1 Title

2 Integrative genomic analysis in African American children with asthma finds 3 novel loci associated with lung
3 function

4 Authors

5 Pagé C. Goddard^{1,2,*}, Kevin L. Keys^{2,3,*}, Angel C.Y. Mak², Eunice Yujung Lee⁴, Amy K. Liu⁵, Lesly-Anne Samedy-
6 Bates⁴, Oona Risse-Adams^{2,6}, María G. Contreras^{2,7}, Jennifer R. Elhawary², Donglei Hu², Scott Huntsman², Sam
7 S. Oh², Sandra Salazar², Celeste Eng², Blanca E. Himes⁸, Marquitta J. White^{2,+}, Esteban G. Burchard^{2,4,+}

8 ¹Department of Genetics, Stanford University, Stanford, CA, USA

9 ²Department of Medicine, University of California, San Francisco, CA, USA

10 ³Berkeley Institute for Data Science, University of California, Berkeley, CA, USA

11 ⁴Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco, CA, USA

12 ⁵Memory and Aging Center, Department of Neurology, University of California, San Francisco, CA, USA

13 ⁶Department of Biology, University of California, Santa Cruz, CA, USA

14 ⁷Department of Biology, San Francisco State University, San Francisco, CA, USA

15 ⁸Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania, Philadelphia, PA, USA

16 * These authors share principal authorship equally

17 + These authors share senior authorship equally

18

19 Corresponding Author:

20 Kevin L. Keys, PhD

21 Lung Biology Center, Department of Medicine

22 UCSF Box 2911

23 San Francisco, CA 94158 USA

24 Telephone: +1 415 514 9931

25 Fax: +1 415 514 4365

26 Email: klkeys@g.ucla.edu

27 Abstract

28 Bronchodilator drugs are commonly prescribed for treatment and management of obstructive lung function
 29 present with diseases such as asthma. Administration of bronchodilator medication can partially or fully restore
 30 lung function as measured by pulmonary function tests. The genetics of baseline lung function measures taken
 31 prior to bronchodilator medication has been extensively studied, and the genetics of the bronchodilator
 32 response itself has received some attention. However, few studies have focused on the genetics of post-
 33 bronchodilator lung function. To address this gap, we analyzed lung function phenotypes in 1,103 subjects from
 34 the Study of African Americans, Asthma, Genes, and Environment (SAGE), a pediatric asthma case-control
 35 cohort, using an integrative genomic analysis approach that combined genotype, locus-specific genetic
 36 ancestry, and functional annotation information. We integrated genome-wide association study (GWAS) results
 37 with an admixture mapping scan of three pulmonary function tests (FEV₁, FVC, and FEV₁/FVC) taken before and
 38 after albuterol bronchodilator administration on the same subjects, yielding six traits. We identified 18 GWAS
 39 loci, and 5 additional loci from admixture mapping, spanning several known and novel lung function candidate
 40 genes. Most loci identified via admixture mapping exhibited wide variation in minor allele frequency across
 41 genotyped global populations. Functional fine-mapping revealed an enrichment of epigenetic annotations from
 42 peripheral blood mononuclear cells, fetal lung tissue, and lung fibroblasts. Our results point to three novel
 43 potential genetic drivers of pre- and post-bronchodilator lung function: *ADAMTS1*, *RAD54B*, and *EGLN3*.

44 Keywords

45 African-American, admixture, GWAS, lung function, asthma, integrative genomic analysis

46 Introduction

47 Asthma is a disease characterized by episodic obstruction of airways that affects nearly 339 million people
 48 worldwide (The Global Asthma Network, 2018) and is the most common chronic disease among children.
 49 Asthma constitutes a massive global economic burden, representing \$81.9 billion in medical costs in the United
 50 States alone (Nurmagambetov et al., 2018). As a complex disease, asthma results from both environmental and
 51 genetic factors, with genetic heritability estimates ranging from 0.35 to 0.90 (Ober & Yao, 2011). The advent of
 52 genome-wide association studies (GWAS) (Risch & Merikangas, 1996), combined with progressively larger
 53 sample sizes in recent years, has enabled researchers to query the genetic basis of asthma at unprecedented
 54 scale, with numerous loci identified in autoimmune and inflammatory pathways (Demenais et al., 2018).
 55 However, these loci account for a small portion of asthma liability (Demenais et al., 2018).

56 Pulmonary function tests are recommended to guide in the diagnosis of asthma and monitor patient status
 57 (Asthma and Allergy Foundation of America, 2019). During these tests, patients breathe through a spirometer
 58 that captures key measures of lung function, including the forced expiratory volume in 1 second (FEV₁), which
 59 measures initial forced exhalatory capacity; the forced vital capacity (FVC), which measures the maximum total
 60 volume of air that a patient can forcibly exhale; and their ratio (FEV₁/FVC). Lung function measures can be
 61 population-normalized according to expected lung function values that account for age, sex, height and
 62 ethnicity of the patient (Hankinson et al., 1999). Spirometric measurements can be taken both before
 63 bronchodilator treatment (Pre-BD) and after (Post-BD) to further understand lung function status. Historically,
 64 baseline lung function is measured with Pre-BD measures, but among people with asthma, post-BD lung
 65 function may best reflect lung health (Brehm et al., 2015).

66 While the genetic contribution to asthma and lung function has been extensively studied via GWAS, most
 67 analyses have relied on subjects of European descent (Demenais et al., 2018; Johansson et al., 2019; Pickrell et
 68 al., 2016; Z. Zhu et al., 2018). This overrepresentation of ethnically white subjects in biomedical research has

69 impaired the generalizability of genetic studies of complex disease (Burchard, 2014; Bustamante et al., 2011;
70 Popejoy & Fullerton, 2016). Ethnic differences in lung function, particularly between African Americans and
71 European Americans, have been reported for over 40 years (Binder et al., 1976; Glindmeyer et al., 1995; Hsi et
72 al., 1983; Rossiter & Weill, 1974; Schwartz et al., 1988). Ethnic disparities in lung function were attributed to
73 population differences in sitting height, as increased height leads to increased lung capacity. However,
74 adjustment for sitting height only explains 42-50% of ethnic differences in lung function between African
75 Americans and European Americans (Harik-Khan et al., 2004), suggesting that a simplistic reduction to ethnic
76 differences in height cannot account for the observed disparity in lung function. Unequal socioeconomic
77 conditions were also thought to contribute to ethnic differences in lung function (Braun, 2015; Quanjer, 2013,
78 2015), but socioeconomic factors only account for 7-10% of unexplained variance (Harik-Khan et al., 2004). Self-
79 identified race or ethnicity are commonly used in the clinic to interpret lung function measures, but these are
80 not ideal variables for understanding *genetic* differences in lung function between populations. Kumar *et al.*
81 observed that the proportion of global African genetic ancestry is inversely correlated with lung function (Kumar
82 et al., 2010). Spear *et al.* later observed population differences among African Americans, Mexican Americans,
83 and Puerto Ricans in bronchodilator drug response to albuterol, the short-acting β_2 -adrenergic receptor agonist
84 that is the most commonly prescribed drug for the treatment of acute asthma symptoms (Spear et al., 2019).
85 Specifically, Spear *et al.* performed admixture mapping, a technique designed to identify regions of the genome
86 where locus-specific ancestry drives variation in a disease trait (Shriner, 2013) that has been helpful in studies
87 of complex diseases, including asthma and breast cancer (Féjerman et al., 2012; Pino-Yanes et al., 2015).
88 However, admixture mapping studies comparing baseline and post-bronchodilator lung function have not yet
89 been performed in African Americans. In this study, we address this gap in knowledge by evaluating the effect
90 of locus-specific ancestry on both pre- and post-bronchodilator lung function measures in a pediatric case-
91 control cohort of African Americans children and adolescents.

92 **Methods**

93 **Study Population**

94 The Study of African Americans, Asthma, Genes and Environments (SAGE) is a case-control cross-sectional
 95 cohort study of genetics and gene-environment interactions in African American children and adolescents in
 96 the USA. SAGE includes detailed clinical, social, and environmental data on both asthma and asthma-related
 97 conditions. Full details of the SAGE study protocols are described in detail elsewhere (Borrell et al., 2013;
 98 Nishimura et al., 2013; Thakur et al., 2013; Mak et al., 2018). Briefly, SAGE was initiated in 2006 and recruited
 99 participants with and without asthma through a combination of clinic- and community-based recruitment
 100 centers in the San Francisco Bay Area. All participants in SAGE self-identified as African American and self-
 101 reported that all four grandparents were African American.

102 Pulmonary function tests were taken prior to administration of albuterol bronchodilator medication for all
 103 individuals, both those with and without asthma. Post-bronchodilator spirometry measures were performed
 104 only for individuals with asthma. Analyses of pre-bronchodilator lung function measures included all 1,103
 105 asthma cases and controls with complete covariate information. Post-bronchodilator analyses were performed
 106 on the 831 asthma cases with post-bronchodilator measurements.

107 **Genotyping and Quality Control**

108 DNA was isolated from whole blood collected from SAGE participants at the time of study enrollment as
 109 described previously (Borrell et al., 2013). DNA was extracted using the Wizard® Genomic DNA Purification kits
 110 (Promega, Fitchburg, WI). Samples were genotyped with the Affymetrix Axiom LAT1 array (World Array 4,
 111 Affymetrix, Santa Clara, CA).

112 Genotype quality control was performed in PLINK v1.9 (Chang et al., 2015). Of the 772,703 genotyped variants,
 113 111,901 SNPs were excluded from analysis due to genotype missingness more than 5% ($n = 28,211$), minor

114 allele frequency (MAF) less than 1% ($n = 80,420$) or deviation from Hardy Weinberg expectations (HWE) at $p <$
 115 0.001 ($n = 3,270$). The final set of 660,802 genotyped markers. (Supplementary Table 1).

116 Genotyped SNPs were submitted to the Michigan Imputation Server (Das et al., 2016), phased using EAGLE v2.3
 117 (Loh et al., 2016), and imputed from the 1000 Genomes Project reference panel (The 1000 Genomes Project
 118 Consortium, 2015) using Minimac3 (Das et al., 2016). Imputed SNPs with imputation $R^2 < 0.3$, with deviation
 119 from Hardy-Weinberg equilibrium (HWE) p -value $< 10^{-4}$, or with minor allele frequency (MAF) $< 1\%$ were
 120 discarded. Of the 47,101,126 imputed SNPs, a total of 31,146,322 were culled due to either low MAF ($n =$
 121 31,095,418) or deviation from HWE ($n = 50,904$). All variants in the imputed set showed a genotype missingness
 122 of no more than 5%. The final number of SNPs used in association analyses was 15,954,804 (Supplementary
 123 Table 1).

124 Outcome Phenotypes

125 Pulmonary function testing was performed at the time of recruitment according to the American Thoracic
 126 Society / European Respiratory Society standards (Miller et al., 2005; Pellegrino et al., 2005; Wanger et al.,
 127 2005) with a KoKo PFT Spirometer (nSpire Health Inc., Louisville, CO). Spirometry was performed both before
 128 and 15 minutes after administration of four puffs of albuterol (90ug per puff) through a 5-cm plastic mouthpiece
 129 from a standard metered-dose inhaler. Patients were assessed for the following spirometric measures before
 130 and after bronchodilator drug usage (pre-BD and post-BD, respectively): (a) FEV₁, (b) FVC, and (c) FEV₁/FVC. A
 131 total of six phenotypes were assessed for genotype association: pre-BD FEV₁ (Pre-FEV₁), pre-BD FVC (Pre-FVC),
 132 pre-BD FEV₁/FVC (Pre- FEV₁/FVC), post-BD FEV₁ (Post-FEV₁), post-BD FVC (Post-FVC), and post-BD FEV₁/FVC
 133 (Post-FEV₁/FVC). All phenotype values were normalized based on the expected lung function values calculated
 134 from the Hankinson equations (Hankinson et al., 1999), which account for age, sex, height, and self-reported
 135 ethnicity. Phenotype distributions were checked for normality and to detect outliers. Outliers were determined
 136 using the method of Tukey fences (John Tukey, 1977). For each phenotype, we computed the first quartile value

137 (Q1), the third quartile value (Q3), and the interquartile range (IQR). We declared as outliers all values outside
138 of the range

$$139 \quad [Q1 - 3(IQR), Q3 + 3(IQR)].$$

140 Individuals with outlier values for a phenotype were removed from association analyses for that phenotype.

141 Covariates

142 Age, Sex, and BMI

143 Biometric covariates such as age, sex, body mass index (BMI), and height were measured directly at time of
144 recruitment. BMI was categorized into underweight, normal, overweight, and obese, according to CDC
145 guidelines for defining childhood obesity (Barlow, 2007; Cote et al., 2013; Whitlock et al., 2005). An overweight
146 status was defined as a BMI at or above the 85th percentile for the general population of children of the same
147 sex and in the same age group. An obese status was defined as a BMI at or above the 95th percentile.
148 Underweight individuals (bottom 5th percentile, $n = 9$) were excluded from analysis.

149 Asthma status

150 Case status was defined as physician-diagnosed asthma supported by reported asthma medication use and
151 symptoms of coughing, wheezing, or shortness of breath in the 2 years preceding enrollment.

152 Maternal Educational Attainment

153 Maternal educational attainment was measured at recruitment and included in analyses to control for
154 socioeconomic status. It was coded as total years of education completed from the first grade: for example, a
155 complete K-6 education was 6 years, a complete high school education was 12 years, and any additional years
156 (college or trade school and beyond) were counted as 1 year each.

157 Genetic Ancestry

158 Global genetic ancestry was estimated for each individual with the ADMIXTURE software (Alexander et al.,
159 2009) in supervised learning mode assuming one West African and one European ancestral population, with
160 HapMap Phase III YRI and CEU populations as references (The International HapMap 3 Consortium, 2010). Local
161 ancestry estimation was performed with RFMix (Maples et al., 2013; Spear et al., 2019) using the same two-
162 way ancestry reference from HapMap Phase III.

163 Estimation of Genetic Relatedness and Genotype Principal Components

164 Genetic relatedness matrices (GRMs) were generated in R using GENESIS (Gogarten et al., 2019), which provides
165 a computational pipeline for handling complex population structure. We used PCAir (Conomos et al., 2015) to
166 correct for distant population structure accounting for relatedness, and PC-Relate (Conomos et al., 2016) to
167 adjust for genetic relatedness in recently admixed populations. The resulting principal components provide
168 better correction for population stratification in admixed populations compared to standard PCA on genotypes
169 (Patterson et al., 2006).

170 Genetic Association Analyses

171 Genotype association testing was performed with the MLMA-LOCO algorithm from GCTA (Yang et al., 2011,
172 2014) to correct for population structure using GRMs generated with GENESIS. Association of outcome
173 phenotypes with allele dosages at 15,954,804 biallelic SNPs was performed with a “leave one chromosome out”
174 model to avoid double-fitting tested variants. Other variables included in models were age, sex, BMI, maternal
175 educational attainment, and three genotype principal components. Models of Pre-BD also included asthma
176 status.

177 The suggestive and significant association thresholds for each outcome phenotype were determined by the
178 effective number of independent statistical tests (M_{eff}) calculated with CODA (Plummer et al., 2006). CODA

179 computes M_{eff} using the autocorrelation of p -values from GWAS. For our analyses, M_{eff} ranged from 488,819 to
180 507,975 (Supplementary Table 2). The Bonferroni corrected genome-wide significant threshold was computed
181 as $0.05/M_{\text{eff}}$, while the suggestive threshold was computed as $(1/M_{\text{eff}})$, yielding a single pair of thresholds for
182 all six outcome phenotypes considered: $p < 1.99 \times 10^{-6}$ for suggestive association, and $p < 9.95 \times 10^{-8}$ for
183 significant association (Supplementary Table 2).

184 Admixture mapping analyses were performed using linear regression models in R and local ancestry calls from
185 RFMix for 454,322 genotyped SNPs. Counts of 0, 1, or 2 alleles of African descent were computed for each
186 person at each SNP. Phenotypes were then regressed onto ancestral allele counts for each SNP while including
187 age, sex, height, BMI, maternal educational attainment (as a proxy for socioeconomic status), and global African
188 genetic ancestry proportion as covariates. Analyses with pre-BD outcome measures also included asthma status
189 as a covariate.

190 Fine-mapping genetic associations

191 Functional fine-mapping with PAINTOR (Kichaev et al., 2014) was used to identify putative causal variants in
192 novel loci deemed statistically significant by admixture mapping. PAINTOR applies a Bayesian probabilistic
193 framework to integrate functional annotations, association summary statistics (Z-scores), and linkage
194 disequilibrium information for each locus to prioritize the most likely causal variants in a given region.
195 Functional annotations were selected per locus as recommended by the authors of PAINTOR (Kichaev, 2017).
196 A subset of lung- and blood-related functional annotations from the Roadmap Epigenomics Project (Roadmap
197 Epigenomics Consortium et al., 2015) and the ENCODE Consortium (ENCODE Project Consortium, 2012) were
198 assessed for their individual improvement to the posterior probability of causality; the top 5 minimally
199 correlated annotations were selected for each locus.

200 Annotation Tools

201 The NHGRI/EBI GWAS Catalog (Buniello et al., 2019), Ensembl Genome Browser release 98 (Cunningham et al.,
202 2019) and gnomAD browser v3.0 (Karczewski et al., 2019) were used to look up known associations at significant
203 loci according to our analyses. Annotation lookups in the gnomAD browser v3.0 used hg38 coordinates
204 translated from our hg19-aligned genotypes via liftOver (Hinrichs et al., 2006). Data management, statistical
205 analysis, and figure generation made extensive use of GNU parallel (Tange, 2018) and several R packages,
206 including data.table, doParallel, optparse, ggplot2, and the tidyverse bundle (Calaway et al., 2018;
207 Davis et al., 2019; Dowle et al., 2019; Wickham, Hadley, 2016, p. 2; Wickham, Hadley & Grolemond, Garrett,
208 2017).

209 Results

210 Cohort Characteristics

211 Characteristics of all SAGE participants included in analyses are shown in Table 1. Distributions of each lung
212 function measure stratified by case/control status and bronchodilator administration (pre-BD vs. post-BD) are
213 shown in Supplementary Figure 1. FVC showed no significant difference between asthma cases and controls
214 (Kruskal-Wallis p -value = 0.073), while stratification by case/control status yielded significantly different
215 distributions for FEV₁ (Kruskal-Wallis p -value = 4.8×10^{-7}) and FEV₁/FVC (Kruskal-Wallis p -value = 1.5×10^{-7}).
216 Among cases, statistically significant differences were observed between distributions of pre-BD and post-BD
217 measures of FEV₁ (Kruskal-Wallis p -value = 1.2×10^{-38}), FVC (Kruskal-Wallis p -value = 5.4×10^{-16}), and FEV₁/FVC
218 (Kruskal-Wallis p -value = 4.0×10^{-29}), illustrating a measurable effect of bronchodilator medication on lung
219 function.

220 The global African genetic ancestry proportion in our sample varied from 30.7% to 100%, with an average
221 proportion of 80.2% (Supplementary Figure 2), concordant with empirically observed averages (Baharian et al.,

222 2016). Global ancestry contained the same information as the first genotype principal component ($R^2 = 0.984$,
223 Supplementary Figure 3).

224 Genetic association testing finds novel and known loci

225 Figure 1 shows results from GWAS performed on pre-BD phenotypes (Pre-FEV₁, Pre-FVC, and Pre-FEV₁/FVC)
226 and post-BD phenotypes (Post-FEV₁, Post-FVC, and Post-FEV₁/FVC) using linear mixed modeling. The association
227 results showed no evidence of genomic inflation, with genetic control λ ranging from 0.98 to 0.99
228 (Supplementary Table 2, Supplementary Figure 4). Table 2 lists the 18 genome-wide significant associations
229 found, each associated with exactly one of the six lung function measures. An additional 252 variants were
230 suggestively associated with at least one phenotype (Supplementary Tables 3–8). Of the 18 variants, 4 variants
231 on chromosome 13 in a region spanned by the gene *ATP8A2* were associated with Pre-FEV₁/FVC
232 (Supplementary Figure 6). Two variants on chromosome 16 that were associated with Pre-FVC flanked the
233 promoter region of *IRX3* (Supplementary Figure 7). A third variant associated with Pre-FVC was located on
234 chromosome 20 near *THBD* (Supplementary Figure 8), a gene linked to venous thromboembolism in African
235 American and Afro-Caribbean individuals (Hernandez et al., 2016). Two variants associated with Post-FVC were
236 in a gene-rich region on chromosome 19 (Supplementary Figure 9), with the peak near *TMIGD2* and *SHD*, while
237 eight other variants pointed to a second gene-rich region on chromosome 11 near *CXCR5* and *HYOU1*
238 (Supplementary Figure 10). Post-FEV₁/FVC was associated with a region on chromosome 15 near the genes
239 *AKAP13* and *ADAMTS7P4* (Supplementary Figure 11).

240 Among the suggestive associations, a variant on chromosome 12 associated with Post-FEV₁ was near *BTBD11*
241 (Supplementary Figure 12), a gene previously associated with Post-FEV₁, Post-FEV₁/FVC, and Δ FEV₁, the change
242 in lung function due to bronchodilator administration (Hardin et al., 2016; Lutz et al., 2015), as well as BMI
243 (Kichaev et al., 2019). A suggestive association with Pre-FEV₁ on chromosome 12 fell near *SCARB1*
244 (Supplementary Figure 13), which was previously associated with FEV₁ and FVC (Wyss et al., 2018) and HDL

cholesterol levels (Wojcik et al., 2019). Another suggestive association with Pre-FEV₁ on chromosome 20 was near the gene *PTPRT* (Supplementary Figure 14), which was previously associated with thromboembolism susceptibility in 5,334 African American individuals (Heit et al., 2017).

Admixture mapping identified five novel loci not found by GWAS

Table 3 shows five regions where admixture proportions were statistically significantly associated with one of the six phenotypes. The three pre-BD phenotypes (Pre-FEV₁, Pre-FVC, Pre-FEV₁/FVC) were each associated with one region, while Post-FVC was associated with two distinct regions. Post-FEV₁ and Post-FEV₁/FVC had no significant associations. None of the regions overlapped with those significant in our GWAS, and none showed large deviations from mean genome-wide African genetic ancestry. A small region on chromosome 21 that was significantly associated with Pre-FEV₁ flanked the genes *ADAMTS1* and *ADAMTS5* (Supplementary Figure 15). The region on chromosome 4 associated with Pre-FVC pointed to two candidate genes, *RCHY1* and *THAP6*, that had no prior lung disease associations (Supplementary Figure 17). A region on chromosome 19 associated with Pre-FEV₁/FVC spanned the genes *ZNF557* and *INSR* (Supplementary Figure 18). Post-FVC was associated with two regions, one on chromosome 8 spanning the genes *ESRP1*, *INTS8*, *TP53INP1* and *NDUFAF6* (Supplementary Figure 19), and another on chromosome 14 encompassing *EGLN3* and *SNX6* (Supplementary Figure 20).

Functional fine-mapping found three novel putatively causal loci for lung function phenotypes

Table 4 lists the most probable causal SNP for each of the five admixture mapping loci according to PAINTOR. SNP rs13615 showed the highest probability of causality (0.630) with Pre-FEV₁ on locus 1 (Figure 2). This variant falls within the 3' untranslated region of *ADAMTS1*, suggesting that *ADAMTS1* drives the admixture mapping association and not its physical neighbor *ADAMTS5*. The minor allele frequency of rs13615 in African and African diaspora populations was lower than every other global population (2.6% AFR vs. 7.0 – 54.5% other populations, gnomAD v3; see Supplementary Figure 21). The SNP rs10857225 emerged as the most likely causal variant

268 (probability 0.361) for the association of Pre-FVC with locus 2 on chromosome 4 (Figure 3). This variant is
 269 located within an intron of the gene *THAP6*, suggesting that *THAP6* is more likely the causal gene behind the
 270 association with Pre-FVC. In contrast to locus 1, the minor allele frequency of rs10857225 is highest in global
 271 African populations and markedly lower in other global populations (59.1% AFR vs. 28.1 – 38.4% other
 272 populations, gnomAD v3). Locus 3 on chromosome 19 associated with Pre-FEV₁/FVC, and locus 4 on
 273 chromosome 8 associated with Post-FVC, showed little information gain from functional fine-mapping. The
 274 driving variant for locus 3, SNP rs72986681, was located in the 3' untranslated region of *ZNG557*, but showed
 275 a low probability of causality (0.168, Supplementary Figure 22). The most probable marker for locus 4, the SNP
 276 rs2470740, which is located in intron 2 of *RAD54B*, showed an even lower probability of causality (0.109,
 277 Supplementary Figure 23). Functional fine-mapping of locus 5, a region on chromosome 14 associated with
 278 Post-FVC, yielded the SNP rs1351618 with a moderate probability of causality (0.390, Figure 4). rs1351618 is
 279 located in an intron of *EGLN3*. As with locus 2, rs1351618 had a much higher minor allele frequency in
 280 populations of African ancestry versus other global populations (12.4% AFR vs. < 2.2% other populations,
 281 gnomAD v3).

282 Discussion

283 We analyzed the genetic basis of six lung function phenotypes in 1,103 African American children with and
 284 without asthma. The phenotypes consisted of three standard spirometric measures – FEV₁, FVC, and FEV₁/FVC
 285 – measured before and after administration of bronchodilator medication. Our GWAS identified 18 genome-
 286 wide significant loci, while our integrative genetic analysis approach that layered GWAS, admixture mapping,
 287 and functional fine-mapping identified another 5 putatively causal loci that could drive differences between
 288 pre- and post-bronchodilator lung function.

289 The four variants on chromosome 13 associated with Pre-FEV₁/FVC pointed to *ATP8A2* as a candidate gene.
 290 *ATP8A2* encodes an ATPase involved in phospholipid transport and is highly expressed in brain tissue, testes,

291 and the adrenal glands, and to a lesser degree, lung (Fagerberg et al., 2014). Mutations in *ATP8A2* have been
 292 linked to several neurological disorders (Martín-Hernández et al., 2016). Two variants on chromosome 16 that
 293 were associated with Pre-FVC point to *IRX3* as a candidate gene. *IRX3* encodes a homeobox protein crucial for
 294 neural development and its promoters previously showed a long-range interaction with the *FTO* gene.
 295 Expression levels of the *FTO* gene are known to influence BMI and are of great interest in type II diabetes and
 296 obesity research (Smemo et al., 2014). Post-FVC showed associations on two chromosomes. Notable genes
 297 near the association peak on chromosome 19 included *MAP2K2* and *ZBTB7A*, genes associated with variation
 298 in BMI, visceral adiposity, and eosinophil counts (Kichaev et al., 2019; Pulit et al., 2019; Rüeger et al., 2018);
 299 and *CHAF1A*, *HDGFL2*, *PLIN4*, *ANKRD24*, *MPND*, and *SH3GL1*, previously associated with corpuscular volume
 300 and hemoglobin concentration (Aste et al., 2016; Kichaev et al., 2019; van Rooij et al., 2017). Interestingly, the
 301 two genes closest to the association peak, *TMIGD2* and *SHD*, have not been previously associated with any
 302 traits. *TMIGD2* is involved in T-cell co-stimulation and the immune response through an interaction with *HHLA2*,
 303 suggesting that it could possibly play an immune or allergic response role in lung function (Y. Zhu et al., 2013).
 304 Among the genes within or near the chromosome 11 peak, two emerge as potentially key loci. The first is *CXCR5*,
 305 which has been linked to increased risk of childhood onset asthma (M. A. R. Ferreira et al., 2019; Johansson et
 306 al., 2019; Pividori et al., 2019) and respiratory disease (Kichaev et al., 2019), as well as related allergic and
 307 immunological conditions such as eczema, leukocyte count, rheumatoid arthritis, and Sjögren's syndrome (M.
 308 A. Ferreira et al., 2017; Kichaev et al., 2019; Laufer et al., 2019; Lessard et al., 2013). The second is *HYOU1*,
 309 which has been associated with BMI and Post-FEV₁/FVC (Lutz et al., 2015; Pulit et al., 2019). Post-FEV₁/FVC was
 310 associated with two genes, *AKAP13* and *ADAMTS7P4*. *AKAP13* has been previously associated with numerous
 311 conditions, including interstitial lung disease and psoriasis in European individuals (Fingerlin et al., 2013; Tsoi
 312 et al., 2015) as well as weight, BMI, and cardiovascular traits such as blood pressure and hemoglobin count in
 313 multiple populations (Giri et al., 2019; Kichaev et al., 2019). *ADAMTS7P4* was previously associated with red
 314 blood cell volume (Kichaev et al., 2019). The statistically suggestive association of Post-FEV₁ with *BTBD11*

pointed to previous associations with various lung function measures, including Post-FEV₁, Post-FEV₁/FVC, and Δ FEV₁ (Hardin et al., 2016; Lutz et al., 2015). These previously detected associations were based on much larger sample sizes than what was available to us: the associations with Post-FEV₁ and Post-FEV₁/FVC found by Lutz et al. were discovered in a population of 10,094 European and 3,260 African American smokers with chronic obstructive pulmonary disorder (COPD), while the association with Δ FEV₁ found by Hardin et al. was based on 5,766 Europeans and 811 African Americans with COPD, suggesting that our inability to reach genome-wide significance in our sample was insufficient statistical power.

Among significant and suggestive GWAS loci, the association of Post-FVC with variants in or near *CXCR5* and *HYOU1* is the only one that replicates known lung function loci: *CXCR5* was previously associated with asthma (M. A. R. Ferreira et al., 2019; Johansson et al., 2019; Pividori et al., 2019), and *HYOU1* was previously associated with Post-FEV₁/FVC (Lutz et al., 2015). The association with Post-FEV₁/FVC comes from an adult COPD cohort ascertained by smoking status; in contrast, SAGE is a pediatric asthma cohort. The mechanism by which *HYOU1* affects lung function in both youth and adults is unclear. Nevertheless, the overlap of post-bronchodilator pulmonary function measures at this locus suggests that the region encompassing *CXCR5* and *HYOU1* plays a role in lung disease among people with obstructive lung function.

Admixture mapping identified 5 genomic regions where variation in genetic ancestry was significantly associated with phenotypic variation. Locus 1 on chromosome 21 spanned the genes *ADAMTS1* and *ADAMTS5*, which encode extracellular proteases within the same protein family but with different consequences for disease. Although both genes have been linked to blood protein levels (Suhre et al., 2017), *ADAMTS1* has been associated with pre-FVC (Kichaev et al., 2019) and is expressed in arterial, adipose, and lung tissue, while *ADAMTS5* is not appreciably expressed in the lung (Supplementary Figure 16). Further fine-mapping with PAINTOR places the most likely causal SNP (rs13615) within the 3' UTR of *ADAMTS1*, suggesting that *ADAMTS1* may be the gene that is functionally related to lung function. Interestingly, the association of *ADAMTS1* with pre-FVC (Kichaev et al., 2019) was discovered in a European sample of substantially larger size than our cohort,

339 highlighting the ability of admixture mapping to detect associations in scenarios with low statistical power.

340 Locus 3, spanning a region on chromosome 19 that was associated with Pre-FEV₁/FVC, contains the genes

341 *ZNF557* and *INSR*. *ZNF557* has not been previously associated with any traits, while *INSR* is the well-known

342 insulin receptor that has been previously associated with childhood onset asthma in our own cohort (White et

343 al., 2016), as well as blood pressure levels, triglyceride levels, HDL cholesterol levels, and hypothyroidism across

344 multiple populations (Bentley et al., 2019; Ehret et al., 2016; Kichaev et al., 2019; Klarin et al., 2018). Post-FVC

345 showed two distinct admixture mapping signals. The first region on chromosome 8, which we call Locus 4,

346 includes the genes *ESRP1*, *INTS8*, *TP53INP1* and *NDUFA6* was previously associated with type II diabetes and

347 eosinophil counts (Kichaev et al., 2019; Mahajan et al., 2018). The second region, Locus 5, spans *EGLN3* and

348 *SNX6*, both of which show previous associations with blood phenotypes such as blood pressure and hematocrit

349 levels (Astle et al., 2016; Evangelou et al., 2018).

350 Overall, evaluation of our GWAS and admixture mapping lung function results suggests that genetics of this

351 trait underlies some pleiotropy observed across pulmonary, hematological, cardiovascular, and obesity-related

352 traits. Such pleiotropy has been observed in UK Biobank participants: as lung function decreases, BMI and type

353 II diabetes incidence increases, as well as levels of eosinophils and neutrophils, both of which are common

354 biomarkers for allergic disease (Supplementary Figure 25)(McInnes et al., 2019; Stanford Global Biobank

355 Engine, 2020). The link between obesity and lung function is particularly interesting since obesity is a known

356 asthma comorbidity, and lung function may play a role in obese asthma (Baffi et al., 2015)(Gruchala-

357 Niedoszytko et al., 2015). Our findings suggest that genetically-based differences in lung function may provide

358 a link between obesity and asthma.

359 It is curious that the regions identified by admixture mapping and subjected to functional fine-mapping did not

360 overlap with the statistically significant GWAS loci. We attribute this in part to the different types of information

361 used by each approach: GWAS analyzes how allelic variation affects a trait, while admixture mapping analyzes

362 the phenotypic consequences of variation in genetic ancestry. By integrating GWAS summary statistics with loci

363 identified via admixture mapping, we found that three of the admixture mapping-based loci -- *ADAMTS1*,
 364 *THAP6*, and *EGLN3* -- had evidence of causal effects. Each of the sentinel SNPs tagging these genes showed a
 365 notable difference in ancestral allele frequency: populations of African descent had either the highest or the
 366 lowest minor allele frequency among all global populations, likely the result of admixture mapping prioritizing
 367 loci that varied by genetic ancestry. None of these loci have been previously associated with lung traits,
 368 highlighting the strength of our integrative analysis. The association with *EGLN3* is particularly curious since it
 369 has been previously associated with a variety of traits, including heart rate response to beta-blocker therapy
 370 (Shahin et al., 2018). Short-acting beta-2 agonists such as albuterol selectively target beta-2 receptors in the
 371 lungs, while the first-generation beta-blockers taken for cardiac conditions bind to both beta-1 and beta-2
 372 receptors, affecting the heart as well the lungs. Bronchospasm and FEV₁ reduction are clinically significant side
 373 effects of first-generation beta-1 selective and nonselective beta-blockers for cardiac conditions. Consequently,
 374 these non-selective beta-blockers must be initiated with caution and close monitoring in patients with asthma
 375 (Christiansen & Zuraw, 2019). Beta-blockers lower blood pressure by reducing heart rate and cardiac
 376 contractility and are less effective in people with high levels of African genetic ancestry (Brewster & Seedat,
 377 2013; Whelton et al., 2018). It has been previously observed that African Americans with asthma demonstrate
 378 lower bronchodilator drug response than European Americans (Blake et al., 2008), suggesting a possible
 379 pharmacological interaction between beta-2 receptors and African ancestry. Furthermore, *EGLN3* is strongly
 380 expressed in cardiac tissue, suggesting that *EGLN3* could possibly influence Post-FVC through cardiac
 381 phenotypes (Supplementary Figure 24). Further functional studies are required to elucidate the role of *EGLN3*
 382 on lung function and bronchodilator drug response.

383 Our integrative analysis approach leverages available functional annotations and genetic ancestry estimates in
 384 the absence of molecular data to yield some promise for discovery of novel loci. Our study is limited to three
 385 tiers – genotypes, genetic ancestry, and functional annotations – and makes use of gene expression results
 386 from GTEx v8. However, it does not directly incorporate any transcriptomic, metabolomic, proteomic, or

387 methylomic information. As large multi-omic datasets from NHLBI TOPMed, UK Biobank, and the NIH Million
 388 Veterans Program become available, the need for integrative genomic approaches to studying complex
 389 diseases will increase. Future multi-omic models of complex diseases, including obstructive lung function
 390 disorders, may deliver on the promise of precision medicine and provide actionable clinical translation of
 391 biomedical and pharmacogenomic insights into novel therapies.

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423 **Author Contributions**

424 PCG, KKL, and MJW designed the study. SSO, SS, CE, and EGB recruited study subjects and generated the data.
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429 **Conflicts of Interest**

430 The authors declare no competing financial interests.

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829 Tables and Figures

Characteristics	Cases	Controls	Total
Subjects (n)	831	272	1,103
Age (yr)	14.1 (3.66)	16.3 (3.77)	14.7 (3.8)
Female (n)	406	166	572
Height (cm)	158 (14.34)	162.4 (13.26)	159.1 (14.2)
African ancestry (%)	80.4 (0.1)	79.6 (0.1)	80.2 (0.1)
Maternal Education (yr)	12.4 (1.47)	12.2 (1.5)	12.3 (1.48)
Obesity status			
Obese (n)	276	74	350
Non-obese (n)	555	198	753
Pre-FEV ₁	103 (13.79)	98.1 (13.02)	99.3 (13.77)
Pre-FVC	103.4 (12.84)	105.1 (13.09)	103.8 (12.92)
Pre-FEV ₁ /FVC	95.1 (9.35)	98.4 (8.2)	95.9 (9.19)
Post-FEV ₁	107 (13.44)	n/a	n/a
Post-FVC	109 (14.42)	n/a	n/a
Post-FEV ₁ /FVC	99 (7.83)	n/a	n/a

830 Table 1: Summary statistics of phenotypes and covariates from the SAGE cohort. Displayed numbers are either counts (n) or averages
831 followed by standard errors in parentheses. Units are listed where appropriate. An “n/a” appears where measurements taken on
832 cases only.

833

Manhattan Plots

834

835 Figure 1: Manhattan plots summarizing GWAS p -values for all six lung function phenotypes. The solid red line denotes genome-wide
836 significance (p -value $< 9.95 \times 10^{-8}$), while the dashed blue line marks the suggestive threshold (p -value $< 1.99 \times 10^{-6}$), per CODA
837 calculations. Variants with a p -value greater than 0.05 were deemed uninformative and therefore not plotted.

838

Phenotype	Chr	Position (bp)	A1	A2	MAF	β	Std Err	P-value	Genes
Post-FEV1/FVC	15	85798401	A	G	0.018	-6.7846	1.27	9.05×10^{-8}	<i>ADAMTS74P, AKAP13</i>
Post-FVC	11	118932913	C	T	0.010	18.9094	3.29	9.47×10^{-9}	<i>CXCR5, HYOU1</i>
Post-FVC	11	118902275	C	T	0.010	17.9775	3.29	4.83×10^{-8}	<i>CXCR5, HYOU1</i>
Post-FVC	11	118905095	A	G	0.010	17.9775	3.29	4.83×10^{-8}	<i>CXCR5, HYOU1</i>
Post-FVC	11	118905316	T	C	0.010	17.9775	3.29	4.83×10^{-8}	<i>CXCR5, HYOU1</i>
Post-FVC	11	118906065	A	G	0.010	17.9775	3.29	4.83×10^{-8}	<i>CXCR5, HYOU1</i>
Post-FVC	11	118906240	T	C	0.010	17.9775	3.29	4.83×10^{-8}	<i>CXCR5, HYOU1</i>
Post-FVC	11	118906745	C	G	0.010	17.9775	3.29	4.83×10^{-8}	<i>CXCR5, HYOU1</i>
Post-FVC	11	118907923	G	T	0.010	18.2978	3.41	7.85×10^{-8}	<i>CXCR5, HYOU1</i>
Post-FVC	19	4289259	T	C	0.106	5.1672	0.967	9.21×10^{-8}	<i>TMIGD2, SHD</i>
Post-FVC	19	4291817	T	C	0.111	5.2674	0.963	4.52×10^{-8}	<i>TMIGD2, SHD</i>
Pre-FEV1/FVC	13	26235394	G	A	0.010	-10.5334	1.94	5.80×10^{-8}	<i>ATP8A2</i>
Pre-FEV1/FVC	13	26247080	G	A	0.010	-10.5334	1.94	5.80×10^{-8}	<i>ATP8A2</i>
Pre-FEV1/FVC	13	26262378	T	G	0.011	-10.5325	1.94	5.81×10^{-8}	<i>ATP8A2</i>
Pre-FEV1/FVC	13	26268604	A	C	0.011	-10.5325	1.94	5.81×10^{-8}	<i>ATP8A2</i>
Pre-FVC	20	22900228	G	A	0.010	18.0953	2.93	6.77×10^{-10}	<i>THBD</i>
Pre-FVC	16	54327903	G	A	0.023	9.8543	1.78	2.83×10^{-8}	<i>IRX3, FTO</i>
Pre-FVC	16	54327610	A	G	0.034	8.3689	1.53	4.85×10^{-8}	<i>IRX3, FTO</i>

839 Table 2: Significant association results from GWAS. The p-values for all SNPs listed here met the significance threshold of 9.95×10^{-8} .
840 SNPs were specified by chromosome (Chr) and physical position in base pairs (bp). A1 denotes the major allele, while A2 denotes
841 the minor allele. MAF denotes the minor allele frequency (MAF). B denotes the effect size. "Std Err" is the standard error of the
842 estimate of β . "Genes" denotes any genes within proximity of the associated variants.

Locus	Phenotype	Chr	Start (bp)	End (bp)	Length (Kb)	Threshold	SNP _{Admix} (n)	SNP _{GWAS} (n)	AFR (%)	Genes
1	Pre-FEV1	21	28,209,667	28,240,392	30.72	1.03 x 10 ⁻⁴	4	215	78.7	ADAMTS1
2	Pre-FVC	4	75,555,658	76,873,740	1318.08	9.64 x 10 ⁻⁵	102	7905	79.8	RCHY1, THAP6
3	Pre-FEV1/FVC	19	7,068,207	7,127,294	59.09	1.04 x 10 ⁻⁴	18	376	80.4	INSR, ZNF557
4	Post-FVC	8	95,387,941	95,820,594	432.65	9.93 x 10 ⁻⁵	45	2822	80.8	ESRP1, INTS8, TP53INP1, NDUFAF6
5	Post-FVC	14	34,283,561	34,595,061	311.50	9.93 x 10 ⁻⁵	95	1982	80.5	EGLN3, SNX6

844 Table 3: Admixture mapping in SAGE identified five regions with statistically significant association to at least one phenotype. The regions are arbitrarily numbered from 1 to 5
845 and defined by phenotype, chromosome (Chr), physical starting point (in base pairs), and end point (in base pairs). Physical positions are given in hg19 coordinates. The total
846 length of the region is given in kilobasepairs (Kb). The threshold for statistical significance is given for each region. SNP_{Admix} counts the number (n) of genotyped SNPs from
847 admixture mapping that met the significance threshold. SNP_{GWAS} counts the total number of GWAS SNPs (genotyped and/or imputed) in the admixture mapping region. AFR
848 denotes the percentage (%) of local genetic ancestry of African origin. The column “Genes” lists genes physically within and near the associated regions.

Locus	Phenotype	Chr	Position (bp)	SNP	Ref allele	Alt allele	MAF (%)	P-value	Annotation	Pr(causal)
1	Pre-FEV ₁	21	28,209,667	rs13615	A	G	2.55%	6.95 x 10 ⁻³	ADAMTS1, 3' UTR	0.630
2	Pre-FVC	4	76,464,584	rs10857225	A	C	59.07%	3.11 x 10 ⁻⁶	THAP6, Intron Variant	0.361
3	Pre-FEV ₁ /FVC	19	7,087,789	rs72986681	G	A	1.54%	7.25 x 10 ⁻⁴	ZNF557, 3' UTR	0.168
4	Post-FVC	8	95,399,551	rs2470740	A	T	23.82%	2.04 x 10 ⁻³	RAD54B, Intron Variant	0.109
5	Post-FVC	14	34,531,633	rs1351618	C	T	12.40%	1.99 x 10 ⁻⁴	EGLN3, Intron Variant	0.390

850 Table 4: Results from PAINTOR highlighting the most probably causal SNPs for each locus as defined by admixture mapping. Similar to Table 3, the loci are arbitrarily numbered
851 from 1 to 5 and defined by phenotype and chromosome (Chr). The physical position (in basepairs) of the most likely causal SNP is given in hg19 coordinates. Minor allele
852 frequencies (MAF) are taken from global populations from the gnomAD server v3. The displayed *p*-values are from our discovery GWAS. The probability of causality (Pr(causal))
853 is computed from PAINTOR.

854

855 Figure 2: A CANVIS plot of results from PAINTOR functional fine-mapping for locus 1, an association with Pre-FEV₁ on chromosome
 856 21. The SNP rs13615, which sits in the 3' UTR of the gene *ADAMTS1*, attains a posterior probability of causality of 0.630. The panels
 857 show, from top to bottom, the posterior probability of causality; the 5 most informative functional annotations; GWAS p-values; and
 858 local linkage disequilibrium expressed as a signed Pearson correlation.

859

860 Figure 3: PAINTOR results for locus 2, an association on chromosome 4 with Pre-FVC. The sentinel SNP, rs10857225, corresponds
861 with a GWAS peak that does not pass Bonferroni correction for statistical significance. The highlighted peak tags the intron of the
862 gene *THAP6*.

863

864 Figure 4: PAINTOR fine-mapping results for locus 5, corresponding to a region on chromosome 14 associated with Post-FVC. The most
865 likely causal SNP, rs1351618, tags an intron of the gene *EGLN3*.

Supplementary Tables and Figures

167

	Individuals (<i>n</i>)		Genotyped (<i>n</i>)		Imputed (<i>n</i>)	
	<i>retained</i>	<i>removed</i>	<i>retained</i>	<i>removed</i>	<i>retained</i>	<i>removed</i>
Initial	1985	-	772,703	-	47,101,126	-
(1) remove saliva	1949	36	772,703	0	47,101,126	0
(2) --geno 0.05	1949	0	744,492	28,211	47,101,126	0
(3) --maf 0.01	1949	0	664,072	80,420	16,005,708	31,095,418
(4) --mind 0.05	1948	1	664,072	0	16,005,708	0
(5) --hwe 0.0001	1948	0	660,802	3,270	15,954,804	50,904
Final	1948	37	660,802	31,561	15,954,804	31,146,322

168 Supplementary Table 1: Counts of individuals and variants retained and removed during quality control, including filtering flags from
169 PLINK 1.9. Initial indicates the starting number of individuals and variants in the unfiltered datasets. The subsequent row names
170 refer to the plink command and threshold used for each step: (1) Individuals whose DNA was obtained from saliva rather than blood
171 were removed; (2) Variants with genotyping efficiency below 95% were purged; (3) Variants with minor allele frequencies below 1%
172 were excluded; (4) Individuals with genotyping efficiency below 95% were removed. (5) Variants that deviate from Hardy-Weinberg
173 equilibrium with p-value < 0.0001 were purged.

174

GWAS Trait	λ	Effective Tests	Significance Threshold	Suggestive Threshold
Post-FEV ₁ /FVC	0.9776	503667.1	9.93x 10 ⁻⁸	1.99 x 10 ⁻⁷
Post-FEV ₁	0.9791	512041	9.76 x 10 ⁻⁸	1.95 x 10 ⁻⁷
Post-FVC	0.9732	488818.5	1.02 x 10 ⁻⁷	2.05 x 10 ⁻⁷
Pre-FEV ₁ /FVC	0.9885	499624.2	1.00 x 10 ⁻⁷	2.00 x 10 ⁻⁷
Pre-FEV ₁	0.9870	507975.4	9.84 x 10 ⁻⁸	1.97 x 10 ⁻⁷
Pre-FVC	0.9893	502450.9	9.95 x 10 ⁻⁸	1.99 x 10 ⁻⁷
average	0.9824	502429.5	9.95 x 10⁻⁸	1.99 x 10⁻⁷

175 Supplementary Table 2: Genomic inflation factors (λ), effective numbers of tests (M_{eff}), and both significance and suggestive thresholds
176 are presented for the GWAS of each phenotype. The genomic inflation values were calculated in R. The number M_{eff} was estimated in
177 R using the autocorrelation method from CODA. The significance threshold was calculated as $1/M_{\text{eff}}$, and the suggestive threshold was
178 determined with $0.5/M_{\text{eff}}$.

179

81

82 Supplementary Figure 1: Distributions of lung function measures stratified by asthma case status and bronchodilator treatment. Lung
 83 function values are normalized against predictions given by the Hankinson equations (% Predicted). Asthma controls (blue) received
 84 no bronchodilator medication. Asthma cases are separated by lung function values measured pre-bronchodilator (pre-BD, green) and
 85 post-bronchodilator (post-BD, red) administration.

86

Supplementary Figure 2: A plot of global admixture proportions for SAGE subjects, ordered in descending proportion of African ancestry. In SAGE, the mean genetic ancestry proportion of African origin is 80.2%.

90

91 Supplementary Figure 3: A plot of the first genotype principal component (PC1) versus the proportion of global African genetic ancestry
 92 (African) shows that the two covariates are essentially exchangeable ($R^2 = 0.984$).

93

QQ Plots

94

95 Supplementary Figure 4: Quantile-quantile plots for all six phenotypes subjected to GWAS. The left column contains Pre-BD
 96 phenotypes, while the right column contains the corresponding Post-BD phenotypes.

Volcano Plots

97

Beta

98 Supplementary Figure 5: Volcano plots showing the relationship between GWAS p -values and effect sizes β . As in Supplementary
99 Figure 4, pre-BD traits are on the left, while post-BD traits are on the right. Variants meeting the CODA-adjusted suggestive threshold
100 (1.99×10^{-6}) are highlighted in salmon pink; variants with a p -value $\leq 1 \times 10^{-7}$ and $|\beta| \geq 2$ are highlighted in purple. A positive value of
101 β indicates that the minor allele is associated with higher lung function, while $\beta < 0$ indicates that the minor allele tracks with lower
102 lung function compared to the major allele. Non-significant variants are shown in grey. Variants with a p -value < 0.05 were deemed
103 uninformative and therefore not plotted.

104

Phenotype	Chr	SNP	Position (bp)	A1	A2	MAF	β	Std Err	P-value
Pre-FEV ₁	1	1:158003840	158003840	C	G	0.012	12.4180	2.59	1.61 x 10 ⁻⁶
Pre-FEV ₁	1	1:158004676	158004676	C	T	0.011	12.4151	2.59	1.62 x 10 ⁻⁶
Pre-FEV ₁	2	2:34321239	34321239	C	T	0.293	-3.0486	0.639	1.82 x 10 ⁻⁶
Pre-FEV ₁	6	6:12318099	12318099	A	G	0.081	-4.9768	1.05	1.92 x 10 ⁻⁶
Pre-FEV ₁	10	10:109510095	109510095	T	G	0.161	3.7327	0.782	1.79 x 10 ⁻⁶
Pre-FEV ₁	10	10:109519015	109519015	A	G	0.405	-2.7360	0.569	1.54 x 10 ⁻⁶
Pre-FEV ₁	10	10:109531399	109531399	C	T	0.330	3.1622	0.607	1.93 x 10 ⁻⁷
Pre-FEV ₁	10	10:109531773	109531773	A	G	0.331	3.1622	0.607	1.93 x 10 ⁻⁷
Pre-FEV ₁	10	10:109532399	109532399	G	A	0.331	3.1409	0.607	2.24 x 10 ⁻⁷
Pre-FEV ₁	10	10:109532529	109532529	G	T	0.331	3.1755	0.607	1.66 x 10 ⁻⁷
Pre-FEV ₁	10	10:109533077	109533077	C	T	0.331	3.1174	0.608	2.89 x 10 ⁻⁷
Pre-FEV ₁	10	10:109538187	109538187	A	C	0.381	-2.8430	0.580	9.71 x 10 ⁻⁷
Pre-FEV ₁	10	10:109538400	109538400	T	C	0.328	3.1254	0.610	2.98 x 10 ⁻⁷
Pre-FEV ₁	10	10:109542795	109542795	C	T	0.318	2.9032	0.610	1.94 x 10 ⁻⁶
Pre-FEV ₁	10	10:109543483	109543483	G	A	0.328	3.1689	0.609	1.98 x 10 ⁻⁷
Pre-FEV ₁	12	12:125410562	125410562	T	G	0.336	-2.9360	0.594	7.68 x 10 ⁻⁷
Pre-FEV ₁	14	14:20641690	20641690	C	T	0.410	2.6744	0.563	1.99 x 10 ⁻⁶
Pre-FEV ₁	14	14:20641707	20641707	T	A	0.410	2.6744	0.563	1.99 x 10 ⁻⁶
Pre-FEV ₁	14	14:20641788	20641788	A	T	0.410	2.6795	0.563	1.93 x 10 ⁻⁶
Pre-FEV ₁	14	14:20642034	20642034	A	T	0.410	2.6878	0.562	1.76 x 10 ⁻⁶
Pre-FEV ₁	17	17:1307087	1307087	A	G	0.087	-5.0185	1.05	1.90 x 10 ⁻⁶
Pre-FEV ₁	17	17:10856828	10856828	G	A	0.065	5.4992	1.14	1.42 x 10 ⁻⁶
Pre-FEV ₁	17	17:66947338	66947338	G	A	0.017	-9.9925	2.09	1.72 x 10 ⁻⁶
Pre-FEV ₁	17	17:66947385	66947385	G	A	0.017	-9.9925	2.09	1.72 x 10 ⁻⁶
Pre-FEV ₁	19	19:45780813	45780813	G	A	0.072	-4.9503	1.03	1.42 x 10 ⁻⁶
Pre-FEV ₁	19	19:45782169	45782169	T	C	0.073	-4.9651	1.02	1.03 x 10 ⁻⁶
Pre-FEV ₁	19	19:45782594	45782594	G	A	0.073	-5.1489	1.03	5.24 x 10 ⁻⁷
Pre-FEV ₁	20	20:42117790	42117790	T	C	0.016	12.0182	2.31	2.05 x 10 ⁻⁷

105 Supplementary Table 3: Suggestive associations with Pre-FEV₁.

Phenotype	Chr	SNP	Position (bp)	A1	A2	MAF	β	Std Err	P-value
Pre-FVC	3	3:136065565	136065565	G	A	0.137	3.9445	0.804	9.28×10^{-7}
Pre-FVC	3	3:136073920	136073920	T	C	0.165	3.6839	0.736	5.62×10^{-7}
Pre-FVC	3	3:140836152	140836152	A	G	0.011	12.0836	2.52	1.60×10^{-6}
Pre-FVC	3	3:172005706	172005706	G	T	0.026	8.4445	1.61	1.67×10^{-7}
Pre-FVC	6	6:45961727	45961727	T	G	0.017	9.6273	2.01	1.68×10^{-6}
Pre-FVC	6	6:162713288	162713288	A	G	0.014	11.4754	2.31	6.98×10^{-7}
Pre-FVC	11	11:86410675	86410675	A	G	0.010	13.3956	2.73	8.98×10^{-7}
Pre-FVC	14	14:51754057	51754057	T	C	0.216	3.2204	0.636	4.11×10^{-7}
Pre-FVC	15	15:68708723	68708723	T	C	0.142	-3.7504	0.781	1.57×10^{-6}
Pre-FVC	16	16:54327610	54327610	A	G	0.034	8.3689	1.53	4.85×10^{-8}
Pre-FVC	16	16:54327903	54327903	G	A	0.023	9.8543	1.78	2.83×10^{-8}
Pre-FVC	19	19:7732700	7732700	C	T	0.030	7.4308	1.54	1.30×10^{-6}
Pre-FVC	19	19:36353880	36353880	A	G	0.121	-3.8618	0.796	1.21×10^{-6}
Pre-FVC	19	19:36372775	36372775	T	C	0.129	-3.7039	0.773	1.67×10^{-6}
Pre-FVC	20	20:22900228	22900228	G	A	0.010	18.0953	2.93	6.77×10^{-7}
Pre-FVC	20	20:22960678	22960678	A	G	0.012	13.3932	2.67	5.17×10^{-7}
Pre-FVC	20	20:49240699	49240699	G	A	0.070	4.9814	1.03	1.46×10^{-6}
Pre-FVC	20	20:58734941	58734941	A	T	0.010	14.1234	2.86	7.61×10^{-7}
Pre-FVC	20	20:58735391	58735391	C	G	0.010	14.1234	2.86	7.61×10^{-7}
Pre-FVC	21	21:25030141	25030141	G	T	0.015	-12.0039	2.42	7.24×10^{-7}
Pre-FVC	21	21:25045811	25045811	A	G	0.016	-11.3463	2.34	1.30×10^{-6}
Pre-FVC	21	21:26032912	26032912	C	G	0.011	12.9973	2.73	1.87×10^{-6}
Pre-FVC	22	22:35972126	35972126	G	A	0.052	-5.8582	1.21	1.34×10^{-6}

107 Supplementary Table 4: Suggestive associations with Pre-FVC.

Phenotype	Chr	SNP	Position (bp)	A1	A2	MAF	β	Std Err	P-value
Pre-FEV ₁ /FVC	2	2:37977506	37977506	C	T	0.035	-4.9670	1.01	9.81 x 10 ⁻⁷
Pre-FEV ₁ /FVC	2	2:236936348	236936348	C	G	0.469	1.8358	0.385	1.85 x 10 ⁻⁶
Pre-FEV ₁ /FVC	3	3:31401513	31401513	A	T	0.020	-6.4871	1.32	8.34 x 10 ⁻⁷
Pre-FEV ₁ /FVC	3	3:31401514	31401514	C	T	0.020	-6.4871	1.32	8.34 x 10 ⁻⁷
Pre-FEV ₁ /FVC	4	4:96879482	96879482	C	T	0.019	-7.8595	1.59	7.62 x 10 ⁻⁷
Pre-FEV ₁ /FVC	4	4:96913583	96913583	C	T	0.011	-9.2573	1.82	3.89 x 10 ⁻⁷
Pre-FEV ₁ /FVC	5	5:49943626	49943626	A	G	0.465	-1.9196	0.398	1.44 x 10 ⁻⁶
Pre-FEV ₁ /FVC	5	5:49943944	49943944	G	A	0.465	-1.9191	0.399	1.48 x 10 ⁻⁶
Pre-FEV ₁ /FVC	5	5:49980285	49980285	G	C	0.476	-1.9524	0.398	9.30 x 10 ⁻⁷
Pre-FEV ₁ /FVC	5	5:50028474	50028474	A	G	0.481	-1.9960	0.402	6.79 x 10 ⁻⁷
Pre-FEV ₁ /FVC	5	5:50033254	50033254	A	C	0.481	-1.9960	0.402	6.79 x 10 ⁻⁷
Pre-FEV ₁ /FVC	5	5:50068245	50068245	T	A	0.481	-1.9881	0.403	8.07 x 10 ⁻⁷
Pre-FEV ₁ /FVC	5	5:50089919	50089919	A	G	0.482	-1.9828	0.402	8.18 x 10 ⁻⁷
Pre-FEV ₁ /FVC	5	5:50140456	50140456	A	G	0.471	-1.9802	0.403	9.11 x 10 ⁻⁷
Pre-FEV ₁ /FVC	5	5:50140616	50140616	C	T	0.477	-2.0583	0.405	3.66 x 10 ⁻⁷
Pre-FEV ₁ /FVC	7	7:23773818	23773818	C	T	0.408	1.9154	0.394	1.14 x 10 ⁻⁶
Pre-FEV ₁ /FVC	7	7:23819271	23819271	G	T	0.288	2.0651	0.433	1.90 x 10 ⁻⁶
Pre-FEV ₁ /FVC	7	7:23819738	23819738	C	G	0.343	2.0170	0.410	8.82 x 10 ⁻⁷
Pre-FEV ₁ /FVC	7	7:23820068	23820068	A	T	0.343	2.0105	0.411	9.95 x 10 ⁻⁷
Pre-FEV ₁ /FVC	7	7:23821784	23821784	C	A	0.343	2.0105	0.411	9.95 x 10 ⁻⁷
Pre-FEV ₁ /FVC	7	7:23823355	23823355	G	A	0.329	2.0050	0.416	1.44 x 10 ⁻⁶
Pre-FEV ₁ /FVC	7	7:23824013	23824013	G	C	0.330	2.0254	0.416	1.10 x 10 ⁻⁶
Pre-FEV ₁ /FVC	7	7:52038019	52038019	G	A	0.011	-9.6564	1.99	1.20 x 10 ⁻⁶
Pre-FEV ₁ /FVC	7	7:52041108	52041108	C	G	0.011	-9.6564	1.99	1.20 x 10 ⁻⁶
Pre-FEV ₁ /FVC	7	7:52042215	52042215	A	C	0.011	-9.6564	1.99	1.20 x 10 ⁻⁶
Pre-FEV ₁ /FVC	10	10:4647237	4647237	C	T	0.015	-7.8359	1.61	1.17 x 10 ⁻⁶
Pre-FEV ₁ /FVC	10	10:4706126	4706126	A	G	0.040	-4.6870	0.956	9.48 x 10 ⁻⁷
Pre-FEV ₁ /FVC	10	10:24126147	24126147	T	A	0.010	-8.3860	1.73	1.22 x 10 ⁻⁶
Pre-FEV ₁ /FVC	10	10:69368950	69368950	C	T	0.037	-4.6094	0.969	1.95 x 10 ⁻⁶
Pre-FEV ₁ /FVC	10	10:69373810	69373810	A	G	0.037	-4.6094	0.969	1.95 x 10 ⁻⁶
Pre-FEV ₁ /FVC	10	10:69434683	69434683	G	A	0.038	-4.7908	0.964	6.73 x 10 ⁻⁷
Pre-FEV ₁ /FVC	10	10:69471854	69471854	A	G	0.038	-4.8378	0.968	5.81 x 10 ⁻⁷
Pre-FEV ₁ /FVC	10	10:69493149	69493149	C	T	0.038	-4.8378	0.968	5.81 x 10 ⁻⁷
Pre-FEV ₁ /FVC	10	10:69512750	69512750	G	A	0.039	-4.7482	0.963	8.23 x 10 ⁻⁷
Pre-FEV ₁ /FVC	10	10:69543254	69543254	A	G	0.033	-5.1457	1.04	7.20 x 10 ⁻⁷
Pre-FEV ₁ /FVC	10	10:69583770	69583770	T	C	0.030	-5.2467	1.08	1.28 x 10 ⁻⁶
Pre-FEV ₁ /FVC	10	10:69600576	69600576	T	C	0.051	-4.1251	0.806	3.10 x 10 ⁻⁷
Pre-FEV ₁ /FVC	10	10:69607048	69607048	C	T	0.052	-4.1152	0.803	3.02 x 10 ⁻⁷
Pre-FEV ₁ /FVC	10	10:69622074	69622074	A	T	0.052	-3.9272	0.795	7.74 x 10 ⁻⁷
Pre-FEV ₁ /FVC	10	10:69622076	69622076	G	A	0.052	-3.9272	0.795	7.74 x 10 ⁻⁷
Pre-FEV ₁ /FVC	10	10:69629302	69629302	A	G	0.028	-5.4903	1.10	6.68 x 10 ⁻⁷
Pre-FEV ₁ /FVC	10	10:69629812	69629812	T	G	0.028	-5.4903	1.10	6.68 x 10 ⁻⁷
Pre-FEV ₁ /FVC	10	10:69631004	69631004	A	G	0.028	-5.4903	1.10	6.68 x 10 ⁻⁷

Pre-FEV ₁ /FVC	10	10:69655216	69655216	T	C	0.052	-3.9421	0.791	6.20 x 10 ⁻⁷
Pre-FEV ₁ /FVC	10	10:69655466	69655466	A	G	0.028	-5.4903	1.10	6.68 x 10 ⁻⁷
Pre-FEV ₁ /FVC	10	10:69668476	69668476	A	T	0.029	-5.1320	1.07	1.52 x 10 ⁻⁶
Pre-FEV ₁ /FVC	10	10:69668477	69668477	T	G	0.028	-5.4554	1.11	9.05 x 10 ⁻⁷
Pre-FEV ₁ /FVC	10	10:69673174	69673174	T	C	0.028	-5.5138	1.14	1.21 x 10 ⁻⁶
Pre-FEV ₁ /FVC	10	10:69693013	69693013	C	A	0.051	-3.9993	0.797	5.25 x 10 ⁻⁷
Pre-FEV ₁ /FVC	10	10:69699710	69699710	A	G	0.051	-4.1297	0.800	2.41 x 10 ⁻⁷
Pre-FEV ₁ /FVC	10	10:69701403	69701403	T	C	0.051	-4.1297	0.800	2.41 x 10 ⁻⁷
Pre-FEV ₁ /FVC	10	10:69702559	69702559	T	C	0.051	-4.1303	0.800	2.40 x 10 ⁻⁷
Pre-FEV ₁ /FVC	11	11:23684142	23684142	G	C	0.011	-8.5207	1.76	1.30 x 10 ⁻⁶
Pre-FEV ₁ /FVC	11	11:116627541	116627541	T	C	0.013	-8.3846	1.67	5.49 x 10 ⁻⁷
Pre-FEV ₁ /FVC	13	13:26171336	26171336	C	T	0.012	-8.8936	1.82	1.09 x 10 ⁻⁶
Pre-FEV ₁ /FVC	13	13:26172491	26172491	G	A	0.012	-8.8941	1.82	1.09 x 10 ⁻⁶
Pre-FEV ₁ /FVC	13	13:26173637	26173637	C	G	0.012	-8.8936	1.82	1.09 x 10 ⁻⁶
Pre-FEV ₁ /FVC	13	13:26178584	26178584	G	T	0.012	-9.2967	1.82	3.35 x 10 ⁻⁷
Pre-FEV ₁ /FVC	13	13:26179307	26179307	A	G	0.012	-9.4254	1.86	3.97 x 10 ⁻⁷
Pre-FEV ₁ /FVC	13	13:26179851	26179851	G	A	0.012	-9.4264	1.86	3.97 x 10 ⁻⁷
Pre-FEV ₁ /FVC	13	13:26180215	26180215	C	G	0.012	-9.4264	1.86	3.97 x 10 ⁻⁷
Pre-FEV ₁ /FVC	13	13:26180560	26180560	T	C	0.012	-9.4272	1.86	3.96 x 10 ⁻⁷
Pre-FEV ₁ /FVC	13	13:26180708	26180708	C	A	0.012	-9.4264	1.86	3.97 x 10 ⁻⁷
Pre-FEV ₁ /FVC	13	13:26180788	26180788	C	T	0.012	-9.4264	1.86	3.97 x 10 ⁻⁷
Pre-FEV ₁ /FVC	13	13:26181052	26181052	A	T	0.012	-9.4264	1.86	3.97 x 10 ⁻⁷
Pre-FEV ₁ /FVC	13	13:26181377	26181377	T	A	0.012	-9.4264	1.86	3.97 x 10 ⁻⁷
Pre-FEV ₁ /FVC	13	13:26181548	26181548	T	C	0.012	-9.4264	1.86	3.97 x 10 ⁻⁷
Pre-FEV ₁ /FVC	13	13:26181808	26181808	T	C	0.012	-9.4264	1.86	3.97 x 10 ⁻⁷
Pre-FEV ₁ /FVC	13	13:26182111	26182111	G	A	0.012	-9.4264	1.86	3.97 x 10 ⁻⁷
Pre-FEV ₁ /FVC	13	13:26186904	26186904	C	T	0.012	-9.4272	1.86	3.96 x 10 ⁻⁷
Pre-FEV ₁ /FVC	13	13:26187050	26187050	T	C	0.012	-9.4264	1.86	3.97 x 10 ⁻⁷
Pre-FEV ₁ /FVC	13	13:26187226	26187226	G	A	0.012	-9.4272	1.86	3.96 x 10 ⁻⁷
Pre-FEV ₁ /FVC	13	13:26187654	26187654	G	A	0.012	-9.4264	1.86	3.97 x 10 ⁻⁷
Pre-FEV ₁ /FVC	13	13:26190577	26190577	T	C	0.011	-10.0394	1.90	1.23 x 10 ⁻⁷
Pre-FEV ₁ /FVC	13	13:26191329	26191329	T	C	0.012	-9.4272	1.86	3.96 x 10 ⁻⁷
Pre-FEV ₁ /FVC	13	13:26191597	26191597	G	T	0.012	-9.4272	1.86	3.96 x 10 ⁻⁷
Pre-FEV ₁ /FVC	13	13:26198053	26198053	T	G	0.011	-9.7840	1.90	2.52 x 10 ⁻⁷
Pre-FEV ₁ /FVC	13	13:26201829	26201829	G	C	0.011	-9.7840	1.90	2.52 x 10 ⁻⁷
Pre-FEV ₁ /FVC	13	13:26235394	26235394	G	A	0.010	-10.5334	1.94	5.80 x 10 ⁻⁸
Pre-FEV ₁ /FVC	13	13:26247080	26247080	G	A	0.010	-10.5334	1.94	5.80 x 10 ⁻⁸
Pre-FEV ₁ /FVC	13	13:26262378	26262378	T	G	0.011	-10.5325	1.94	5.81 x 10 ⁻⁸
Pre-FEV ₁ /FVC	13	13:26268604	26268604	A	C	0.011	-10.5325	1.94	5.81 x 10 ⁻⁸
Pre-FEV ₁ /FVC	13	13:26280122	26280122	A	G	0.011	-9.5140	1.90	5.52 x 10 ⁻⁷
Pre-FEV ₁ /FVC	14	14:94463882	94463882	C	T	0.028	-5.9224	1.23	1.35 x 10 ⁻⁶
Pre-FEV ₁ /FVC	14	14:94467860	94467860	T	C	0.028	-5.9224	1.23	1.35 x 10 ⁻⁶
Pre-FEV ₁ /FVC	14	14:94472407	94472407	G	A	0.036	-5.5247	1.13	9.25 x 10 ⁻⁷
Pre-FEV ₁ /FVC	14	14:94472871	94472871	G	T	0.036	-5.4523	1.12	1.10 x 10 ⁻⁶
Pre-FEV ₁ /FVC	14	14:94479922	94479922	A	G	0.033	-5.8213	1.15	3.74 x 10 ⁻⁷

Pre-FEV ₁ /FVC	15	15:78801396	78801396	C	A	0.139	-2.6943	0.560	1.53 x 10 ⁻⁶
Pre-FEV ₁ /FVC	15	15:78805789	78805789	C	G	0.140	-2.7840	0.559	6.37 x 10 ⁻⁷
Pre-FEV ₁ /FVC	15	15:78807732	78807732	A	C	0.140	-2.7840	0.559	6.37 x 10 ⁻⁷
Pre-FEV ₁ /FVC	15	15:78811677	78811677	C	T	0.140	-2.7233	0.560	1.14 x 10 ⁻⁶
Pre-FEV ₁ /FVC	15	15:78821368	78821368	A	C	0.139	-2.6730	0.561	1.90 x 10 ⁻⁶
Pre-FEV ₁ /FVC	15	15:93817218	93817218	A	G	0.034	-5.0102	1.01	7.11 x 10 ⁻⁷
Pre-FEV ₁ /FVC	15	15:93818088	93818088	G	C	0.035	-5.0107	1.01	7.10 x 10 ⁻⁷
Pre-FEV ₁ /FVC	16	16:19508306	19508306	A	G	0.062	-3.8078	0.786	1.25 x 10 ⁻⁶
Pre-FEV ₁ /FVC	16	16:19597633	19597633	C	G	0.043	-4.5022	0.945	1.88 x 10 ⁻⁶
Pre-FEV ₁ /FVC	18	18:55422267	55422267	A	G	0.013	-7.9629	1.67	1.80 x 10 ⁻⁶

108 Supplementary Table 5: Suggestive associations with Pre-FEV₁/FVC.

Phenotype	Chr	SNP	Position (bp)	A1	A2	MAF	β	Std Err	P-value
Post-FEV ₁	5	5:16893255	16893255	A	G	0.034	-9.3027	1.81	2.59×10^{-7}
Post-FEV ₁	8	8:24930702	24930702	A	C	0.017	11.1005	2.33	1.91×10^{-6}
Post-FEV ₁	8	8:24938579	24938579	C	G	0.017	11.1005	2.33	1.91×10^{-6}
Post-FEV ₁	8	8:25008509	25008509	G	C	0.017	11.1653	2.29	1.12×10^{-6}
Post-FEV ₁	8	8:25026871	25026871	A	G	0.016	11.5466	2.37	1.11×10^{-6}
Post-FEV ₁	9	9:86916173	86916173	A	G	0.130	-4.5789	0.884	2.23×10^{-7}
Post-FEV ₁	10	10:85216527	85216527	C	T	0.053	6.4536	1.35	1.69×10^{-6}
Post-FEV ₁	12	12:107647422	107647422	G	A	0.104	-5.0244	1.03	1.01×10^{-6}
Post-FEV ₁	12	12:107647912	107647912	G	A	0.104	-5.0244	1.03	1.01×10^{-6}
Post-FEV ₁	12	12:107658715	107658715	G	A	0.104	-4.9197	1.02	1.30×10^{-6}
Post-FEV ₁	12	12:107662094	107662094	T	C	0.103	-5.3677	1.02	1.45×10^{-7}
Post-FEV ₁	18	18:9406106	9406106	A	G	0.029	-8.2028	1.72	1.80×10^{-6}
Post-FEV ₁	18	18:9407212	9407212	A	G	0.029	-8.2021	1.72	1.80×10^{-6}
Post-FEV ₁	18	18:9409089	9409089	C	A	0.029	-8.2880	1.73	1.73×10^{-6}
Post-FEV ₁	19	19:45782594	45782594	G	A	0.073	-5.3018	1.09	1.22×10^{-6}
Post-FEV ₁	22	22:45424732	45424732	T	C	0.024	9.6769	1.85	1.75×10^{-7}
Post-FEV ₁	22	22:45426957	45426957	A	G	0.023	9.2725	1.89	9.40×10^{-7}

Supplementary Table 6: Suggestive associations with Post-FEV₁.

Phenotype	Chr	SNP	Position (bp)	A1	A2	MAF	β	Std Err	P-value
Post-FVC	1	1:195763875	195763875	C	T	0.255	-3.3983	0.700	1.21×10^{-6}
Post-FVC	1	1:195771663	195771663	T	C	0.259	-3.4962	0.698	5.52×10^{-7}
Post-FVC	1	1:195771841	195771841	G	A	0.259	-3.4962	0.698	5.52×10^{-7}
Post-FVC	1	1:195778940	195778940	A	T	0.246	-3.6116	0.720	5.29×10^{-7}
Post-FVC	2	2:115966363	115966363	C	T	0.072	6.0241	1.26	1.61×10^{-6}
Post-FVC	2	2:115978242	115978242	C	T	0.071	6.1979	1.27	9.64×10^{-7}
Post-FVC	2	2:115982589	115982589	C	T	0.074	6.0001	1.24	1.37×10^{-6}
Post-FVC	6	6:162713288	162713288	A	G	0.014	14.0917	2.68	1.45×10^{-7}
Post-FVC	8	8:83741379	83741379	A	C	0.094	-5.0755	1.07	1.89×10^{-6}
Post-FVC	8	8:119895298	119895298	C	A	0.021	11.6893	2.31	4.31×10^{-7}
Post-FVC	11	11:118902275	118902275	C	T	0.010	17.9775	3.29	4.83×10^{-8}
Post-FVC	11	11:118905095	118905095	A	G	0.010	17.9775	3.29	4.83×10^{-8}
Post-FVC	11	11:118905316	118905316	T	C	0.010	17.9775	3.29	4.83×10^{-8}
Post-FVC	11	11:118906065	118906065	A	G	0.010	17.9775	3.29	4.83×10^{-8}
Post-FVC	11	11:118906240	118906240	T	C	0.010	17.9775	3.29	4.83×10^{-8}
Post-FVC	11	11:118906745	118906745	C	G	0.010	17.9775	3.29	4.83×10^{-8}
Post-FVC	11	11:118907923	118907923	G	T	0.010	18.2978	3.41	7.85×10^{-8}
Post-FVC	11	11:118932913	118932913	C	T	0.010	18.9094	3.29	9.47×10^{-9}
Post-FVC	12	12:107662094	107662094	T	C	0.103	-5.1924	1.05	6.91×10^{-7}
Post-FVC	12	12:115797499	115797499	G	A	0.060	6.6259	1.33	6.34×10^{-7}
Post-FVC	17	17:74377172	74377172	T	C	0.110	4.8181	0.955	4.54×10^{-7}
Post-FVC	18	18:67404762	67404762	A	C	0.010	16.4840	3.40	1.28×10^{-6}
Post-FVC	18	18:67404973	67404973	A	G	0.010	16.4840	3.40	1.28×10^{-6}
Post-FVC	18	18:67404990	67404990	T	G	0.010	16.4840	3.40	1.28×10^{-6}
Post-FVC	19	19:4289259	4289259	T	C	0.106	5.1672	0.967	9.21×10^{-8}
Post-FVC	19	19:4291817	4291817	T	C	0.111	5.2674	0.963	4.52×10^{-8}
Post-FVC	19	19:4294011	4294011	C	A	0.140	4.3027	0.885	1.15×10^{-6}
Post-FVC	19	19:4294410	4294410	C	T	0.157	4.0184	0.829	1.25×10^{-6}
Post-FVC	19	19:4298416	4298416	A	G	0.153	4.1478	0.847	9.85×10^{-7}
Post-FVC	19	19:4302569	4302569	G	A	0.156	4.0985	0.840	1.05×10^{-6}
Post-FVC	19	19:36372775	36372775	T	C	0.129	-4.2774	0.889	1.49×10^{-6}
Post-FVC	19	19:36374386	36374386	G	T	0.272	-3.3295	0.698	1.87×10^{-6}
Post-FVC	19	19:36376980	36376980	A	G	0.129	-4.2471	0.890	1.82×10^{-6}
Post-FVC	21	21:18234328	18234328	T	C	0.012	12.7085	2.62	1.19×10^{-6}
Post-FVC	21	21:18234404	18234404	A	G	0.012	12.7085	2.62	1.19×10^{-6}
Post-FVC	21	21:43755177	43755177	G	A	0.091	5.5767	1.15	1.25×10^{-6}

111 Supplementary Table 7: Suggestive associations with Post-FVC.

Phenotype	Chr	SNP	Position (bp)	A1	A2	MAF	β	Std Err	P-value
Post-FEV ₁ /FVC	1	1:117580100	117580100	G	A	0.015	-7.0892	1.45	1.01 x 10 ⁻⁶
Post-FEV ₁ /FVC	1	1:117580363	117580363	C	T	0.015	-7.0892	1.45	1.01 x 10 ⁻⁶
Post-FEV ₁ /FVC	1	1:180886944	180886944	C	T	0.015	-7.0382	1.35	1.76 x 10 ⁻⁷
Post-FEV ₁ /FVC	1	1:180959189	180959189	G	A	0.010	-7.7534	1.58	9.13 x 10 ⁻⁷
Post-FEV ₁ /FVC	1	1:180970045	180970045	C	T	0.010	-7.7534	1.58	9.13 x 10 ⁻⁷
Post-FEV ₁ /FVC	1	1:185527158	185527158	G	C	0.013	-9.4499	1.86	3.80 x 10 ⁻⁷
Post-FEV ₁ /FVC	2	2:26387193	26387193	G	C	0.125	-2.4299	0.510	1.90 x 10 ⁻⁶
Post-FEV ₁ /FVC	2	2:26390965	26390965	A	G	0.131	-2.4049	0.504	1.79 x 10 ⁻⁶
Post-FEV ₁ /FVC	2	2:26392354	26392354	A	C	0.131	-2.4220	0.504	1.56 x 10 ⁻⁶
Post-FEV ₁ /FVC	2	2:171008016	171008016	G	A	0.014	-6.9043	1.37	4.70 x 10 ⁻⁷
Post-FEV ₁ /FVC	3	3:22321021	22321021	A	G	0.013	-7.8568	1.52	2.17 x 10 ⁻⁷
Post-FEV ₁ /FVC	3	3:49908748	49908748	A	G	0.012	-8.5469	1.70	5.07 x 10 ⁻⁷
Post-FEV ₁ /FVC	3	3:49908976	49908976	C	T	0.012	-8.5469	1.70	5.07 x 10 ⁻⁷
Post-FEV ₁ /FVC	3	3:49945028	49945028	G	A	0.010	-9.0560	1.86	1.11 x 10 ⁻⁶
Post-FEV ₁ /FVC	4	4:55555416	55555416	G	A	0.031	-4.4167	0.923	1.69 x 10 ⁻⁶
Post-FEV ₁ /FVC	4	4:55568875	55568875	A	G	0.030	-4.4141	0.922	1.70 x 10 ⁻⁶
Post-FEV ₁ /FVC	4	4:70284767	70284767	A	T	0.010	-9.5784	1.87	2.89 x 10 ⁻⁷
Post-FEV ₁ /FVC	4	4:70338226	70338226	A	G	0.012	-8.7913	1.71	2.53 x 10 ⁻⁷
Post-FEV ₁ /FVC	5	5:89139642	89139642	G	A	0.011	-8.3271	1.65	4.85 x 10 ⁻⁷
Post-FEV ₁ /FVC	5	5:89174965	89174965	T	C	0.011	-8.3271	1.65	4.85 x 10 ⁻⁷
Post-FEV ₁ /FVC	5	5:89201706	89201706	T	C	0.011	-8.3265	1.65	4.86 x 10 ⁻⁷
Post-FEV ₁ /FVC	8	8:4110597	4110597	A	G	0.066	-3.3772	0.704	1.60 x 10 ⁻⁶
Post-FEV ₁ /FVC	10	10:69583770	69583770	T	C	0.030	-4.7114	0.982	1.59 x 10 ⁻⁶
Post-FEV ₁ /FVC	11	11:35570480	35570480	A	G	0.016	-6.1461	1.27	1.20 x 10 ⁻⁶
Post-FEV ₁ /FVC	11	11:35573791	35573791	T	A	0.017	-6.1468	1.27	1.20 x 10 ⁻⁶
Post-FEV ₁ /FVC	11	11:35577589	35577589	A	G	0.016	-6.2517	1.30	1.66 x 10 ⁻⁶
Post-FEV ₁ /FVC	12	12:4773488	4773488	C	A	0.015	-7.0233	1.35	1.91 x 10 ⁻⁷
Post-FEV ₁ /FVC	12	12:4773489	4773489	C	G	0.015	-7.0233	1.35	1.91 x 10 ⁻⁷
Post-FEV ₁ /FVC	12	12:4777393	4777393	A	G	0.015	-7.0361	1.40	4.98 x 10 ⁻⁷
Post-FEV ₁ /FVC	12	12:4784518	4784518	T	C	0.018	-6.3324	1.27	6.11 x 10 ⁻⁷
Post-FEV ₁ /FVC	12	12:4784582	4784582	T	G	0.018	-6.3324	1.27	6.11 x 10 ⁻⁷
Post-FEV ₁ /FVC	12	12:4786418	4786418	A	G	0.018	-6.1523	1.25	8.81 x 10 ⁻⁷
Post-FEV ₁ /FVC	12	12:4787767	4787767	G	A	0.018	-6.1514	1.25	8.83 x 10 ⁻⁷
Post-FEV ₁ /FVC	12	12:4788226	4788226	A	G	0.018	-6.1531	1.25	8.80 x 10 ⁻⁷
Post-FEV ₁ /FVC	12	12:4793670	4793670	A	G	0.020	-5.7624	1.20	1.63 x 10 ⁻⁶
Post-FEV ₁ /FVC	14	14:38963901	38963901	C	T	0.084	-3.3320	0.673	7.50 x 10 ⁻⁷
Post-FEV ₁ /FVC	15	15:76052762	76052762	T	G	0.344	-1.8331	0.372	8.07 x 10 ⁻⁷
Post-FEV ₁ /FVC	15	15:76057486	76057486	A	G	0.336	-1.8270	0.373	9.50 x 10 ⁻⁷
Post-FEV ₁ /FVC	15	15:76057493	76057493	T	C	0.355	-1.8888	0.368	2.96 x 10 ⁻⁷
Post-FEV ₁ /FVC	15	15:85798401	85798401	A	G	0.018	-6.7846	1.27	9.05 x 10 ⁻⁸
Post-FEV ₁ /FVC	15	15:85819723	85819723	C	T	0.020	-5.8136	1.21	1.68 x 10 ⁻⁶
Post-FEV ₁ /FVC	15	15:85885031	85885031	A	C	0.034	-4.9213	0.955	2.55 x 10 ⁻⁷
Post-FEV ₁ /FVC	15	15:88957199	88957199	G	T	0.089	-2.8154	0.591	1.93 x 10 ⁻⁶

Post-FEV ₁ /FVC	15	15:93817218	93817218	A	G	0.034	-5.0171	0.968	2.19 x 10 ⁻⁷
Post-FEV ₁ /FVC	15	15:93818088	93818088	G	C	0.035	-5.0166	0.968	2.20 x 10 ⁻⁷
Post-FEV ₁ /FVC	17	17:57263393	57263393	A	G	0.346	-1.8380	0.380	1.30 x 10 ⁻⁶
Post-FEV ₁ /FVC	17	17:57273681	57273681	C	T	0.345	-1.8303	0.379	1.35 x 10 ⁻⁶
Post-FEV ₁ /FVC	17	17:57274481	57274481	C	T	0.345	-1.8303	0.379	1.35 x 10 ⁻⁶
Post-FEV ₁ /FVC	17	17:57276710	57276710	A	G	0.345	-1.8301	0.379	1.35 x 10 ⁻⁶
Post-FEV ₁ /FVC	17	17:78917207	78917207	T	G	0.015	-7.8302	1.58	7.44 x 10 ⁻⁷

12 Supplementary Table 8: Suggestive associations with Post-FEV₁/FVC.

Supplementary Figure 6: The region encompassing four variants on chromosome 13 significantly associated with Pre-FEV₁/FVC.

Supplementary Figure 7: The region encompassing two variants on chromosome 16 significantly associated with Pre-FVC.

Supplementary Figure 8: The region encompassing a variant on chromosome 20 significantly associated with Pre-FVC.

Supplementary Figure 9: The region encompassing two variants on chromosome 19 significantly associated with Post-FVC.

21

22 Supplementary Figure 10: The region encompassing eight variants on chromosome 11 significantly associated with Post-FVC.

23

24 Supplementary Figure 11: The region surrounding a single variant on chromosome 15 significantly associated with Post-FEV₁/FVC.

Supplementary Figure 12: The region around four variants suggestively associated with Post-FEV₁.

Supplementary Figure 13: The region around a variant on chromosome 12 suggestively associated with Pre-FEV₁.

Supplementary Figure 14: The region around a variant on chromosome 20 suggestively associated with Pre-FEV₁.

Supplementary Figure 15: The region on chromosome 21 identified by admixture mapping as significantly associated with Pre-FEV₁.

133

134 Supplementary Figure 16: Tissue-specific gene expression for *ADAMTS1* (top) and *ADAMTS5* (bottom) from GTEx v8. Both genes are
 135 expressed in certain tissues, such as ovary and vagina. However, *ADAMTS1* shows markedly higher expression in lung and arterial
 136 tissue, while *ADAMTS5* is more strongly expressed in breast, fibroblast, cervix, adipose, and whole blood.

137

138 Supplementary Figure 17: The region on chromosome 4 identified by admixture mapping as significantly associated with Pre-FVC.

139

140 Supplementary Figure 18: The region on chromosome 19 identified by admixture mapping as significantly associated with Pre-

141 FEV₁/FVC.

142

143 Supplementary Figure 19: The region on chromosome 8 identified by admixture mapping as significantly associated with Post-FVC.

144

145 Supplementary Figure 20: The region on chromosome 14 identified by admixture mapping as significantly associated with Post-FVC.

chr21:28209667 G/A

146

147 Supplementary Figure 21: Distribution of minor allele frequencies for SNP rs13615 in 1000 Genomes populations (hg19 build). The
148 derived allele G shows strong separation by distance, with high prevalence in East Asia, moderately high prevalence in the Americas,
149 and low prevalence in Europeans and South Asians. However, in Africans and African-derived populations from 1000 Genomes, the
150 G allele occurs at very low frequency, if at all.

51

52 Supplementary Figure 22: A CANVIS plot of results from PAINTOR fine-mapping for locus 3, an association on chromosome 19 with
53 Pre-FEV₁/FVC. The SNP with highest posterior probability of causality (0.168) is rs72986681.

154

155 Supplementary Figure 23: A CANVIS plot of results from PAINTOR fine-mapping for locus 4, an association on chromosome 8 with
156 Post-FVC. The SNP with highest posterior probability of causality (0.109) is rs2470740.

157

158 Supplementary Figure 24: Expression profile for the gene *EGLN3* across tissue types from GTEx v8. *EGLN3* is most strongly expressed
159 in skin and bladder, but also shows nontrivial expression in heart and arterial tissue.

160

161 Supplementary Figure 25: Genetic correlations between lung, heart, blood, and obesity traits, computed from the UK Biobank.