SNP were searched against a database of expression SNPs (eSNPs) from lymphoblastoid cell lines[105]. We report eSNP associations exceeding a threshold of P<1.2x10^{-7}.

SNP rs3130805, a proxy for rs6903823 in *ZKSCAN3/ZNF323* (r^2=0.69), was significantly associated (P=1.3x10^{-15}) with transcript levels of *ZFP57*. The two top eSNPs in this region showing association with *ZFP57* were rs2535238 (P=2.8x10^{-34}) and rs2747457 (P=3.3x10^{-34}) which were ~350kb away from, and not independent of, rs3130805 (r^2=0.43 and 0.38, respectively).

SNP rs3799499, another proxy for rs6903823 (r^2=0.66), was significantly associated with transcript levels of ZSCAN12 (P=7.8x10^{-10}). This SNP is 7.3Kb away from, and in strong linkage disequilibrium (r^2=1) with, the top eSNP for transcript levels of ZSCAN12 (rs7774981, P=4.1x10^{-10}).

SNP rs2857595, upstream of *NCR3*, showed significant association with transcript levels of *HLA-DRB1* (3 probes, strongest P=1x10^{-10}) and *HLA-DQA1* (P=3.9x10^{-9}). The top eSNP associated with transcript levels of both of these

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genes was rs3129763 (P=2x10^{-36} for *HLA-DRB1* and P=2.8x10^{-39} for *HLA-DQA1*) which is 1.02Mb away from, and in weak LD (r^2= 0.30) with, rs2857595.

SNP rs1424013, a proxy for rs2865531 (r^2=0.82), is one of two top eSNPs for transcript levels of *CFDP1* (P=3.3x10^{-10}). The other top eSNP is rs999675 (P=2.9x10^{-10}) is 190Kb from rs1424013, downstream of *CFDP1*, and in linkage disequilibrium with rs1424013 (r^2=0.78).

SNP rs4478891, a proxy for rs7068966 in *CDC123* on chromosome 10, showed significant association with transcript levels of *OSBPL1A* on chromosome 18 (P=1x10^{-7}) suggesting a possible *trans* regulatory effect of rs4478891. No other SNP in the eSNP database showed significant association with transcript levels of *OSBPL1A*.

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Individual study descriptions

Stage 1 GWAS samples and phenotype measurement

This section describes study-specific characteristics that are not presented in the tables. All participants provided written informed consent and studies were approved by local Research Ethics Committees and/or Institutional Review boards.

The Reykjavik Study cohort originally comprised a random sample of 30,795 men and women born in 1907-1935 and living in Reykjavik in 1967. A total of 19,381 attended, resulting in 71% recruitment rate. The study sample was divided into six groups by birth year and birth date within month. One group was designated for longitudinal follow-up and was examined in all stages. One group was designated a control group and was not included in examinations until 1991. Other groups were invited to participate in specific stages of the study. Between 2002 and 2006, the **AGES**-Reykjavik study re-examined 5,764 survivors of the original cohort who had participated before in the Reykjavik Study. Pulmonary function was obtained by spirometry (Vitalograph). Testing was conducted with the participant in a standing position and a disposable mouthpiece. Participants were shown how to perform the maneuver by the technician before testing. A successful test session was defined as at least three acceptable maneuvers.

Atherosclerosis Risk in Communities (**ARIC**), is a population based study of risk factors for atherosclerosis and its sequelae[106] in adults from four U.S. field centers aged 45-64 at recruitment in 1987-1989. ARIC spirometry measurements were made with a Collins Survey II water-seal spirometer (Collins Medical, Inc.) and Pulmo-Screen II software (PDS Healthcare Products, Inc.). Genotyping was done using the Affymetrix GeneChip SNP Array 6.0 and imputation was performed using MACH. Quality control steps for genotyping data included exclusions for call rate <95%, minor allele frequency <1%, HWE P<10-5, no chromosomal location, suspected first-degree relative of an included individual based on genotype data, or more than 8 standard deviations for any of the first ten principal components. The current analysis includes 9,078 Caucasian subjects with genotyping data, pulmonary function measures and complete covariate information.

Details of the **British 1958 Birth Cohort** biomedical follow-up have been previously reported[107] and a full technical report is available online (http://www.b58cgene.sgul.ac.uk/report.php). Spirometry at age 44–45 years was done in the standing position without nose clips, using a Vitalograph handheld spirometer as previously described[108,109]. In the analysis, all readings with a best-test variation greater than 10% were excluded.

The **Busselton Health Study** (BHS) is a longitudinal survey of the town of Busselton in the south-western region of Western Australia that began in 1966. In 1994/1995 a cross-sectional community follow-up study was undertaken where blood was taken for DNA extraction. A sample of 1,168 European-ancestry individuals were genotyped using the Illumina 610-Quad BeadChip (BHS1), and subsequent genotyping was carried out on an independent group of 3,038 European-ancestry individuals (BHS2). Spirometric measures of forced expired volume in one second (FEV1) and forced vital capacity (FVC) were assessed as described previously[110,111].

The **CHS** is a population-based cohort study of risk factors for CHD and stroke in adults > 65 years conducted across four U.S. field centers[112]. CHS spirometry measurements were made with a Collins Survey I water-seal spirometer (Collins Medical, Inc.) and software from S&M Instruments. CHS genotyped 3,980 participants free of cardiovascular disease at baseline with available DNA and consent to genetic testing. After exclusions for call rate < 95%, sex mismatch or discordance with prior genotyping, 3,291 self-identified white participants remained. Of these, 3,140 had pulmonary function measures and complete covariate information.

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The **CROATIA-Korcula** study is a family-based, cross-sectional study in the isolated island of Korcula that included about 1,000 examinees aged 18-95. Spirometry was performed in the sitting upright position without nose clips, using a Jaegger Toennisen spirometer. Three readings were taken for each examinee, at least 15 seconds apart[113]. Population stratification was partially taken into account after adjusting the measures for the 3 first principal components drawn from the population genomic kinship matrix computed using the ibs function of the GenABEL[114]. Additional correction of the standard error of effect estimates was undertaken by genomic control[115]. Effect estimates were obtained using the palinear function of the ProbABEL package.

The **CROATIA-Vis** study is a family-based, cross-sectional study in the isolated island of Vis that included about 1,000 examinees aged 18-93. Spirometry was performed in the sitting upright position without nose clips, using a Jaegger Toennisen spirometer. Three readings were taken for each examinee, at least 15 seconds apart[113]. Population stratification was partially taken into account after adjusting the measures for the 3 first principal components drawn from the population genomic kinship matrix computed using the ibs function of the GenABEL[114]. Additional correction of the standard error of effect estimates was undertaken by genomic control[115]. Effect estimates were obtained using the palinear function of the ProbABEL package.

Details of the methods of **ECRHS I** and **ECRHS II**, a multicentre international cohort study, have been published elsewhere[116,117]. Participants within the ECRHS were eligible for inclusion in this analysis if they were identified by random sampling of those who fulfilled the following criteria 1) lived in centres that took part in genome-wide genotyping initiative under the auspices of GABRIEL[118] AND 2) were initially selected to take part in the ECRHS clinical measurements as part of the random sample (ie not specifically selected for inclusion because of any pre-existing disease). Participants were included in this analyses if they also provided a technically satisfactory forced expiratory manoeuvre, compliant with ATS spirometry criteria, at the time of the first survey (aged 20-48). Most centres used the BIOMEDIN water-sealed spirometer for lung function measures and all centres conducted manoeuvres in the sitting position with nose clips on. Further details are available in[119].

The **EPIC Norfolk** GWA cohort includes 2,566 participants randomly selected from the EPIC-Norfolk Study, a population-based cohort study of 25,663 men and women of European descent aged 39-79 years recruited in Norfolk, UK between 1993 and 1997[109]. Respiratory function was assessed by spirometry[120,121]. Forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) were measured twice using a portable spirometer (Micro Medical, Rochester, United Kingdom). The higher values of the two readings for FEV1 and FVC were used for the analyses.

The **FHS** is a longitudinal community-based family study that originated in 1948 with the recruitment of adults from the town of Framingham, MA. The offspring of the original cohort were recruited to participate in 1971, and the third generation (Gen3) was recruited starting in 2002. Spirometry has been measured on all three generations of the participating families as part of the clinical examinations. For the original and offspring cohorts, spirometry was performed using a 6-L water-filled Collins survey spirometer connected to an Eagle II microprocessor (Collins Medical, Braintree, MA) or in later offspring examinations to a personal computer running software developed by S&M Instruments, Doylestown, PA. For the Gen3 cohort, spirometry was performed using the CPL System (Collins Medical, Braintree, MA) with a dry rolling-seal spirometer. All of these systems provided an automatic correction for body temperature and pressure, saturated, and provided quality assurance information. Each Framingham participant's latest examination with acceptable pulmonary function data was used in this analysis. Eligible examinations included original cohort examinations 19, 17, 16 and 13; offspring cohort examinations 7, 6, 5, and 3; and Gen3 cohort examination 1. A total of 9,274 subjects were genotyped and exclusions were based on a call rate < 97%, heterozygosity more than 5 standard deviations from the mean, or excessive non-inheritance. A total of 8,481 participants passed the genotyping quality control criteria. Of these, 7,914 participants with complete spirometry and covariate data were used in the final analysis data set.

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The subjects for the **Finnish Twin Cohort** (FTC) came from two clinical substudies of twins in Finland: 1. The FinnTwin16 study is a nationwide longitudinal cohort study of health behaviors in twins and their families[122]. The participants were 34 MZ twin pairs, who were a subset of 347 twins recruited from the FinnTwin16 study of five consecutive birth cohorts (1975–1979) of twins (n = 4929 individuals), and who participated in a clinical study of body composition and cardiorespiratory fitness. The study protocol included a bicycle ergometer exercise test with gas exchange analysis. A mass flow sensor of the gas exchange device (Sensormedics Co) was used to measure forced expiratory volume in one second and forced vital capacity before exercise. 2. The Finnish Twin Study on Ageing (FITSA). Participants were recruited from the older Finnish Twin Cohort for a clinical study of functional limitations in older women. Clinical assessment was conducted in 2000-2001 at the University of Jyväskylä. The final sample consisted of 103 monozygotic (MZ) and 114 dizygotic (DZ) twin pairs. Lung function was measured in the standing position using an electronic spirometer (Medikro 202, Kuopio, Finland). The subject was asked to inhale maximally and to exhale as fast as possible into a mouthpiece connected to a flow transducer and a flow-volume curve was created. At least two tests were performed and the best result taken for the analyses. Spirometer was calibrated daily with a three-litre pump and was accurate to within 1%. Both substudies were mainly genotyped as part of the GenomEUtwin project of female MZ pairs [123]. To avoid taking into account the statistical dependence of two related individuals in a family, we selected one twin at random for inclusion in the analysis if both of the MZ twins in a pair had the phenotype.

The Health Aging and Body Composition (**Health ABC**) study is a prospective observational cohort of well functioning individuals aged 70–79 years. The Health ABC study recruited 3,075 community-dwelling African and European Americans, men and women, at two field centers at the University of Pittsburgh, Pennsylvania and the University of Tennessee, Memphis. Spirometry was performed with a horizontal dry rolling seal spirometer (SensorMedics Corporation, Yorba Linda, CA) connected to a computer. Pulmonary function testing followed ATS guidelines for the standardization of spirometry, and is described in detail elsewhere[124]. Health ABC genotyped 1,794 self-described white participants at baseline with available DNA and consent to genetics testing; of these 1,661 passed quality control benchmarks (call rate > 97%, no sex mismatch, and cryptic relatedness), and 1,472 had pulmonary function measurements and complete data on covariates.

The DNA archive established from the **Health 2000** Survey Cohort was used. Details of this study population and phenotyping procedures have been previously reported[125]. Spirometry was done in the standing position without nose clips, using a Vitalograph 2150 spirometer. In the analysis, the maximum permissible difference between the two highest FEV1 and FVC values was 10%.

The **KORA F4** study (Cooperative Health Research in the Region of Augsburg) is a follow-up study to the KORA-Survey 2000 (S4, 10/1999 – 7/2001)[126]. Lung function tests were performed in a subsample of the KORA F4 cohort corresponding to a random population sample of subjects born between 1946 and 1965 (age range 41 – 63 years). A total of 1321 individuals (618 men, 703 women) were examined. Age was 51.6 ± 5.7 years (mean ± SD), weight was 79.2 ± 16.8 kg, and height was 1.70 ± 0.09 m. Spirometry was performed in line with the ATS recommendations [127] using a pneumotachograph-type spirometer (Masterscreen PC, CardinalHealth, Würzburg, Germany) before and after inhalation of 200 µg salbutamol. The spirometer was calibrated daily using a 1L-calibration pump (CardinalHealth, Würzburg, Germany), and additionally, an internal control was used to ensure constant instrumental conditions. The participants performed at least three forced expiratory lung function manoeuvres in order to obtain a minimum of two acceptable and reproducible values. The final values of FVC and FEV1 were determined based on the best maneuver as defined by the highest sum of FVC and FEV1. For participants who did not manage to perform at least two acceptable and reproducible values out of nine trials no lung function measurements were recorded. The presence of acute or chronic respiratory diseases as well as medication was assessed by a standardized questionnaire.

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The **KORA S3** study (Cooperative Health Research in the Region of Augsburg) is also known as the third MONICA survey, which was performed 1994-95 in Augsburg, Germany. The objective and protocol of this survey have been published earlier[126]. The third MONICA survey consisted of a random sample of all registered residents of the city of Augsburg aged 25–74 years. For all participants younger than 60, who did not smoke or use inhalers one hour before the test, FEV1 and FVC were determined by spirometry in 1997-98. All spirometric tests were performed strictly adhering to the ECRHS protocol [116]. Tests were accounted valid if at least two technically satisfactory manoeuvres could be obtained throughout a maximum of nine trials. Based on the best manoeuvre, which was defined as the trail with the highest sum of FVC and FEV1, the values of FVC and FEV1 were determined.

The **Northern Finland Birth Cohort** (NFBC) study programme was initiated in the 1960s. The cohort of women and their offspring was established in the provinces of Oulu and Lapland and had an expected date of birth in 1966 comprising 12231 children (NFBC1966, 15). The NFBC1966 had spirometry and other measurements done at the age of 31 years. In NFBC1966, we used a Vitalograph P-model spirometer (Vitalograph Ltd., Buckingham, UK), with a volumetric accuracy of ±2% or ±50 mL whichever was greater. The spirometer was calibrated regularly using a 1-Litre precision syringe. The spirometric manoeuvre was performed three times but was repeated if the coefficient of variation between two maximal readings was >4%.

The **Orkney Complex Disease Study** (ORCADES) is an ongoing family-based, cross-sectional study in the isolated Scottish archipelago of Orkney. Spirometry was performed in the sitting position without nose clips, using a Spida handheld spirometer. Measurements were repeated once and the better reading was used for analysis. Population stratification was partially taken into account after adjusting the measures for the 3 first principal components drawn from the population genomic kinship matrix computed using the ibs function of the GenABEL[114]. Additional correction of the standard error of effect estimates was undertaken by genomic control[115]. Effect estimates were obtained using the palinear function of the ProbABEL package.

The **Rotterdam Study** is a prospective population-based cohort study founded in 1990 in a suburb of Rotterdam, the Netherlands. The first cohort (RS I) consists of 7,983 participants, aged 55 years and over. The second cohort (RS II) was recruited in 2000 with the same inclusion criteria. Performing of spirometry was introduced in 2004. Spirometry was performed by trained paramedical personnel using a SpiroPro® portable spirometer (Erich Jaeger, Hoechberg, Germany), according to American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines. FEV1, FVC and FEV1/FVC ratio were measured. A total of 6,240 subjects were genotyped in RS I and a total of 2,516 in RS II. Exclusions were based on a call rate < 98%, Hardy-Weinberg p-value < 10^{-6} and MAF < 0.01%. A total of 5,974 for RS I and 2,157 for RS II passed genotyping quality control. Since spirometry was introduced in only 2004, full data with regard to spirometry and covariate data was available in 1,224 participants and 852 for RS II and were used in the final analysis dataset. Further details can be found in Hofman A et al., 2009[128] and Estrada K et al., 2009[129].

The **Study of Health in West Pomerania** (SHIP) is a cross-sectional, population based survey in a region in the Northeast of Germany. Study details are given elsewhere[130,131]. The examinations were conducted using a bodyplethysmograph equipped with a pneumotachograph (VIASYS Healthcare, JAEGER, Hoechberg, Germany) which meets the American Thoracic Society (ATS) criteria[132]. The volume signal of the equipment was calibrated with a 3.0 litre syringe connected to the pneumotachograph in accordance with the manufacturer´s recommendations and at least once on each day´s testing. Barometric pressure, temperature and relative humidity were registered every morning. Calibration of reference gas and volume was examined under ATS-conditions (Ambient Temperature Pressure) and the integrated volumes were BTPS (Body Temperature Pressure Saturated) corrected[132,133]. Lung function variables were measured continuously throughout the baseline breathing and the forced manoeuvres using a VIASYS HEALTHCARE system (MasterScreen Body/Diff.). Spirometry flow volume loops were conducted in accordance with ATS recommendations[133] in a sitting position and with wearing noseclips. The participants performed at least three forced expiratory lung function manoeuvres in order to obtain a minimum of two acceptable and reproducible values[134]. Immediate on-screen error codes indicating the major acceptability (including

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start, duration and end of test) and reproducibility criteria supported the attempt for standardised procedures. The procedure was continuously monitored by a physician. The best results for forced vital capacity (FVC), forced expiratory volume in one second (FEV 1), peak expiratory flow (PEF) and expiratory flow at 75%, 50%, 25% of FVC (MEF 75, MEF 50, MEF 25) were taken. The ratio of FEV 1 to FVC was calculated from the largest FEV 1 and FVC.

The **TwinsUK** cohort consisted of a group of twins ascertained to study the heritability and genetics of age-related diseases (www.twinsUK.ac.uk). These unselected twins were recruited from the general population through national media campaigns in the UK and shown to be comparable to age-matched population singletons in terms of disease-related and lifestyle characteristics[135]. Spirometry (Vitalograph model 2150, Buckingham, England) was conducted at the clinical centre during a visit. Twins were instructed before the test and forced vital capacity (FVC) manoeuvres were performed in a standing position, without the use of nose clips. Three manoeuvres were performed and the maximum obtained values for FEV1 were obtained. Because of the relatedness in the TwinsUK cohort, we utilized the GenABEL software package[114] which incorporates a pair-wise kinship matrix calculated using genotyping data in the polygenic model to correct for relatedness and hidden population stratification. The score test implemented in the software was used to test the association between a given SNP and the lung function phenotypes. Two sets of the samples (TwinsUK-I and TwinsUK-II) derived from the TwinsUK were genotyped. The first set – TwinsUK-I, was genotyped using the Infinium assay (Illumina, San Diego, USA) with four fully compatible SNP arrays as previously described[136]. Normalised intensity data were pooled and genotypes called on the basis of the Illluminus algorithm[137]. No calls were assigned if the most likely call was less than a posterior probability of 0.95. Validation of pooling was done by visual inspection of 100 random, shared SNPs for overt batch effects; none were observed. Quality checks similar to those for the WTCCC Study [138] were applied. The second set – TwinsUK-II, were typed with the Infinium 610k assay (Illumina, San Diego, USA) at two different centres, namely the Centre for Inherited Diseases Research (USA) and the Wellcome Trust Sanger Institute. The same pooling procedure used for the TwinsUK-I was applied to the TwinsUK-II. Further, we excluded SNPs that had a low call rate (<95%), Hardy-Weinberg p values < 10−4 and minor allele frequencies < 1%. We also removed subjects if the sample call rate was less than 95%, autosomal heterozygosity was outside the expected range, genotype concordance was over 97% with another sample and the sample was of lesser call rate, non-Caucasian ancestry either self-identified or identified by cluster analysis in STRUCTURE [139] or multidimensional scaling by comparison to the three HapMap phase 2 reference populations (CEU, YRI, CHB+JPT), or unexplained relatedness (estimated proportion of allele shared identical by descent >0.05) to >120 other samples where genotyping failed for >2 % of SNPs [140]. The overall genotyping efficiency of the GWA was 98.7 %. Imputation of genotypes was carried out using the software IMPUTE [141] for both TwinsUK-I and TwinsUK-II.

Stage 2 follow-up samples and phenotype measurement

The **ADONIX** study was established in 2001, and for the period 2001-2004 the study base was established in cooperation with the INTERGENE study. Details of the ADONIX study[142,143] and INTERGENE study[144,145] have been previously reported. Spirometry was done in the standing position with nose clips, using a Vitalograph dry-wedge spirometer as previously described[143]. All readings fulfilled the ATS requirements for standardization of spirometry.

Details of the **British Regional Heart Study** (BRHS) design have been previously reported [146]. Spirometry was done at age 60-79 years. A minimum of 3 measurements of FVC and FEV1 were obtained standing and without noseclips, using a Vitalograph Compact II instrument (Vitalograph Ltd, Buckingham, United Kingdom) as previously described[147]. FEV1 and FVC were recorded for the best test, which was defined in accordance with American Thoracic Society recommendations[148].

Full details of the selection of participants and measurements used in the British **Women's Heart and Health Study** (BWHHS) have been previously reported[149,150]. Lung function tests were carried out using a digital meter Vitalograph with an attached printout of forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), peak expiratory flow (PEF) and forced mid expiratory flow rate (FEF25–75). The Vitalograph was calibrated each day using a 1 litre syringe and automated so that results were adjusted for ambient temperature. The women then performed some

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practice efforts. They were then required to perform a minimum of three reproducible FVC measures (within 5% of maximum FVC produced). The output that produced the highest sum of FVC and FEV1 were used in the analyses. Women who could not perform three reproducible measures or who were unable to attempt the lung function assessment were excluded.

Cross-sectional analyses of data from year 0 examination of the **Coronary Artery Risk Development in Young Adults** (CARDIA) cohort was performed. During 1985-1986, CARDIA randomly recruited 5,115 black and white men and women, aged 18 to 30 years, from the general population at Birmingham, Alabama; Chicago, Illinois; and Minneapolis, Minnesota; and from the membership of the Oakland Kaiser-Permanente Health Plan in Oakland, California. Detailed methods, instruments, and quality control procedures are described at the CARDIA website (http://www.cardia.dopm.uab.edu/ex_mt.htm) and in other published reports[151,152]. Spirometric pulmonary function testing were performed using the Collins survey 8-liter water-sealed spirometer and the Eagle II microprocessor (Warren E. Collins, Inc., Braintree, MA) in a sitting position with noseclips, as per the 1979 American Thoracic Society criteria[153]. Specifically, each subject performed a minimum of three trials with expirations recorded to the FVC plateau, which occurs after six seconds of expiration in adult males and was maintained for at least one second before terminating the forced expiratory maneuver. If, at the end of the three trials, there were at least three acceptable tracings, and with the maximum FVC and FEV1 reproduced to within 5% or 100 mL, whichever is greater, no more trials were performed.

The **CROATIA-Split** study,is an ongoing population-based, cross-sectional study in the Dalmatian City of Split for which 499 of the examinees, aged 18-95, have genotype data available. Spirometry was performed in the sitting upright position without nose clips, using a Jaegger Toennisen spirometer. Three readings were taken for each examinee, at least 15 seconds apart 12. Population stratification was partially taken into account after adjusting themeasures for the3 first principal components drawn from the population genomic kinship matrix computed using the ibs function of the GenABEL package. Additional correction of the standard error of effect estimates due to related individuals was undertaken using the mmscore function in GenABEL Effect estimates were obtained using the palinear function of the ProbABEL package.

The **Gedling** cohort is a general population sample recruited in Nottingham in 1991 (18 to 70 yr of age, n=2,633)[154] and was then followed-up in 2000 (n=1346) when blood samples were taken for DNA extraction and FEV1 and FVC were measured using a calibrated dry bellows spirometer (Vitalograph, Buckingham, UK), recording the best of three satisfactory attempts[155].

Details of the **Generation Scotland: Scottish Family Health Study** (GS:SFHS) population and phenotyping procedures have been previously reported[156]. Spirometry was performed without nose clips using the Ndd Easy One Spirometer (Model 2001). Spirometry was performed a maximum of 4 times until satisfactory readings were obtained, all readings with a best test variation of greater than 10% were excluded. Generalised Estimating Equations (GEE) with robust standard errors were used to adjust for familial correlations.

The **Hertfordshire Cohort Study** (HCS) comprises a nationally unique study of 3,000 men and women born during the period 1931-39 in the English county of Hertfordshire and still resident there[157]. Lung function was measured using a Micro Spirometer (Micro Medical Ltd) in the seated position without noseclips. After at least one practice blow, three FEV1 and FVC readings were recorded. The highest FEV1 and FVC values from satisfactory manoeuvres were used in the analyses - these did not necessarily come from the same blow. DNA on all participants has been collected and is stored in the MRC Epidemiology Resource Centre, University of Southampton.

Details of the **Lothian Birth Cohort 1936** have been previously reported[158]. Lung function assessing peak expiratory flow rate, forced expiratory volume in 1 s, and forced vital capacity (each the best of three), using a Micro Medical Spirometer was assessed, sitting down without nose clips, at age 70 years. The accuracy of the spirometer is ±3% (to ATS recommendations Standardisation of Spirometry 1994 update for flows and volumes).

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LifeLines is an observational follow-up study in a large representative sample of the population of the northern provinces of the Netherlands covering three generations[159]. Firstly, a random sample of persons aged between 25 and 50 years are invited to participate. Subsequently their family members if present are invited to also take part (parents, partner, parents in law, children), resulting in a three-generation study. The core of the LifeLines project consists of dedicated data collection and biological sample storage, including genetic samples (''biobank''). All participants receive a number of questionnaires and a basic medical examination and are followed for many years with extensive standardized measurements. Spirometry was performed following ATS guidelines using a Welch Allyn Version 1.6.0.489, PC-based SpiroPerfect with Ca Workstation software. Genotyping was performed on 3078 unrelated individuals with IlluminaCytoSNP-12 arrays[160].

Details of the **Multi-Ethnic Study of Atherosclerosis** (MESA) and MESA Lung Study have been previously reported [161,162] and a full technical report of MESA procedures is available online (www.mesa-nhlbi.org). Spirometry was conducted in 2004-2006 in accordance with the 2005 ATS/ERS recommended guidelines[127] using a dry-rolling-sealed spirometer with automated quality control software (Occupational Marketing, Inc. Houston, TX). All spirometry exams were centrally reviewed by at least one (JLH) of the authors[163].

The **Nottingham Smokers** cohort is an ongoing collection in Nottingham using the following criteria; Caucasian, > 40 years of age and smoking history of > 10 pack years (currently n=538). Lung function measurements (FEV1 and FVC) were recorded at enrolment using a MicroLab ML3500 spirometer (Micro Medical Ltd, UK) recording the best of three satisfactory attempts.

The DNA archive established from the MRC National Survey of Health and Development (**NSHD**, also known as the British 1946 Birth Cohort) was used. Details of this study population have been previously reported[164]. In brief, NSHD is an ongoing prospective birth cohort study consisting of a stratified sample of all births in England, Scotland and Wales in one week in March 1946. The cohort is ethnically homogeneous and initially consisted of 2,547 females and 2,815 males who have been followed up over 20 times since their birth, mostly by means of home interviews. During 1999 when cohort members were all aged 53 years, all those still in contact with the study team and living in the UK were invited to be examined by a trained research nurse at home: 3,035 were successfully contacted[164] and adequate blood samples for DNA extraction obtained from 2,756. Spirometry at age 53 years was done in the standing position without nose clips, using a Micromedical turbine electronic spirometer (Cardinal Health UK 232 Ltd, Basingstoke, UK) as previously described[165,166]. Two measurements were taken and the maximum reading with recorded satisfactory technique (as assessed by the nurse conducting the test) was used for these analyses.

The **Rotterdam Study** is a prospective population-based cohort study founded in 1990 in a suburb of Rotterdam, the Netherlands. The third cohort (RS IIII) consists of 3,932 participants, aged 45 years and over and was recruited in 2006. Spirometry was performed by trained paramedical personnel using a SpiroPro® portable spirometer (Erich Jaeger, Hoechberg, Germany), according to American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines. FEV1, FVC and FEV1/FVC ratio were measured. A total of 2,420 subjects were genotyped in RS II. Exclusions were based on a call rate < 98%, Hardy-Weinberg p-value < 10^{-6} and MAF < 0.01%. A total of 2,082 passed genotyping quality control. Of these, 1,247 participants with complete spirometry and covariate data were used in the final analysis data set. Further details can be found in Hofman A et al., 2009[128] and Estrada K et al., 2009[129].

Details of the **SAPALDIA** Cohort have been previously reported[118,167-169] and technical details are available online (http://www.sapaldia.net/en/content/view/88/305/). SAPALDIA is a cohort study initiated in 1991 recruiting adults aged 18-60 years from the general population in eight areas of Switzerland. A first follow-up examination was done in 2002 and included the establishment of a DNA- and blood biobank, a second follow-up is currently under way. All participants were administered a detailed health questionnaire. Spirometry was done using a Sensormedics 2200

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spirometer and complying to the ATS quality criteria as previously described [167,170]. High quality genotype data was available on up to 5646 participants with complete spirometry and smoking information at baseline.

Look up samples and phenotype measurement

The **Avon Longitudinal Study of Parents and their Children** (ALSPAC) is a population-based birth cohort study consisting initially of over 13 000 women and their children recruited in the county of Avon, UK in the early 1990s[171]. At 8–9 years of age, children's lung function was measured by spirometry (Vitalograph 2120, Maids Moreton, UK) according to American Thoracic Society criteria. Flow-volume curves were reviewed by a respiratory physician to ensure adherence to standards. GWA data and lung function measurements were available on 5062 of the children from this study.

The **GIANT consortium** study description can be found in Lango Allen, H. et al[90].

The **International Lung Cancer Consortium** (ILCC) GWAS meta-analysis was conducted based on 14 lung cancer genomewide association studies with a total of 13,300 lung cancer patients and 19,666 controls[37]. The GWAS studies included in this meta-analysis are the Environment and Genetics in Lung Cancer Etiology (EAGLE), the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC), the Prostate, Lung, Colon, Ovary Screening Trial (PLCO), the Cancer Prevention Study II Nutrition Cohort (CPS-II), the UK study from the Institute for Cancer Research, the International Agency for Research on Cancer (IARC) study in central Europe, the MD Anderson study in Texas, the DeCODE study in Iceland, the Helmholtz-Gemeinschaft Deutscher Forschungszentren (HGF) study in Germany, the Carotene and Retinol Efficacy Trial (CARET) cohort, the HUNG2/Tromso study, the Canadian study from the Samuel Lunenfeld Research Institute, the lung cancer study in France and lung cancer study in Estonia. The detailed study methods and descriptions have been published previously[37].

The **Oxford-GlaxoSmithKline study** (OX-GSK) is a collaborative effort to investigate the genetic basis of smoking-related behavioral traits[89]. The study combines genome-wide chip and imputed genotype from 20 disease, population and control cohorts totaling 41,150 samples. Three smoking related behavioural traits were measured on these samples (a) a smoking quantity phenotype, defined as a semi-quantitative trait based on the self-reported variable of cigarettes smoked per day (N = 15,574) , (b) a smoking initiation binary phenotype, defined as Ever smoker (N=18,598) versus Never smoker (N=15,041), and (c) a smoking cessation phenotype, defined as Current smoker (N=10,123) versus Non-current smoker (N=19,903). Association analyses separately within each cohort under an additive model using covariate effects for age, sex, disease case or control status where applicable, and other cohort-specific covariates. A meta-analysis was then carried out by combining study-specific regression coefficient estimates using a fixed effects model.

Recruitment of the Western Australian Pregnancy (Raine) cohort has previously been described in detail[172-174]. In brief, between 1989 and 1991 2,900 pregnant women were recruited prior to 18-weeks gestation into a randomised controlled trial to evaluate the effects of repeated ultrasound in pregnancy. Children have been comprehensively phenotyped from birth to 21 years of age (average ages of one, two, three, six, eight, ten, fourteen, seventeen and twenty-one) by trained members the Raine research team. Most of the children are of Caucasian ethnicity. Data collection included questionnaires completed by the child's primary care and by the adolescent from age 14, physical assessments by trained assessors at all follow up years, DNA collection from year 14 follow-up. The study was conducted with appropriate institutional ethics approval, and written informed consent was obtained from all mothers. Study individual genotype data was extracted from the genome-wide Illumina 660 Quad Array.

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Investigators, contributions, funding and acknowledgements per study

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Stage 1 GWAS studies

AGES

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ARIC

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B58C -WTCCC

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BHS1

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CHS

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CROATIA-Korcula

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CROATIA-Vis

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ECRHS

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Cambridge CB2 0SR, UK) for contributions to project conception, design and management and genotyping. I.B. acknowledges funding from the Wellcome Trust (077016/Z/05/Z).

FHS

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Health 2000

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KORA F4

Investigators: Joachim Heinrich, Stefan Karrasch, Norman Klopp, Holger Schulz.

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KORA S3

Investigators: Eva Albrecht, Christian Gieger, Nicole Probst-Hensch, H Erich Wichmann.

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NFBC1966

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SHIP

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TwinsUK

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Stage 2 follow-up studies

ADONIX

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BHS2

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BRHS

Investigators: Aroon D Hingorani, Richard W Morris, S Goya Wannamethee, Peter H Whincup.

Contributions: phenotype collection and data management: R.W.M., S.G.W., P.H.W., genotyping: A.D.H., R.W.M., data analysis: R.W.M. **Funding & Acknowledgements:** Blood collection and spirometric measures were carried out in 1998-2000 as part of a field study funded by the British Heart Foundation (grant PG/97012). DNA was extracted by Geneservice Limited. A.D.H has a British Heart Foundation Senior Research Fellowship (FS05/125).

BWHHS

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CARDIA

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CROATIA-Split

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GS:SFHS

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HCS

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LifeLines

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MESA-Lung

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Nottingham smokers

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NSHD

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Look up studies

ALSPAC

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GIANT

Details of the GIANT consortium can be found in Lango Allen, H. et al [90].

ILCCO

Investigators: International Lung Cancer Consortium.

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