

1 **New genetic signals for lung function highlight pathways and pleiotropy, and chronic obstructive**
2 **pulmonary disease associations across multiple ancestries.**

3 **Authors:**

4 Nick Shrine*¹; Anna L Guyatt*¹; A Mesut Erzurumluoglu*¹; Victoria E Jackson^{1,2,3}; Brian D Hobbs^{4,5};
5 Carl Melbourne¹; Chiara Batini¹; Katherine A Fawcett¹; Kijoung Song⁶; Phuwanat Sakornsakolpat^{4,7};
6 Xingnan Li⁸; Ruth Boxall^{9,10}; Nicola F Reeve¹; Ma'en Obeidat¹¹; Jing Hua Zhao¹²; Matthias Wielscher¹³;
7 Understanding Society Scientific Group¹⁴; Stefan Weiss¹⁵; Katherine A Kentistou^{16,17}; James P Cook¹⁸;
8 Benjamin B Sun¹⁹; Jian Zhou²⁰; Jennie Hui^{21,22,23,24}; Stefan Karrasch^{25,26,27}; Medea Imboden^{28,29}; Sarah E
9 Harris^{30,61}; Jonathan Marten³²; Stefan Enroth³³; Shona M Kerr³²; Ida Surakka^{34,35}; Veronique Vitart³²;
10 Terho Lehtimäki³⁶; Richard J Allen¹; Per S Bakke³⁷; Terri H Beaty³⁸; Eugene R Bleecker⁸; Yohan
11 Bossé^{39,40}; Corry-Anke Brandsma⁴¹; Zhengming Chen⁹; James D Crapo^{42,43}; John Danesh^{19,44,45,46}; Dawn
12 L DeMeo⁴; Frank Dudbridge¹; Ralf Ewert⁴⁷; Christian Gieger⁴⁸; Amund Gulsvik³⁷; Anna L Hansell^{49,50};
13 Ke Hao⁵¹; Josh D Hoffman⁶; John Hokanson⁵²; Georg Homuth¹⁵; Peter K Joshi¹⁶; Philippe Joubert^{40,53};
14 Claudia Langenberg¹²; Xuan Li¹¹; Liming Li⁵⁴; Kuang Lin⁹; Lars Lind⁵⁵; Nick Locantore⁵⁶; Jian'an Luan¹²;
15 Anubha Mahajan⁵⁷; Joseph C Maranville⁵⁸; Alison Murray⁵⁹; David C Nickle⁶⁰; Richard Packer¹;
16 Margaret M Parker⁴; Megan L Paynton¹; David Porteous^{61,30}; Dmitry Prokopenko⁴; Dandi Qiao⁴;
17 Rajesh Rawal⁴⁸; Heiko Runz⁵⁸; Ian Sayers⁶³; Don D Sin^{11,64}; Blair H Smith⁶⁵; María Soler Artigas^{66,67,68};
18 David Sparrow^{69,70}; Ruth Tal-Singer⁵⁶; Paul RHJ Timmers¹⁶; Maarten Van den Berge⁷¹; John C
19 Whittaker⁷²; Prescott Woodruff⁷³; Laura M Yerges Armstrong⁶; Olga G Troyanskaya^{74,75}; Olli T
20 Raitakari^{76,77}; Mika Kähönen⁷⁸; Ozren Polasek^{79,16}; Ulf Gyllensten³³; Igor Rudan¹⁶; Ian J Deary^{30,81};
21 Nicole M Probst-Hensch^{28,29}; Holger Schulz^{25,27}; Alan L James^{21,82,83}; James F Wilson^{16,32}; Beate
22 Stubbe⁴⁷; Eleftheria Zeggini⁸⁵; Marjo-Riitta Jarvelin^{13,86,87,88}; Nick Wareham¹²; Edwin K Silverman^{4,5};
23 Caroline Hayward³²; Andrew P Morris^{18,57}; Adam S Butterworth^{19,46}; Robert A Scott⁷²; Robin G
24 Walters⁹; Deborah A Meyers⁸; Michael H Cho^{4,5}; David P Strachan⁹¹; Ian P Hall*⁶³; Martin D
25 Tobin*^{†1,92}; Louise V Wain*^{†1,92};

26 * = Contributed equally to this work.

27 † = Corresponding Authors.

28 **Abstract**

29 Reduced lung function predicts mortality and is key to the diagnosis of COPD. In a genome-wide
30 association study in 400,102 individuals of European ancestry, we define 279 lung function signals,
31 one-half of which are new. In combination these variants strongly predict COPD in deeply-
32 phenotyped patient populations. Furthermore, the combined effect of these variants showed
33 generalisability across smokers and never-smokers, and across ancestral groups. We highlight
34 biological pathways, known and potential drug targets for COPD and, in phenome-wide association
35 studies, autoimmune-related and other pleiotropic effects of lung function associated variants. This
36 new genetic evidence has potential to improve future preventive and therapeutic strategies for
37 COPD.

38 **Introduction:**

39 Impaired lung function is predictive of mortality¹ and is the key diagnostic criterion for chronic
40 obstructive pulmonary disease (COPD). Globally, COPD accounted for 2.9 million deaths in 2016²,
41 being one of the key causes of both Years of Life Lost and Years Lived with Disability worldwide³.
42 Determinants of maximally attained lung function and of lung function decline can influence the risk

43 of developing COPD. Tobacco smoking is the single largest risk factor for COPD, although other
44 environmental exposures and genetic makeup are important^{4,5}. Genetic variants associated with
45 lung function and COPD susceptibility can be causally informative, assisting with risk prediction, as
46 well as drug target identification and validation⁶. Whilst there has been considerable progress in
47 identifying genetic markers associated with lung function and risk of COPD^{4,7-19} seeking a high yield
48 of associated genetic variants is key to progressing knowledge because: (i) implication of multiple
49 molecules in each pathway will be needed to build an accurate picture of the pathways
50 underpinning development of COPD; (ii) not all proteins identified will be druggable and; (iii)
51 combining information across multiple variants can improve prediction of disease susceptibility.

52 Through new detailed quality control and analyses of spirometric measures of lung function in UK
53 Biobank, completion of genome-wide genotyping in UK Biobank, and expansion of the SpiroMeta
54 Consortium, we undertook the largest genome-wide association study of lung function performed to
55 date. Comprising a total of 400,102 individuals of European ancestry, our study entailed a near
56 seven-fold increase in sample size over previous studies of similar ancestry to address the following
57 aims: (i) to generate a high yield of genetic markers associated with lung function; (ii) to confirm and
58 fine-map previously reported lung function signals; (iii) to investigate the putative causal genes and
59 biological pathways through which lung function associated variants act, and their wider pleiotropic
60 effects on other traits; and (iv) to generate a weighted genetic risk score for lung function and test
61 its association with COPD susceptibility in individuals of European and other ancestries.

62 **Results:**

63 **139 new signals for lung function**

64 Here we present a total of 279 distinct association signals for lung function, of which a half (139
65 variants) are new having reached genome-wide significance ($P < 5 \times 10^{-9}$) in this study. We increased
66 the sample size available for the study of quantitative measures of lung function in UK Biobank by
67 refining the quality control of spirometry based on recommendations of the UK Biobank Outcomes
68 Adjudication Working Group, utilising additional metrics derived from the blow curve time series
69 measurements, and relaxing the reproducibility threshold for repeat measures (**Supplementary**
70 **Note**). Genome-wide association analyses of forced expired volume in 1 second (FEV_1), forced vital
71 capacity (FVC) and FEV_1/FVC were then undertaken in 321,047 individuals in UK Biobank
72 (**Supplementary Table 1**) and in 79,055 individuals from the SpiroMeta Consortium (**Supplementary**
73 **Tables 2 and 3**). A linear mixed model approach implemented in BOLT-LMM²⁰ was used for UK
74 Biobank to account for relatedness and fine-scale population structure (**Online Methods**). A total of
75 19,871,028 variants imputed in both UK Biobank and SpiroMeta were analysed. Peak expiratory flow
76 (PEF) was also analysed genome-wide in UK Biobank and up to 24,218 samples from SpiroMeta. All
77 individuals included in the genome-wide analyses were of European ancestry (**Supplementary Figure**
78 **1 and Supplementary Table 2**).

79 To maximise statistical power for discovery of new signals, whilst maintaining stringent significance
80 thresholds to minimise reporting of false positives, we adopted a study design incorporating both
81 two-stage and one-stage approaches (**Figure 1**). In the two-stage analysis, 99 new distinct signals,
82 defined using conditional analyses, were associated with one or more traits at $P < 5 \times 10^{-9}$ in UK
83 Biobank and showed association ($P < 10^{-3}$) with a consistent direction of effect in SpiroMeta (“Tier 1”
84 signals, **Supplementary Figure 2; Supplementary Table 4**). In the one-stage analysis, we meta-
85 analysed UK Biobank and SpiroMeta (up to 400,102 individuals) and 40 additional new distinct

86 signals associated with one or more lung function traits reaching $P < 5 \times 10^{-9}$ were identified
87 (**Supplementary Figure 2, Supplementary Table 4**) that were also associated with $P < 10^{-3}$ separately
88 in UK Biobank and in SpiroMeta, with consistent direction of effect (“Tier 2” signals). An additional
89 323 signals were significantly associated with one or more lung function traits in the meta-analysis of
90 UK Biobank and SpiroMeta ($P < 5 \times 10^{-9}$) and reached $P < 10^{-3}$ for association in only one of UK Biobank
91 or SpiroMeta (“Tier 3” signals, **Supplementary Table 5**). Only the 139 signals meeting Tier 1 and Tier
92 2 criteria were followed up further. The strength and direction of association of the sentinel variant
93 (the variant in each signal with the lowest P value) for these 139 new signals across all 4 lung
94 function traits are shown in **Figure 2**.

95 To assess whether any of these 139 signals associated with lung function could be driven via an
96 underlying association with smoking, we examined association of the sentinel variants with smoking
97 behaviour in UK Biobank (**Online Methods**). The only new sentinel associated with smoking
98 behaviour was rs193686 (in an intron of *MET*, **Supplementary Table 6**). Therefore, we tested for
99 association between this variant and lung function in never smokers ($n=173,658$). Whilst rs193686
100 was associated with smoking initiation ($P=9.18 \times 10^{-6}$), the allele associated with smoking initiation
101 was associated with increased lung function in never smokers (FEV_1/FVC $P=5.28 \times 10^{-10}$,
102 **Supplementary Table 7**). Therefore, this signal was retained for further analysis.

103 **A total of 279 signals of association for lung function**

104 Of 157 previously published signals of association with lung function and COPD^{3,6-18}, 142 were
105 associated at $P < 10^{-5}$ in UK Biobank (**Online Methods, Supplementary Figure 3, Supplementary Table**
106 **8**). Two sentinel variants (rs1689510 near *RAB5B* and rs11134789 in an intron of *ADAM19*) were
107 associated with smoking initiation ($P=9.72 \times 10^{-6}$ and $P=2.13 \times 10^{-5}$, respectively) (**Supplementary Table**
108 **6**), but were also associated with lung function in never smokers ($P=2.49 \times 10^{-8}$ for FEV_1 and
109 $P=2.94 \times 10^{-45}$ for FEV_1/FVC , respectively, **Supplementary Table 7**). SNP rs17486278 at *CHRNA5* and
110 rs11667314 near *CYP2A6* were each associated with cigarettes per day ($P=1.35 \times 10^{-79}$ and
111 $P=6.47 \times 10^{-24}$, respectively; **Supplementary Table 6**); neither were significantly associated with lung
112 function among never smokers, hence these latter two signals were excluded from further analysis.
113 This brings the total number of distinct signals of association with lung function to 279
114 (**Supplementary Table 9**). None of these variants showed interaction with ever-smoking status
115 ($P > 1.8 \times 10^{-4}$, **Online Methods, Supplementary Table 7**). The 140 previously reported lung function
116 signals showing association in this study (UK Biobank $P < 10^{-5}$) explained 5.0%, 3.4%, 9.2% and 4.5% of
117 the estimated heritability of FEV_1 , FVC, FEV_1/FVC and PEF, respectively (**Online Methods**). The 139
118 new signals reported here, explain an additional 4.3%, 3.3%, 3.9% and 3.3% of the estimated
119 heritability, respectively.

120 **Identification of putative causal genes**

121 Bayesian refinement was undertaken for each signal to identify the set of variants that were 99%
122 likely to contain the underlying causal variant (assuming the causal variant has been analysed). The
123 signals in the HLA region were excluded due to extended linkage disequilibrium. The results from the
124 meta-analysis of UK Biobank and SpiroMeta were used to define the 99% credible sets (**Online**
125 **Methods, Supplementary Table 10, Supplementary File–Region Plots**).

126 To identify putative causal genes for each signal, we identified deleterious variants and variants
127 associated with gene expression (eQTLs) or protein levels (pQTLs) within each 99% credible set for all
128 new and previously reported signals outside the HLA region (**Online Methods**).

129 There were 25 SNPs, located in 22 unique genes, which were exonic, at a splice site or in the
130 untranslated regions and additionally annotated as potentially deleterious (**Online Methods**,
131 **Supplementary Table 11**). Amongst our new signals, there were 10 variants annotated as
132 deleterious in 9 different genes: *DOCK9* (rs117633128, MAF=10.6%), *CEP72* (rs12522955,
133 MAF=20.2%), *BCHE* (rs1799807, MAF=1.95%), *DST* (rs11756977, MAF=28.9%), *KIAA0753*
134 (rs2304977, MAF=37.7%; rs9889363, MAF=37.7%), *LRR45* (rs72861736, MAF=10.9%), *BTC*
135 (rs11938093, MAF=26.6%), *C2orf54* (rs6709469, MAF=49.9%) and *IER5L* (rs184457, MAF=31.5%).
136 Of these, the missense variant in *BCHE* (rs1799807) had the highest posterior probability (0.996) in
137 its respective credible set, was low frequency (MAF=1.95%) and resulted in an amino acid change
138 from aspartic acid (D) to glycine (G), known to affect the function of the encoded
139 butyrylcholinesterase enzyme by altering substrate binding²¹. The two common missense variants in
140 *KIAA0753* were within the credible set of new signal rs4796334. *KIAA0753*, *CEP72* and *LRR45* all
141 encode proteins with a role in ciliogenesis or cilia maintenance²²⁻²⁶, and all are highly expressed in
142 the airway epithelium²⁷.

143 Variants in the 99% credible sets (n=9,698) were queried in three eQTL resources to identify
144 associations with gene expression in lung²⁸⁻³⁰ (sample size n=1,111; **Supplementary Table 12**),
145 blood³¹ (n=4,896) and a subset of GTEx³² tissues (max n=388, **Online Methods**). The tissues included
146 from GTEx were lung and blood, plus nine tissues known to contain smooth muscle (**Online**
147 **Methods**). The latter were chosen based on previous reports of enrichment of lung function GWAS
148 signals in smooth muscle-containing tissues^{18,33}. We identified 88 genes for which the most
149 significant SNP associated with expression of that gene in the respective eQTL resource was within
150 one of the 99% credible sets. These 88 genes were implicated by 58 of the 279 signals
151 (**Supplementary Table 13**).

152 We checked credible set variants for association with protein levels in a pQTL study³⁴ comprising SNP
153 associations for 3,600 plasma proteins. Using a Bonferroni-corrected 5% significance threshold for
154 276 tests for these 3,600 proteins ($P < 5.03 \times 10^{-8}$), we found 1,076 pQTLs in our credible sets covering
155 26 lung function sentinels implicating 34 proteins. For 5 of these proteins the pQTL sentinel was
156 contained within our lung function credible set: *ECM1*, *THBS4*, *NPNT*, *C1QTNF5* and *SCARF2*
157 (**Supplementary Table 14**).

158 In total, 107 putative causal genes were identified (**Table 1**), 8 by both a deleterious variant and an
159 eQTL signal (including *KIAA0753* implicated by two deleterious variants), 1 (*NPNT*) by both an eQTL
160 and a pQTL signal, 1 (*SCARF2*) by both a deleterious variant and a pQTL signal, 13 by a deleterious
161 variant only, 81 by an eQTL signal only and 3 by a pQTL signal only. Among these 107 genes, we
162 highlight 75 for the first time as putative causal genes for lung function (43 implicated by a new
163 signal and 32 newly implicated by a previous signal¹⁸).

164 **Pathway analysis**

165 We tested whether these 107 putative causal genes were enriched in gene sets and biological
166 pathways (**Online Methods**), finding an enrichment of genes in elastic fibre and extracellular matrix
167 organisation pathways, and a number of gene ontologies including gene sets relating to the

168 cytoskeleton and processes involved in ciliogenesis (for example, cytoskeleton organisation,
169 organelle organisation, centriole replication and microtubule-based processes) (**Supplementary**
170 **Table 15**). Whilst the enrichment in elastic fibre-related pathways is consistent with our previous
171 study¹⁸, enrichment in these pathways was further supported in this analysis by two new genes,
172 *ITGAV* (at a new signal) and *GDF5* (a newly implicated gene for a previously reported signal), and by
173 strengthened eQTL evidence for *TGFB2* and *MFAP2* as the putative causal genes at two previously
174 reported signals. The presence of *TGFB2*, *GDF5* and *SMAD3* in our list of 107 genes resulted in
175 enrichment of a TGF- β superfamily signalling pathway (TGF-Core) and multiple related gene ontology
176 terms (**Supplementary Table 15**).

177 **Functional enrichment analyses**

178 We tested for enrichment of the 279 lung function signals in DNase I hypersensitivity sites in 125 cell
179 lines from ENCODE and 299 cell lines and tissues from RoadMap Epigenome Project using
180 FORGE v1.1³⁵. There was significant tissue specific overlap (**Online Methods**) of the 279 signals with
181 DNase1 hotspots in adult and foetal lung, foetal muscle (skeletal), foetal stomach, foetal heart, and
182 fibroblasts (**Supplementary Figure 4**).

183 We used DeepSEA³⁶, a variant effect predictor which utilises a deep-learning algorithm, to identify
184 whether our signals were predicted to have a chromatin effect in lung-related cell lines. We
185 identified 10 signals (including 5 new signals) for which the SNP with the largest posterior probability
186 of being causal also had a significant predicted effect on a DNase I hypersensitivity site in lung-
187 related cells (**Supplementary Table 16**). This included a new signal near *SMURF2* (17q24.1,
188 rs11653958) that also had a predicted functional effect on histone marks (DNase I hypersensitivity
189 sites, H3K9ac, H3K27ac, H3K4me1, H3K4me2, H3K4me3) and on *CEBPB*, *FOSL2*, *SIN2AK-20* and
190 *TCF12* transcription factor binding sites, and a new signal near *PDZRN3-AS1* (rs586936) had a large
191 predicted effect on a CEBPB transcription factor binding site.

192 **Drug targets**

193 All 107 putative causal genes were interrogated against the gene-drug interactions table of the Drug-
194 Gene Interactions Database (DGIDB)³⁷ (**Supplementary Table 17**). We highlight two examples of new
195 genetic signals implicating targets for drugs in development for indications other than COPD. One of
196 our new signals is an eQTL for *ITGAV*. *ITGAV* encodes a component of the $\alpha\beta6$ integrin heterodimer,
197 which is inhibited by a monoclonal antibody, STX-100, in development for pulmonary fibrosis
198 (ClinicalTrials.gov Identifier: NCT01371305) and for which the small molecule GSK3008348
199 (ClinicalTrials.gov Identifier: NCT03069989) is an antagonist³⁸. Integrins have an emerging role as
200 local activators of TGF β and specifically the $\alpha\beta6$ integrin heterodimer can activate latent-TGF β ³⁹. In
201 our study, the allele associated with reduced expression of *ITGAV* (**Supplementary Table 13**) was
202 associated with reduced risk of COPD (**Supplementary Table 9**) suggesting that inhibitors of $\alpha\beta6$
203 integrin might also have a beneficial effect in COPD. Another of our new signals is associated with
204 expression of *TNFSF13* (synonym *APRIL*), a cytokine which is a member of the TNF ligand family.
205 Atacept blocks B cell stimulation by *TNFSF13* (as well as by BlyS) and reduced systemic lupus
206 erythematosus disease activity in a recent Phase IIb trial⁴⁰. In our study, the allele associated with
207 decreased expression of *TNFSF13* was associated with reduced FEV₁, indicating that vigilance for
208 pulmonary consequences of atacept may be warranted.

209 **Genetic Risk Score: association with FEV₁/FVC and COPD in multiple ancestries**

210 We constructed a genetic risk score (GRS) weighted by FEV₁/FVC effect sizes comprising all 279 new
211 or previously reported sentinel variants, and tested the association of the GRS with FEV₁/FVC and
212 GOLD Stage 2-4 COPD (FEV₁/FVC<0.7 and FEV₁<80% predicted) in different ancestry groups in UK
213 Biobank, and China Kadoorie Biobank (**Online Methods, Supplementary Table 18**). The GRS was
214 associated with FEV₁/FVC and COPD in each of the ancestry groups (**Figure 3A**).

215 We tested for a GRS interaction with smoking in European ancestry individuals in UK Biobank⁴¹. No
216 statistical interaction was seen for FEV₁/FVC (interaction term -0.002 per SD change in GRS, 95% CI:
217 [0.009, 0.005], P=0.532), whilst the findings for COPD were consistent with a slightly smaller effect of
218 the GRS in ever-smokers (OR for ever-smoking-GRS interaction term per SD change in GRS 0.96, 95%
219 CI: [0.92, 0.99], P=0.015).

220 The association of the GRS with COPD susceptibility was additionally tested in deeply-phenotyped
221 case-control studies (**Supplementary Table 19**). Similar effect size estimates were seen across each
222 of the 5 European ancestry studies (**Figure 3B**); in the meta-analysis of these studies (n=6,979 cases
223 and 3,915 controls), the odds ratio for COPD per standard deviation of the weighted GRS was 1.55
224 (95% CI: [1.48, 1.62]), P=2.87×10⁻⁷⁵ (**Supplementary Table 20**). The GRS was also associated with
225 COPD in individuals of African-American ancestry in COPDGene (P=8.36×10⁻⁷), albeit with a smaller
226 effect size estimate, odds ratio=1.26 (95% CI: [1.15, 1.37]).

227 To aid clinical interpretation, we divided individuals in each of the European ancestry deeply-
228 phenotyped COPD case-control studies into deciles, according to their value of the weighted GRS.
229 The odds ratio for COPD in members of the highest GRS decile compared to the lowest GRS decile
230 was 4.73 (95% CI: [3.79, 5.90]), P=3.00×10⁻⁴³ (**Figure 3C, Supplementary Table 21**). We calculated the
231 population attributable risk fraction and estimated that the proportion of COPD cases attributable to
232 risk scores above the first GRS decile was 54.6% (95% CI: [50.6%, 58.4%]).

233 **Pleiotropy and phenome-wide association studies**

234 As phenome-wide association studies (PheWAS) can provide evidence mimicking pharmacological
235 interventions of drug targets in humans and informing drug development⁴², we undertook a PheWAS
236 of 2,411 phenotypes in UK Biobank (**Online Methods, Figure 4**); 226 of the 279 sentinel variants
237 were associated (FDR <1%) with one or more traits and diseases (excluding quantitative lung
238 function traits). Eighty-five of the lung function signals were associated with standing height. In
239 order to investigate whether the genetic association signals for lung function were driven by
240 incomplete adjustment for height, we tested for correlation of effects on lung function in UK
241 Biobank and height in the GIANT consortium for 247 of the 279 signals that had a proxy variant in
242 GIANT⁴³; there was no significant correlation (r=-0.096, **Supplementary Figure 5**). Additionally, the
243 PheWAS revealed associations with body composition measures such as fat free mass (54 SNPs) and
244 hip circumference (40 SNPs), as well as muscle strength (32 SNPs, grip strength). One hundred and
245 fourteen of the 279 SNPs were associated with several quantitative measures of blood count,
246 including eosinophil counts and percentages (25 SNPs). Twenty-five of our SNPs were also associated
247 with asthma including 12 SNPs associated both with asthma and eosinophil measures. Five of these
248 SNPs were in LD (r²>0.1) with a SNP reported for association both with asthma and eosinophil
249 measures in previously published genome-wide association studies. To assess whether any of the
250 lung function associations could be driven by an association with asthma, we compared the effect

251 size estimated before and after exclusion of all self-reported asthma cases, observing remarkably
252 similar estimates (**Supplementary Figure 6**) suggesting that the lung function associations we report
253 are not primarily driven via known asthma signals.

254 We examined the specificity of genetic associations, given the potential for this to predict specificity
255 of drug target modification, and found that 53 of the 279 signals were associated only with lung
256 function and COPD-related traits. In contrast, three of our 279 signals were associated with over 100
257 traits across multiple categories – among these rs3844313, a known intergenic signal near *HLA-DQB1*
258 was associated with 163 traits, and also had the strongest signal in the PheWAS, which was for
259 association with intestinal malabsorption and coeliac disease.

260

261 In our 279-variant weighted GRS PheWAS analysis (**Supplementary Table 22**), we found association
262 with respiratory traits including COPD, chronic bronchitis, emphysema, respiratory failure,
263 corticosteroid use and both paediatric and adult-onset asthma (**Figure 5a**). The GRS was also
264 associated with non-respiratory traits including coeliac disease, an intestinal autoimmune disorder
265 (**Figure 5b**). These pleiotropic effects on risk of autoimmune diseases was further confirmed by
266 analysis of previously reported GWAS (**Online Methods, Supplementary Table 23**) which showed
267 overlapping single variant associations with Crohn's disease, ulcerative colitis, psoriasis, systemic
268 lupus erythematosus, IgA nephropathy, pediatric autoimmune disease and type 1 diabetes.

269 **Discussion:**

270 The large sample size of our study, achieved by our refinement of the spirometry in UK Biobank and
271 inclusion of the substantially expanded SpiroMeta consortium data set, has doubled the yield of lung
272 function signals to 279. Fine-mapping of all new and previously reported signals, together with gene
273 and protein expression analyses with improved tissue specificity and stringency, has implicated new
274 genes and pathways, highlighting the importance of cilia development, TGF β -signalling via SMAD3,
275 and elastic fibres in the aetiology of airflow obstruction. Many of the genes and pathways reported
276 here contain druggable targets; we highlight examples where the genetic variants mimicking
277 therapeutic modulation of targets may have opposing effects on lung function. We have developed
278 and applied the first weighted GRS for lung function and tested it in deeply-phenotyped COPD case-
279 control studies. Our GRS shows stronger association and larger effect size estimates (4.73 fold
280 change in COPD risk between highest and lowest risk deciles) than a previous GRS in European
281 ancestry populations¹⁸, as well as generalisability to African, South Asian and Chinese ancestry
282 groups. We undertook the first comprehensive PheWAS for lung function signals, and report genetic
283 variants with apparent specificity of effects and others with pleiotropic effects that might indicate
284 shared biological pathways between different diseases.

285 For the first time in a GWAS of lung function, we report an enrichment of genes involved in
286 ciliogenesis (including *KIAA0753*, *CDK2* and *CEP72*). Defects in primary cilia as a result of highly
287 deleterious mutations in essential genes result in ciliopathies known to affect multiple organ
288 systems. We found an enrichment of genes with a role in centriolar replication and duplication, core
289 processes in primary and motile cilia formation. Mutations in *KIAA0753* cause the ciliopathies
290 Joubert Syndrome and Orofaciodigital Syndrome²³. Reduced airway motile cilia function impacting
291 mucus clearance is a feature of COPD, but it has not been clear whether this is causal or the
292 consequence of damage by external factors such as smoking or infection. Our findings suggest that
293 impaired ciliary function might be a driver of the disease process. We have previously shown,

294 through whole exome re-sequencing, an enrichment of rare variants in cilia-related genes in heavy
295 smokers without airflow obstruction⁴⁴.

296 New signals, implicating *ITGAV* and *GDF5*, as well as stronger support for *TGFB2* and *MFAP2* as likely
297 causal genes, provide new genetic support for the importance of elastic fibre pathways in lung
298 function and COPD¹⁸. The elastic fibres of the extracellular matrix are known to be disrupted in
299 COPD⁴⁵. As the breakdown of elastic fibres by neutrophil elastase leads to emphysema in individuals
300 with alpha₁-antitrypsin deficiency, we also assessed the association with the *SERPINA1* Z allele,
301 which was not associated with lung function in our study (rs28929474, P=0.109 for FEV₁/FVC in UK
302 Biobank).

303 Smoking and genetic risk both have important effects on lung function and COPD. We found no
304 interaction of smoking with individual lung function associated variants. Our weighted 279-SNP GRS
305 showed no interaction with smoking status for FEV₁/FVC, whilst a weak smoking-GRS interaction was
306 observed for COPD susceptibility. Thus our findings are consistent with the effects of smoking and
307 genetic risk being approximately additive on lung function (and multiplicative on COPD risk). Whilst
308 the weighted 279-SNP GRS showed a strong association with COPD susceptibility, and a high
309 attributable risk, we do not claim that this would represent an appropriate method of screening for
310 COPD risk. Incorporation of the GRS into a risk model already comprising available clinical
311 information (including age, sex, height and pack-years of smoking in COPD Gene non-Hispanic
312 Whites) leads to an increase in the area under the curve from 0.751 to 0.771, which although
313 statistically significant ($p=3.33 \times 10^{-10}$) is of modest magnitude. Importantly, our findings demonstrate
314 the high absolute risk among genetically susceptible smokers. Based on our estimated GRS relative
315 risk and absolute risk estimates of COPD shown by Lokke *et al.*⁴⁶, one would expect the highest GRS
316 risk decile group of smokers to have an absolute risk of developing COPD by approximately 70 years
317 of age of 82.4%, versus 17.4% for the lowest GRS decile.

318 The unprecedented sample size of UK Biobank as a single cohort has revolutionised genetic studies.
319 We used two complementary study designs to maximise sample size for discovery and ensure
320 robustness of findings by requiring independent support for association. Furthermore, through
321 additional analysis of the spirometry data in UK Biobank and substantial expansion of the SpiroMeta
322 consortium, we have markedly increased samples sizes to almost seven times those included in
323 previous studies. As no lower MAF threshold was applied in our analyses, an overall threshold of
324 $P < 5 \times 10^{-9}$, as recommended for re-sequencing analyses of European ancestry individuals⁴⁷, was
325 applied. We identified the largest number of new signals in our more stringent two-stage design
326 ("Tier 1", 99 new signals). Amongst the signals that we report as "Tier 3" (and did not include in
327 further analyses), all reached $P < 10^{-3}$ in UK Biobank and 183 met a less stringent threshold of $P < 0.05$
328 in SpiroMeta.

329 Our study is the first to investigate genome-wide associations with PEF. PEF is determined by various
330 physiological factors including lung volume, large airway calibre, elasticity of the lung and expiratory
331 muscle strength, is used for monitoring asthma, and was incorporated in a recently evaluated clinical
332 score for diagnosing COPD and predicting acute exacerbations of COPD⁴⁸. Overall, 133 of the 279
333 signals were also associated with PEF ($P < 10^{-5}$) and for 15 signals (including 4 new signals), PEF was
334 the most significantly associated trait. Of note, a signal near *SLC26A9*, a known cystic fibrosis
335 modifier gene⁴⁹, was highly significantly associated with PEF in UK Biobank ($P=3.97 \times 10^{-66}$) and was
336 nominally significant in SpiroMeta ($P=6.93 \times 10^{-3}$), with consistent direction of effect, but did not meet

337 the Tier 2 criteria ($P < 10^{-3}$ in each of SpiroMeta and UK Biobank). This could reflect the limited power
338 for PEF in SpiroMeta (up to 24,218 for PEF compared to 79,055 for the other three traits).

339 Examining associations of a given genetic variant with a wide range of human phenotypes is a
340 valuable tool in therapeutic target validation. As in our PheWAS, it can highlight variants which show
341 associations with one or more respiratory traits that might be expected to demonstrate greater
342 target specificity than variants associated with many traits. Additionally, in some instances,
343 association with multiple traits may indicate the relevance of drug repurposing. Association of a
344 given SNP with multiple traits does not necessarily imply shared aetiology, and further investigation
345 is warranted. Our GRS PheWAS assesses broader genetic overlap between lung function and other
346 traits and supports the evidence for some shared genetic determinants with autoimmune diseases.

347 In summary, our study has doubled the number of signals for lung function and, based on relating
348 fine-mapped, annotated variants to gene and protein expression, epigenetic marks, gene sets,
349 biological pathways and druggable proteins, it provides new understanding and resources of utility
350 for the development of therapeutics. The 279-variant GRS we constructed was associated with a
351 4.71-fold increased relative risk of moderate-severe COPD between highest and lowest deciles, such
352 that one would expect over 80% of smokers in the highest genetic risk decile to develop COPD. The
353 GRS was also predictive of COPD across multiple ancestral groups. Our PheWAS highlights both
354 expected and unexpected associations relevant to respiratory and other systemic diseases.
355 Investigating the nature of the pleiotropic effects of some of these variants will be of benefit for
356 drug target identification and validation.

357 **Online Methods:**

358 **Study Design Overview and rationale**

359 For the two-stage approach, we firstly selected distinct signals of association (defined using
360 conditional analyses) with one or more traits achieving $P < 5 \times 10^{-9}$ in UK Biobank only (n up to
361 321,047). A threshold of $P < 5 \times 10^{-9}$ was selected to maximise stringency of findings and to be
362 consistent with currently recommended genome-wide significance thresholds for re-sequencing
363 analyses of European ancestry individuals⁵⁰. We then reported as new those signals which
364 additionally met $P < 10^{-3}$ in SpiroMeta (N effective >70% of n up to 79,055; **Supplementary Note,**
365 **Supplementary Figure 7**), with consistent directions of effect and term them “Tier 1” signals as they
366 meet our highest level of stringency.

367 For the one-stage approach, we selected distinct signals of association (defined using conditional
368 analyses) with one or more traits reaching $P < 5 \times 10^{-9}$ in the meta-analysis of UK Biobank and
369 SpiroMeta (n up to 400,102) and reported as new those which additionally met $P < 10^{-3}$ in both UK
370 Biobank and SpiroMeta with a consistent direction of effect. We term these signals “Tier 2” as they
371 meet our second-highest level of stringency.

372 All signals meeting either set of criteria described above, and that had not been previously
373 published, were reported as new signals of association with lung function. Signals that reached
374 $P < 5 \times 10^{-9}$ in the meta-analysis of UK Biobank and SpiroMeta, had a consistent direction of effect in UK
375 Biobank and SpiroMeta, but which did not reach $P < 10^{-3}$ in both UK Biobank and SpiroMeta are
376 presented as “Tier 3” and were not included in further analyses.

377 UK Biobank

378 The UK Biobank data resource is described elsewhere (see URLs). Individuals were selected for
379 inclusion in this study if they met the following criteria: (i) had complete data for age, sex, height and
380 smoking status; (ii) had spirometry meeting quality control requirements (based on analyses of
381 acceptability, reproducibility and blow curve metrics; **Supplementary Note**); (iii) had genome-wide
382 imputed genetic data and; (iv) were of European ancestry based on genetic data (**Supplementary**
383 **Note; Supplementary Figure 1**). Genotyping was undertaken using the Affymetrix Axiom® UK BiLEVE
384 and UK Biobank arrays¹³. Genotypes were imputed to the Haplotype Reference Consortium panel⁵¹
385 (**Supplementary Note**), and retained if minor allele count ≥ 3 and imputation quality (info) > 0.5 . A
386 total of 321,047 individuals were included in this analysis (**Supplementary Table 1**).

387 Residuals from linear regression of each trait (FEV₁, FVC, FEV₁/FVC and PEF) against age, age², sex,
388 height, smoking status (ever/never) and genotyping array were ranked and inverse-normal
389 transformed to obtain adjusted, normally distributed Z-scores. These Z-scores were then used for
390 genome-wide association testing under an additive genetic model using BOLT-LMM v2.3²⁰. Principal
391 components were not included as BOLT-LMM uses a linear mixed model to account for relatedness
392 and fine-scale population structure.

393 Linkage disequilibrium (LD) score regression implemented in LDSC⁵² was used to estimate inflation of
394 test statistics due to confounding. Genomic control was applied, adjusting all test statistics by LD
395 score regression intercepts: 1.12 for FEV₁, 1.14 for FVC, 1.19 for FEV₁/FVC and 1.13 for PEF
396 (**Supplementary Figure 8; Supplementary Table 24**).

397 SpiroMeta consortium

398 The SpiroMeta consortium meta-analysis was comprised of a total of 79,055 individuals from 22
399 studies. Thirteen studies (n=21,436 individuals) were imputed to the 1000 Genomes Project Phase 1
400 reference panel⁵³ (B58C [T1DGC and WTCCC], BHS1&2, three Croatian studies [CROATIA-Korcula,
401 CROATIA-Split and CROATIA-Vis], Health 2000, KORA F4, KORA S3, LBC1936, NSPHS, ORCADES,
402 SAPALDIA and YFS and 9 studies (n=61,682 individuals) were imputed to the Haplotype Reference
403 Consortium (HRC) panel⁵⁴ (EPIC [obese cases and population-based studies], GS:SFHS, NFBC1966,
404 NFBC1986, PIVUS, SHIP, SHIP-TREND, UKHLS and VIKING). See **Supplementary Tables 2 and 3** for the
405 definitions of all abbreviations, study characteristics, details of genotyping platforms and imputation
406 panels and methods). Measurements of spirometry for each study are described in the
407 **Supplementary Note**.

408 In each study, linear regression models were fitted for each lung function trait (FEV₁, FEV₁/FVC, FVC
409 and PEF, where available), with adjustment for age, age², sex and height. For studies with unrelated
410 individuals, these models were fitted separately in ever smokers and never smokers, with additional
411 adjustment for principal components of ancestry. Studies with related individuals fitted mixed
412 models in all individuals to account for relatedness, with ever smoking status as a covariate.

413 In all studies, rank-based inverse normal transformations were undertaken on the residuals, with
414 these transformed residuals used as the phenotype for association testing under an additive genetic
415 model (**Supplementary Table 3**).

416 In the study level results, variants were excluded if they had a very low MAC (**Supplementary Table**
417 **3**) or imputation quality (info) < 0.3 . In studies with unrelated individuals, the ever and never smokers
418 results were combined, using inverse variance weighted meta-analysis, to give an overall study

419 result. Genomic control was then applied to all study level results, before combining results across
420 all studies using inverse variance weighted meta-analysis. LD score regression intercepts for the
421 meta-analysis were close to 1 (**Supplementary Figure 8; Supplementary Table 24**) and so genomic
422 control was not applied.

423 **Meta-analyses**

424 A total of 19,871,028 variants (imputed or genotyped) in both UK Biobank and SpiroMeta were
425 meta-analysed using inverse-variance weighted fixed effect meta-analysis, and no further genomic
426 control was applied as LD score regression intercepts were close to 1 (**Supplementary Table 24**).

427 **Selection of new signals using conditional analyses**

428 All SNPs ± 1 Mb were extracted around each sentinel variant. GCTA⁵⁵ was then used to perform
429 stepwise conditional analysis to select independently associated SNPs within each 2Mb region. Any
430 secondary signals identified within each 2Mb region were required to meet Tier 1 or Tier 2 criteria
431 (described above) after conditioning on the primary sentinel variant. A combined list of distinct lung
432 function signals was then made across the 4 phenotypes, FEV₁, FVC, FEV₁/FVC and PEF as follows:
433 where sentinel variants for 2 signals for different phenotypes were in high LD ($r^2 > 0.5$), we retained
434 the most significant variant; where 2 signals were in moderate LD ($0.1 > r^2 > 0.5$), we retained
435 variants if, after conditional analysis, they still met the Tier 1 or Tier 2 threshold; for signals in low LD
436 ($r^2 < 0.1$) we retained both variants. We then used the same criteria to identify a subset of new
437 signals which were distinct from previously published independent signals (see below).

438 **Assessment of previously reported lung function signals**

439 We identified 184 autosomal signals from previous GWAS analyses of lung function and COPD^{1,4-14}.
440 After LD pruning (keeping only those signals with LD of $r^2 < 0.1$), we removed 24 non-independent
441 SNPs, leaving 160 previously reported independent signals. Of 6 previously reported signals in the
442 HLA region, we included only the 3 independent lung function HLA signals reported from conditional
443 analysis using all imputed HLA genotypes¹⁸: *AGER* (rs2070600), *HLA-DQB1* (rs114544105) and near
444 *ZNF184* (rs34864796) leaving 157 signals.

445 We confirmed association of previously reported signals in our data if they met any of three criteria:
446 (i) the previously reported sentinel was associated ($P < 10^{-5}$) with any lung function trait in UK
447 Biobank; (ii) a proxy for the previously reported sentinel with $r^2 > 0.5$ was associated ($P < 10^{-5}$) with any
448 lung function trait in UK Biobank; (iii) a proxy for the previously reported sentinel with $r^2 > 0.1$ was
449 associated with any lung function trait meeting tier 1 or tier 2 criteria (**Supplementary Figure 3**).

450 **Effect on COPD susceptibility – genetic risk score in multiple ancestries**

451 To test association of all lung function signals and COPD susceptibility, we constructed a 279-variant
452 weighted GRS comprising the 139 novel and 140 previously reported signals; we used the previously
453 reported sentinel SNP for published signals. Weights were derived using the FEV₁/FVC ratio
454 decreasing (i.e. COPD risk *increasing*) alleles. For previously reported signals (n=140), results from
455 the UK Biobank analysis were used to derive weights for the 94 signals that were not discovered
456 using UK Biobank data and weights were taken from SpiroMeta for 46 signals where UK Biobank was
457 included in the discovery of those signals. For novel signals identified in this study, weights were
458 taken from SpiroMeta for two-stage (tier 1) signals (n=99), and the smallest absolute effect size from
459 either of UK Biobank or SpiroMeta was used for one-stage (tier 2) signals (n=40) (**Supplementary**

460 **Table 25).** For the weighted GRS the number of risk alleles at each variant was multiplied by its
461 weight.

462 The GRS was first calculated in unrelated individuals (KING kinship coefficient of < 0.0884) within 6
463 ancestral groups of UK Biobank: Europeans, South Asians, Africans, Chinese, Mixed African and
464 Europeans, and Mixed Other (total sample of unrelated individuals across six ancestries: 323,001)
465 using PLINK. Weights and alleles were as described above. COPD was defined as $FEV_1/FVC < 0.7$ and
466 $FEV_1 < 0.8$ of the predicted value, i.e. GOLD stage 2-4 categorisation. Associations with the GRS were
467 then tested using COPD (in ancestral groups with at least 100 COPD cases) and FEV_1/FVC as the
468 outcomes.

469 In addition, we calculated the GRS in individuals from the China Kadoorie Biobank (CKB). Four of the
470 279 SNPs were not available in CKB (rs1800888, rs56196860, rs72724130 and rs77672322), and for
471 12 SNPs, proxies were used (minimum $r^2=0.3$). Analyses were undertaken in all COPD GOLD stage 2-4
472 cases ($FEV_1/FVC < 0.7$ and $FEV_1 < 0.8$ of the predicted value, in 6,013 cases and 69,567 controls),
473 against an unbiased set of population controls. The GRS was also tested for association with
474 FEV_1/FVC in CKB ($n=72,796$).

475 Logistic regression of COPD case-control status with the GRS in UK Biobank and China Kadoorie
476 Biobank assumed an additive genetic effect and was adjusted for age, age^2 , sex, height, and smoking
477 (**Supplementary Table 18**). Ten principal components were also included in UK Biobank analyses. In
478 China Kadoorie Biobank, analyses were stratified by geographical regions and then meta-analysed
479 using an inverse-variance fixed effect model. Linear models assessing the association with FEV_1/FVC
480 were fitted using the same transformed outcome as in the main GWAS analysis.

481 We then tested association in 5 European ancestry COPD case-control studies: COPDGene (Non-
482 Hispanic White Population) (3,068 cases and 2,110 controls), ECLIPSE (1,713 cases and 147 controls),
483 GenKOLS (836 cases and 692 controls), NETT-NAS (374 cases and 429 controls) and SPIROMICS (988
484 cases and 537 controls) (**Supplementary Table 19**). In addition, we tested this GRS in the COPDGene
485 African American population study (910 cases and 1,556 controls). Logistic regression models using
486 COPD as outcome and the GRS as exposure were adjusted for age, age^2 , sex, height, and principal
487 components (**Supplementary Table 20**).

488 Next, we divided individuals in the external COPD case-control studies into deciles according to their
489 values of the weighted GRS. This was undertaken separately by study group, and for each decile
490 logistic models were fitted, comparing the risk of COPD for members of each decile group compared
491 to those in the lowest decile (i.e. those with lowest values of the weighted GRS). Covariates were as
492 for the COPD analyses. Results were combined across European-ancestry study groups by fixed
493 effect meta-analysis (**Supplementary Table 21**).

494 We calculated the population attributable risk fraction (PARF) as follows:

$$495 \quad PARF = \frac{P(E)(OR - 1)}{1 + P(E)(OR - 1)}$$

496

497 where $P(E)$ is set to 0.9, i.e. the probability of carrying more risk alleles than those in the lowest risk
498 score decile of the risk score (the 'probability of the exposure'). OR refers to the odds of having

499 COPD in individuals across deciles 2 to 10 of the risk score compared to the odds of having COPD for
500 individuals in the lowest decile (decile 1) of the risk score (**Supplementary Note**).

501 **Effects on smoking behaviour**

502 As our discovery GWAS in UK Biobank was adjusted for ever vs. never smoking status, and not for
503 pack years of smoking (pack years information was missing for 32% of smokers), we evaluated
504 whether any signals of association with lung function might be driven by an association with smoking
505 behaviour by testing for association with smoking initiation (123,890 ever smokers vs. 151,706 never
506 smokers) and cigarettes per day (n=80,015) in UK Biobank (full methods in **Supplementary Note**).
507 We also tested for association with lung function in never smokers only (n=173,658). We excluded
508 any signals associated with smoking behaviour (**Supplementary Table 6**), but not with lung function
509 in never smokers.

510 **Smoking interaction**

511 For associated variants (new and previously reported), we repeated association testing for lung
512 function separately in UK Biobank and SpiroMeta (up to 176,701 ever smokers and 197,999 never
513 smokers), and tested for an interaction effect with smoking using the Welch test (**Supplementary**
514 **Note**). A threshold of $P < 1.79 \times 10^{-4}$ (Bonferroni corrected for 279 tests) indicated significance.

515 We further tested for interaction between the weighted GRS and smoking, within 303,619 unrelated
516 individuals of European ancestry in UK Biobank, using COPD and FEV₁/FVC as outcomes (the
517 FEV₁/FVC phenotype was pre-adjusted for age, age², sex, and height, and the residuals transformed
518 as per the main GWAS analysis). For COPD (defined as FEV₁/FVC < 0.7, and FEV₁ < 80% predicted) the
519 following logistic model was fitted:

520 *COPD* ~ *genotyping array + 10 principal components + age + age² + sex + height + smoking status +*
521 *weighted risk score + (smoking status × weighted risk score).*

522 For FEV₁/FVC the following linear model was fitted:

523 *FEV₁/FVC* ~ *genotyping array + 10 principal components + smoking status + weighted risk score +*
524 *(smoking status × weighted risk score).*

525 **Proportion of variance explained**

526 We calculated the proportion of variance explained by each of the previously reported (n=140) and
527 new variants (n=139) associated with lung function using the formula:

528
$$\frac{\sum_{i=1}^n 2f_i(1-f_i)\beta_i^2}{V}$$

529 where n is the number of variants f_i and β_i are the frequency and effect estimate of the i'th variant,
530 and V is the phenotypic variance (always 1 as our phenotypes were inverse-normal transformed).
531 We used the same unbiased effect estimates (β) as used to calculate GRS weights at the same set of
532 279 sentinel variants used for the GRS, which uses either UK Biobank or SpiroMeta effect estimates
533 (described above). Our previously published estimate of proportion of variance explained¹⁸ used
534 effect estimates derived from UK Biobank. We assumed a heritability of 40%^{56,57} to estimate the
535 proportion of additive polygenic variance.

536 **Fine-mapping**

537 A Bayesian method⁵⁸ was used to fine-map lung-function-associated signals to the set of variants
538 that were 99% likely to contain the underlying causal variant (assuming that the causal variant has
539 been analysed). This was undertaken for new signals and for previously reported signals reaching
540 $P < 10^{-5}$ in UK Biobank. For the previously reported signals, the top sentinel variant from the current
541 analysis in UK Biobank was used, instead of the previously reported variant. We used a value of 0.04
542 for the prior W in the approximate Bayes factor formula⁵⁹. Effect sizes and standard errors for fine-
543 mapping were obtained from an inverse variance weighted meta-analysis of UK Biobank and
544 SpiroMeta (n up to 400,102). Signals in the HLA region were not included.

545 **Implication of potentially causal genes**

546 *Annotation of deleterious variants*

547 Variants in the 99% credible sets were checked for predicted functional effect if they were
548 annotated as “exonic”, “splicing”, “ncRNA_exonic”, “5’ UTR” or “3’ UTR” (untranslated region) by
549 ANNOVAR⁶⁰. We then used SIFT, PolyPhen-2 (implemented using the Ensembl GRCh37 Variant
550 Effect Predictor, see URLs, accessed 1 February 2018) and FATHMM⁶¹ to annotate missense variants,
551 and CADD (also implemented using VEP) to annotate non-coding variation. Variants were annotated
552 as deleterious in our study if they were labelled 'deleterious' by SIFT, 'probably damaging' or
553 'possibly damaging' by PolyPhen-2, 'damaging' by FATHMM (specifying the 'Inherited disease' option
554 of the coding variants methods, and setting the prediction algorithm to 'Unweighted') or had a CADD
555 scaled score ≥ 20 ⁴. The union of the four methods was taken to establish the number of potentially
556 deleterious variants and their unique genes.

557 *Gene expression and protein levels*

558 At each novel and previously reported signal, the sentinel variant and 99% credible set⁵⁸ were used
559 to query three eQTL resources: lung eQTL (n=1,111)¹³, blood eQTL (n=4,896)⁶² and GTEx (V7; with n
560 up to 388 depending on tissue: Artery Aorta (n=267), Artery Coronary (n=152), Artery Tibial (n=388),
561 Colon Sigmoid (n=203), Colon Transverse (n=246), Esophagus Gastroesophageal Junction (n=213),
562 Esophagus Muscularis (n=335), Lung (n=383), Small Intestine Terminal Ileum (n=122), Stomach
563 (n=237), and Whole Blood (n=369))⁶³, and one blood pQTL resource (n=3,301)³⁴.

564 A gene was classified as a 'putative causal gene' if the sentinel SNP or any SNP in the respective 99%
565 credible set was associated with expression of this gene or its protein levels (FDR<5% for eQTL,
566 $P < 5.03 \times 10^{-8}$ [for 276 tests at 3,600 proteins] for pQTL) and if the GWAS sentinel SNP or any SNP in
567 the respective 99% credible set was also the variant most strongly associated with expression of the
568 respective gene or level of the respective protein (i.e. the sentinel eQTL/pQTL SNP) in one or more of
569 the eQTL and pQTL data sets. The HLA region was excluded from these analyses.

570 **Pathway analysis**

571 We tested for enrichment of genes identified via variant function annotation, gene expression or
572 protein level analyses in pathway and gene set ontology databases using ConsensusPathdb.
573 Pathways or gene sets represented entirely by genes implicated by the same association signal were
574 excluded. Gene sets and pathways with FDR<5% are reported.

575 **Functional enrichment analyses**

576 We tested for cell-specific enrichment of lung function associated variants in regulatory regions
577 using FORGE³⁵ (v1.1). One thousand background SNP set repetitions were used. Thresholds
578 $P < 1.68 \times 10^{-4}$ (FDR < 2%; > 99th percentile) and $P < 3.37 \times 10^{-5}$ (FDR < 0.5%; > 99.9th percentile) were taken
579 as being 'indicative' and 'significant', respectively. FORGE analysis was carried out for the cell lines in
580 the RoadMap Epigenome project³³ (n=299 cell lines) and ENCODE projects⁶⁴ (n=125) separately.

581 Using DeepSEA³⁶, we analysed all SNPs in the 99% credible set for predicted chromatin effects. We
582 reported effects for any chromatin effect and lung-related cell line that had an E-value < 0.05 (i.e. the
583 expected proportion of SNPs with a larger predicted effect based on empirical distributions of
584 predicted effects for 1000 Genomes SNPs) and an absolute difference in probability of > 0.1
585 (threshold for "high confidence") between the reference and alternative allele.

586 **Drug targets**

587 Genes identified as potentially causal using eQTL, pQTL or variant annotation were interrogated
588 against the gene-drug interactions table of the Drug-Gene Interactions Database (DGIDB) (see URLs),
589 accessed 16th October 2017. Drugs were mapped to ChEMBL IDs (see URLs), and indications (as
590 MeSH headings) were added.

591 **Phenome-wide association studies**

592 To identify whether any of the new or previously reported signals overlap with signals of association
593 for other traits and diseases, the 279 variant weighted GRS was calculated in UK Biobank samples (n
594 up to 379,337) and a phenome-wide association study (PheWAS) across all available traits was
595 performed, with the risk score as the exposure. Traits included UK Biobank baseline measures (from
596 both questionnaires and physical measures), self-reported medication usage, and operative
597 procedures, as well as those captured in Office of Population Censuses and Surveys codes from the
598 electronic health record. We also included self-reported disease variables and those from hospital
599 episode statistics (ICD-10 codes truncated to three-character codes and combined in block and
600 chapter groups) as well as combining both self-report and hospital diagnosed diseases where
601 possible to maximise power. The GRS analysis included 2,453 traits, of which 2,411 were also
602 included in the single-variant analysis (traits with > 200 cases were included for the individual SNP
603 PheWAS, whereas traits with > 50 cases were included in the risk score PheWAS). Analyses were
604 conducted in unrelated European ancestry individuals (KING kinship coefficient of < 0.0442), and
605 were adjusted for age, sex, genotyping array, and ten principal components. Logistic models were
606 fitted for binary outcome, and linear models were fitted for quantitative outcomes. False discovery
607 rates were calculated according to the number of the traits in each analysis (2,453 or 2,411, for the
608 risk score and single-variant PheWAS, respectively).

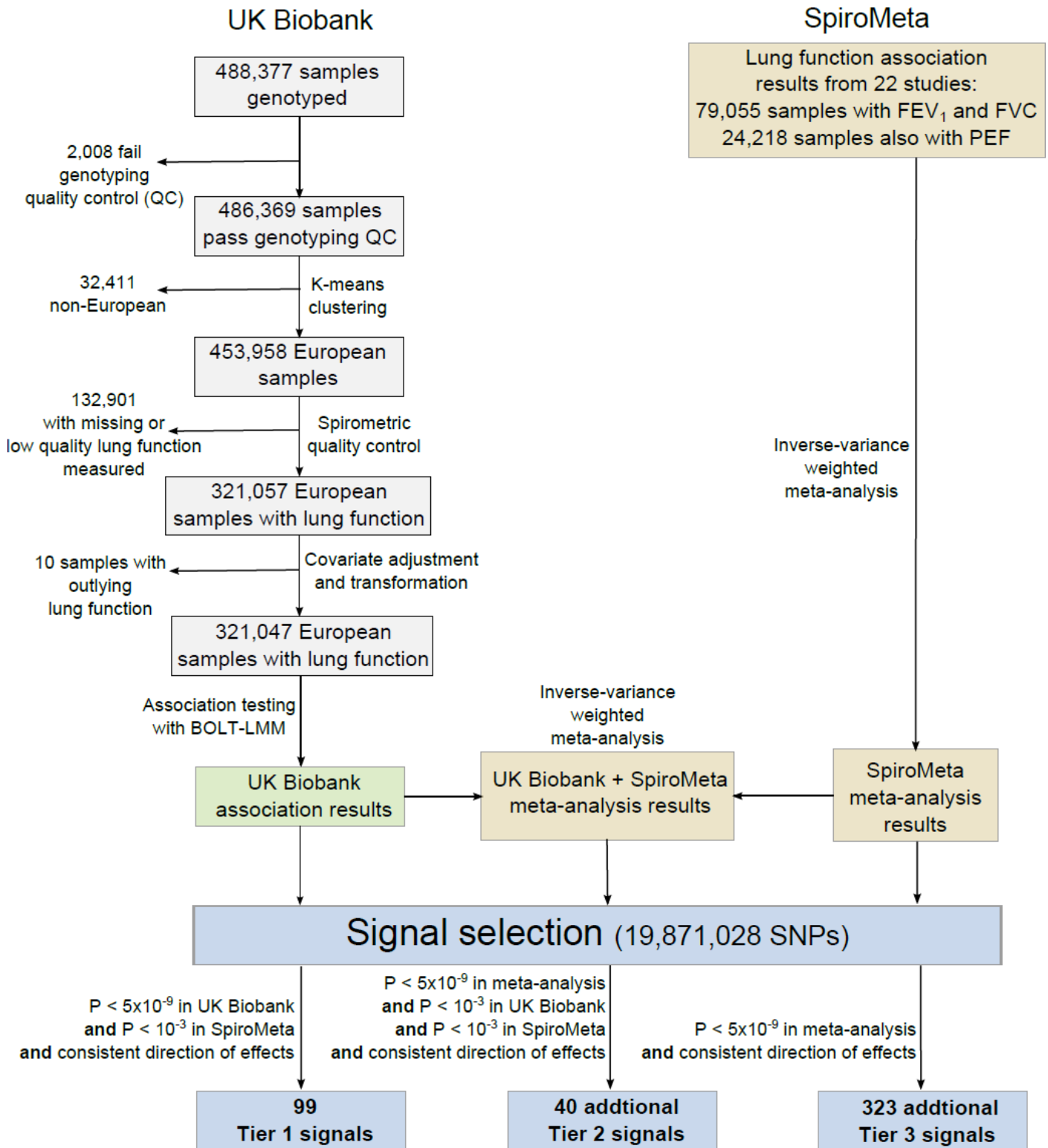
609 In addition, the sentinel variants and variants within the 99% credible sets were queried against the
610 GWAS catalog⁶⁵ (see URLs, accessed 5th February 2018) and GRASP⁶⁶ (see URLs, accessed 6th
611 February 2018) for reported associations significant at $P < 5 \times 10^{-8}$. Associations relating to
612 methylation, expression, metabolite or protein levels, as well as lung function and COPD, were not
613 included.

614 **Data availability statement**

615 UK Biobank GWAS summary statistics will be available via UK Biobank

616 (<http://www.ukbiobank.ac.uk/>). SpiroMeta GWAS summary statistics, and single-variant PheWAS

617 results will be made available by request.



618

619

Figure 1: Study design

620

Tier 1 signals had $P < 5 \times 10^{-9}$ in UK Biobank and $P < 10^{-3}$ in SpiroMeta with consistent direction of effect.

621

Tier 2 signals had $P < 5 \times 10^{-9}$ in the meta-analysis of UK Biobank and SpiroMeta with $P < 10^{-3}$ in UK Biobank and $P < 10^{-3}$ in SpiroMeta with consistent directions of effect. Signals with $P < 5 \times 10^{-9}$ in the meta-analysis of UK Biobank and SpiroMeta, and that had consistent directions of effect but did not meet $P < 10^{-3}$ in both cohorts were reported as Tier

622

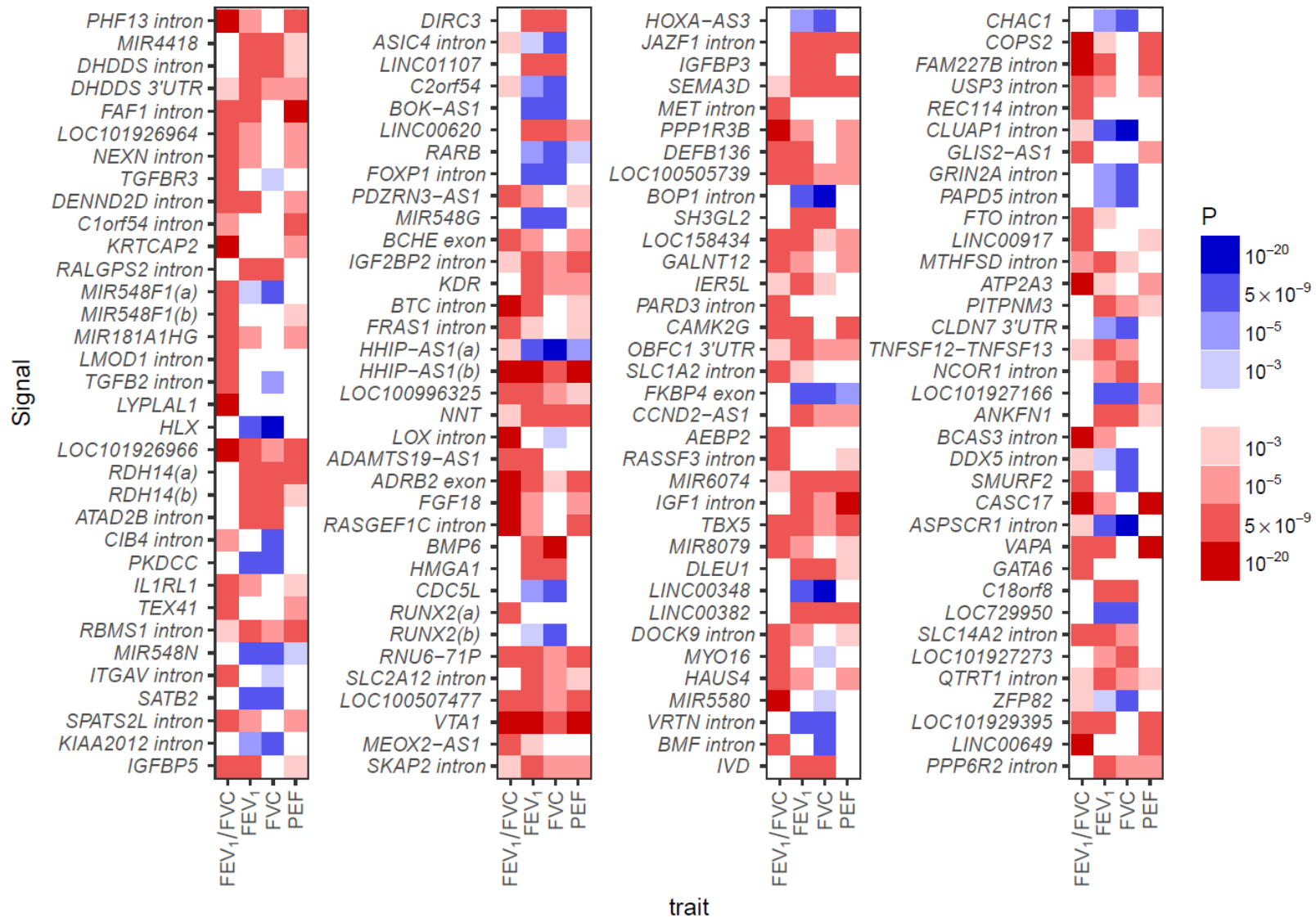
3.

623

3.

624

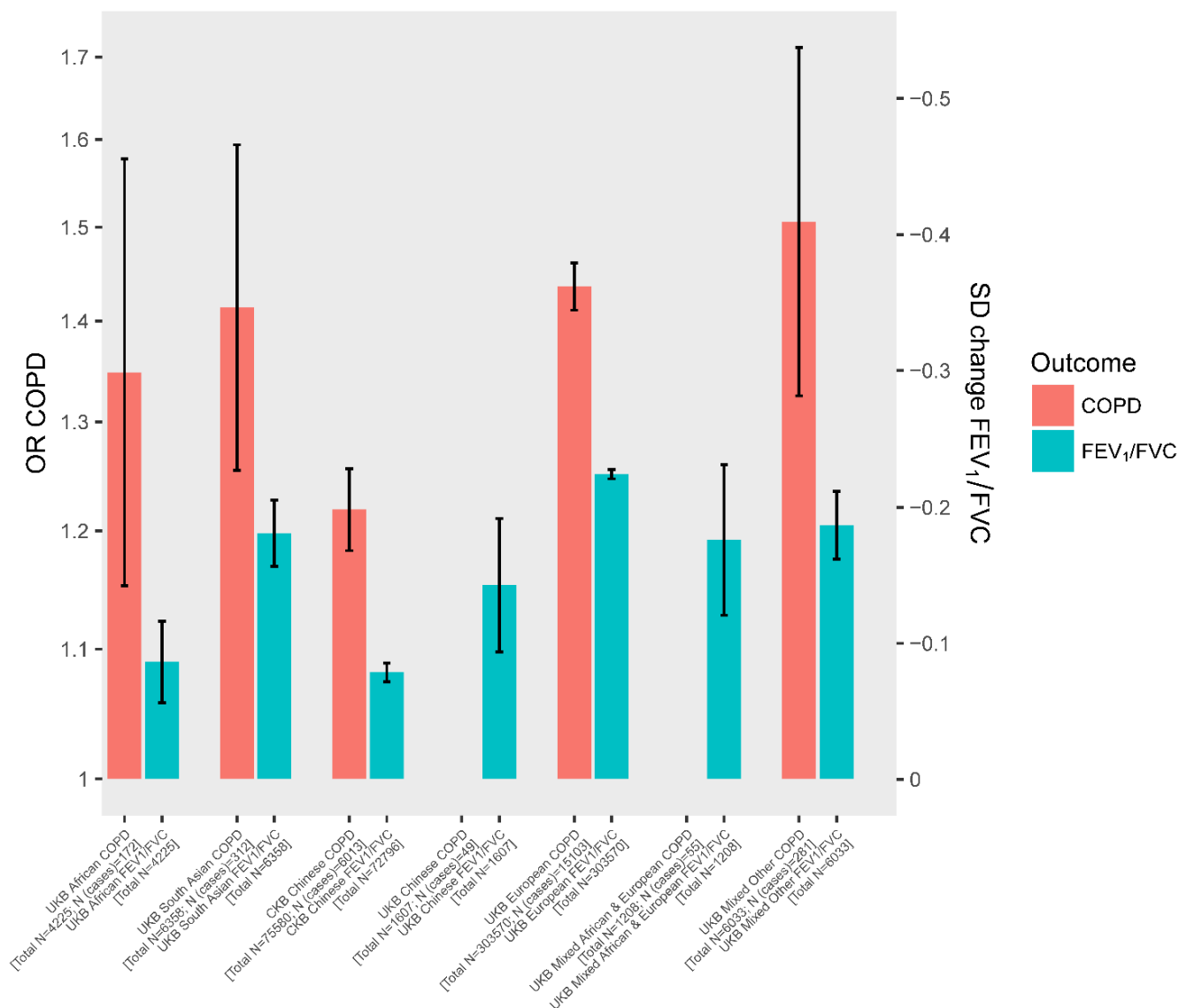
3.



625
626
627
628
629

Figure 2: Strength and direction of association across four lung function traits for 139 novel signals: Red indicates decrease in the lung function trait; blue indicates an increase. All effects are aligned to the allele associated with decreased FEV₁/FVC, hence the FEV₁/FVC column is only red or white. P-values are from the meta-analysis of UK Biobank and SpiroMeta (n=400,102). The scale points are thresholds used for (i) confirmation in 2-stage analysis and 1-stage analysis (P<10⁻³); (ii) confirmation of association of previous signals (P<10⁻⁵); (iii) signal selection in 2-stage and 1-stage analysis (P<5×10⁻⁹); capped at (P<10⁻²⁰).

Weighted risk score associations with FEV₁/FVC and COPD in population-based studies



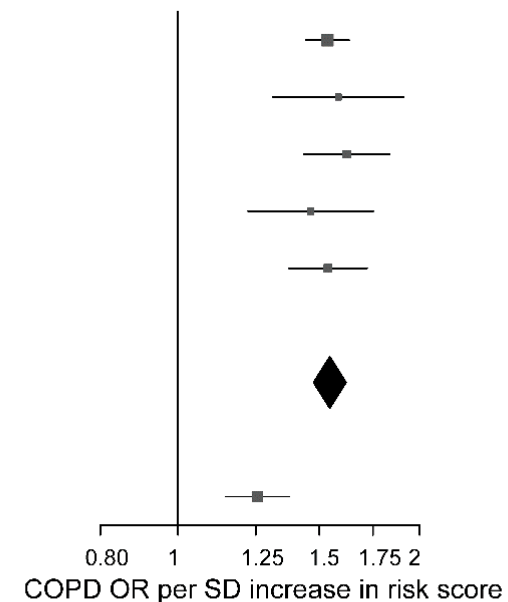
Ancestral group and phenotype studied in UK Biobank or China Kadoorie Biobank

631 **Figure 3: Association of weighted genetic risk score (GRS) with COPD and FEV₁/FVC.**

632 **A.** Association of weighted genetic risk score (GRS) with COPD and FEV₁/FVC in UK Biobank and China Kadoorie
633 Biobank (CKB). The left axis denotes odds ratios (OR) for COPD per 1 standard deviation (SD) increase in
634 weighted GRS (OR for COPD shown only for ancestries in UK Biobank with > 100 cases of COPD). COPD was
635 defined as FEV₁/FVC < 0.7 and FEV₁ < 0.8 of the predicted value, i.e. GOLD stage 2-4 categorisation. Bars (in
636 red) are labelled with ancestral groups, and the total sample size and number of COPD cases are given. The
637 right-hand axis denotes change in standard deviation (SD) units of FEV₁/FVC per 1 SD increase in weighted
638 GRS in the same individuals (blue bars). For means and standard deviations of the risk scores in each group,
639 see **Supplementary Table 18**. Note some variants featuring in the GRS were discovered in UK Biobank
640 individuals of European ancestry. The height of the bars represents the effect estimate, and the black
641 whiskers represent 95% confidence intervals. There were 13 SNPs with MAF < 0.1% in at least one ancestral
642 group: 13/279 in Chinese (of which 4/13 were monomorphic). Two of the 13 SNPs that were monomorphic in
643 Chinese people had MAF < 0.1% in Africans.

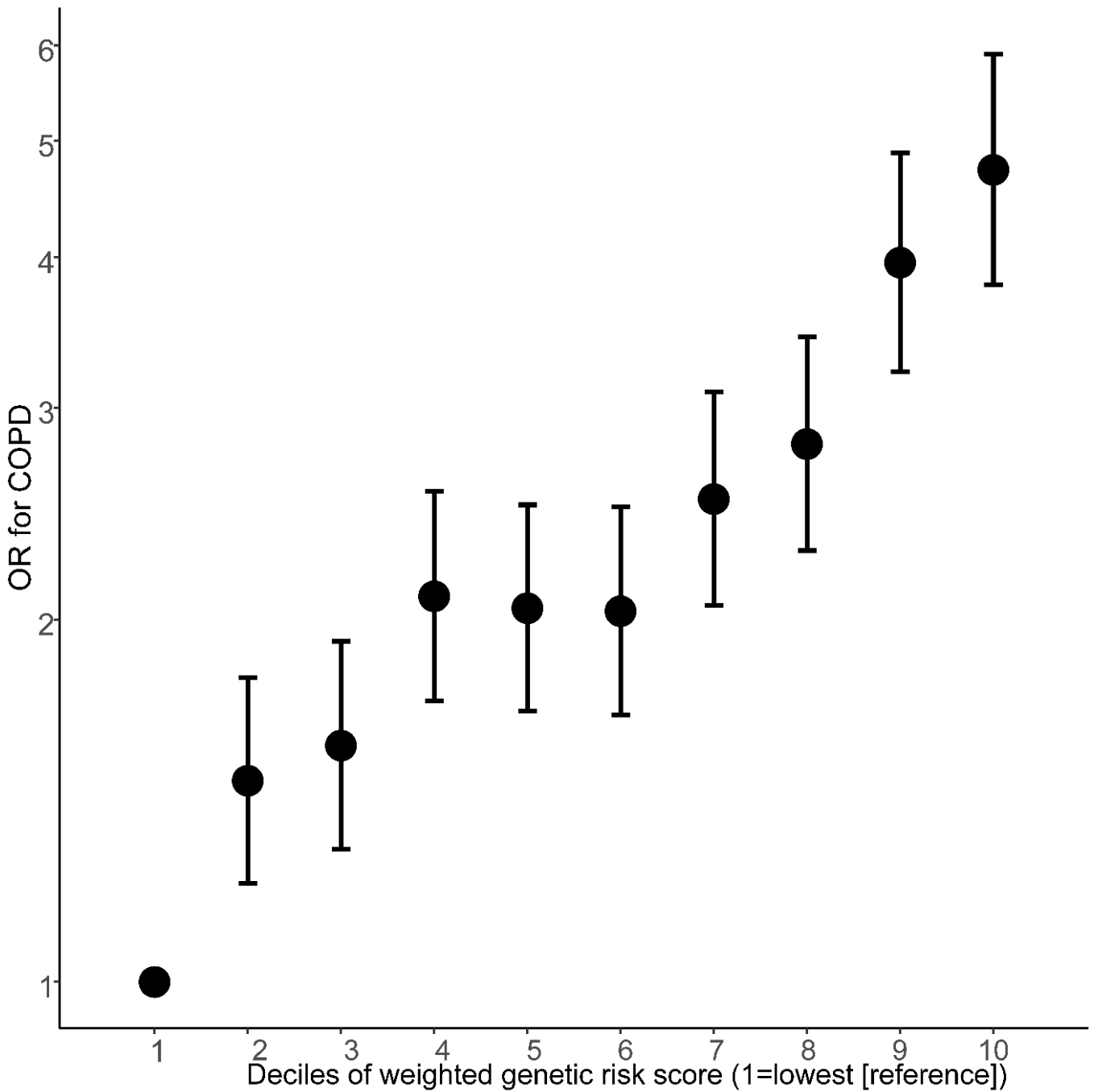
Weighted risk score associations with COPD susceptibility in COPD case-control studies

Ancestry	Cohort	OR	95%LCI	95%UCI	P	Cases	Controls
European	COPDGene (EUR)	1.54	1.44	1.63	1.97x10 ⁻⁴¹	3068	2110
	ECLIPSE	1.59	1.31	1.91	1.42x10 ⁻⁰⁶	1713	147
	GenKOLS	1.62	1.44	1.83	8.99x10 ⁻¹⁵	836	692
	NETT-NAS	1.46	1.22	1.75	3.13x10 ⁻⁰⁵	374	429
	SPIROMICS	1.54	1.38	1.72	4.47x10 ⁻¹⁴	988	537
	Meta-analysis	1.55	1.48	1.62	1.48x10⁻⁷⁵	6979	3915
African	COPDGene (AFR)	1.26	1.15	1.37	8.36x10 ⁻⁰⁷	910	1556



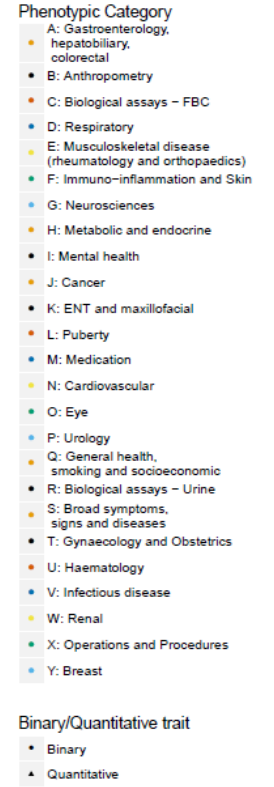
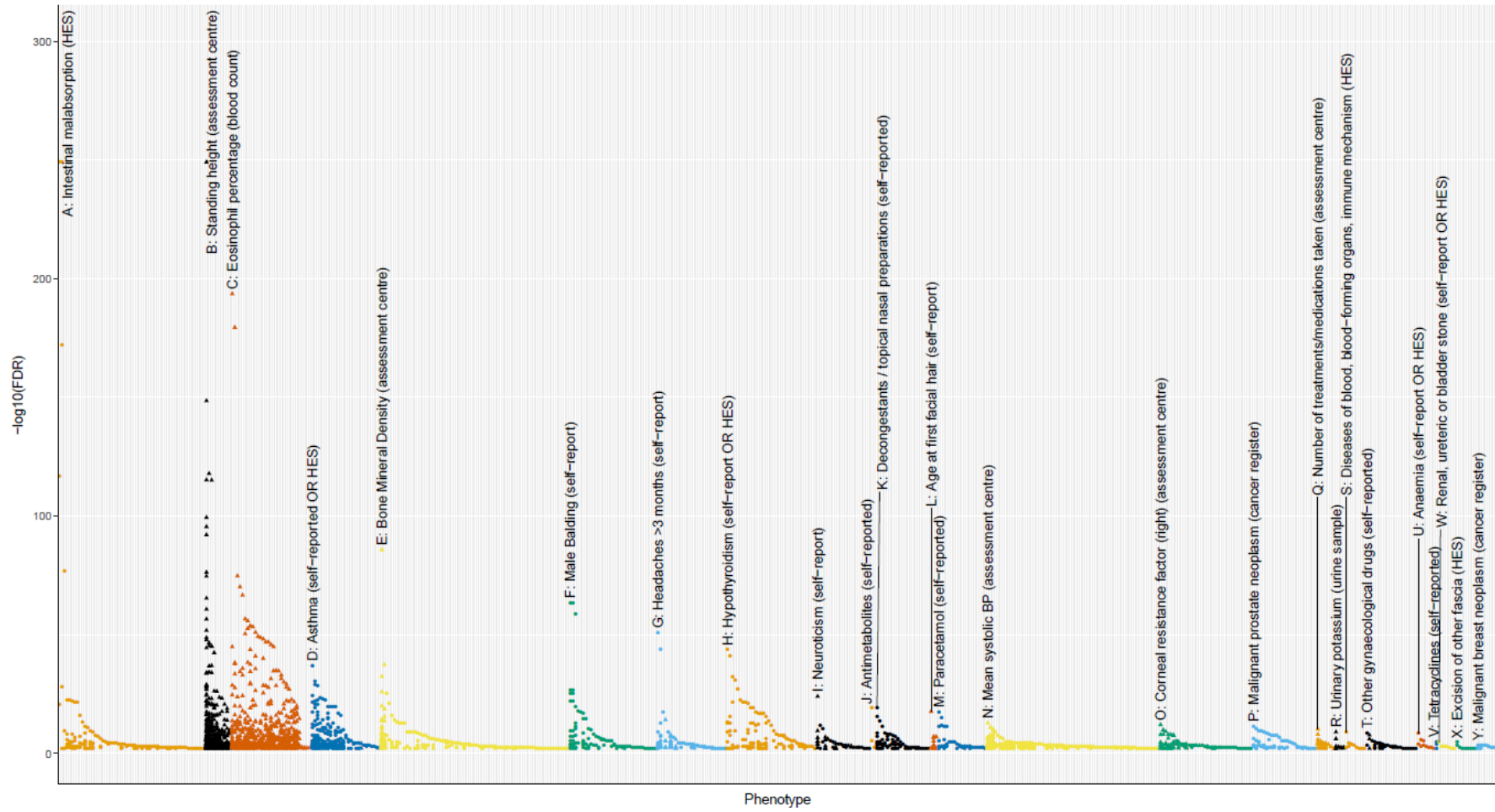
645 B. Odds ratio (OR) for COPD per 1 standard deviation (SD) increase in weighted genetic risk score in each of six study groups (COPDGene [Non-Hispanic White],
646 COPDGene [African-American], ECLIPSE, GenKOLS, SPIROMICS, NETT-NAS). COPD was defined using GOLD 2-4 criteria. For means and standard deviations of the risk
647 scores in each group see **Supplementary Table 20**. The vertical black line indicates the null effect (an OR of 1). The point estimate of each study is represented by a
648 box proportional to the study's weight, with the lines representing the lower and upper bounds of the 95% confidence interval. A fixed effect meta-analysis of the
649 five European-ancestry groups is denoted with a diamond, the width of which represents the 95% confidence interval for the estimate (I^2 statistic=0).

Odds ratio of COPD per decile increase in the weighted genetic risk score

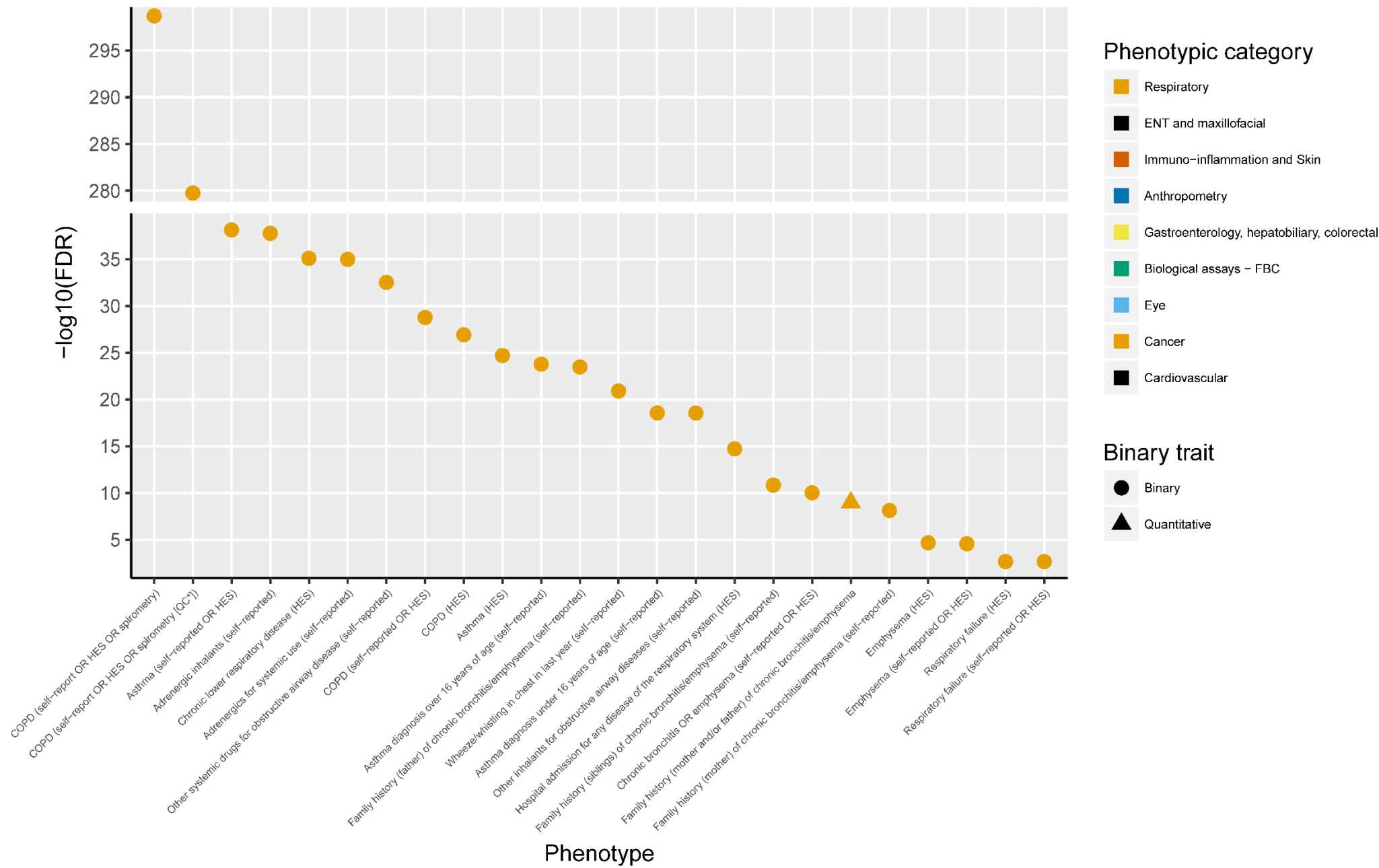


650
651
652
653
654
655
656
657

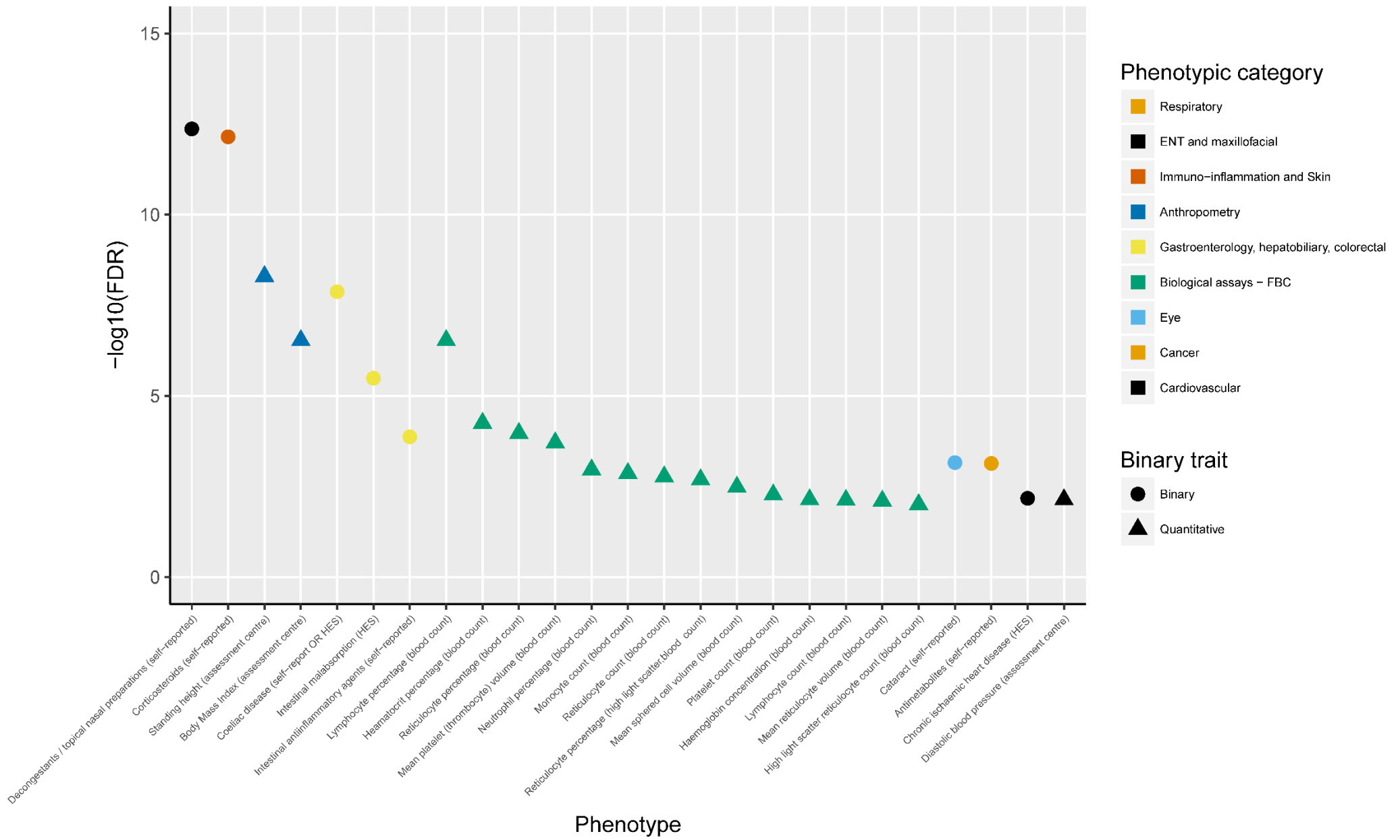
- C. Odds ratios (OR) for COPD according to membership of deciles 2-10 of the weighted genetic risk score, with decile 1 as the reference group (the 10% of individuals with the lowest genetic risk score). Each point represents a meta-analysis of results for a given comparison (i.e. decile 2 vs reference, decile 3 vs reference ... decile 10 versus reference) in five external European-ancestry study groups (COPDGene, ECLIPSE, GenKOLS, SPIROMICS, NETT-NAS). Deciles were calculated and models were run in each group separately. Points represent odds ratios, and error bars correspond to 95% confidence intervals (**Supplementary Table 21**).



659 **Figure 4: Individual PheWAS with 279 variants (traits passing FDR 1% threshold)**
660 Separate association of 279 variants with 2,411 traits (FDR<1%) in UK Biobank (n up to 379,337). In each category, the trait with the strongest association, i.e. highest –
661 $-\log_{10}(\text{FDR})$, is shown first, followed by other traits in that category in descending order of $-\log_{10}(\text{FDR})$. Categories are colour-coded, and outcomes are denoted with a
662 circular or triangular point, according to whether they were coded as binary or quantitative. The top association per-category is labelled with its rsID number, and a plain
663 English label describing the trait. The letter at the beginning of each label allows easy cross-reference with the categories labelled in the legend. Zoomed in versions of each
664 category with visible trait names are available in **Supplementary Figure 9**.



666 **Figure 5: PheWAS with genetic risk score (traits passing FDR 1% threshold)**
667 Association of 279 variant weighted genetic risk score with 2,453 traits (FDR<1%) in UK Biobank (n up to 379,337). In each panel, the category with the strongest
668 association, i.e. highest $-\log_{10}(\text{FDR})$, is shown first, followed by all other associations in that category, ordered by descending order of $-\log_{10}(\text{FDR})$. Sample sizes varied
669 across traits and are available in **Supplementary Table 22**, along with the full summary statistics for each association, plus details of categorisation and plain English labels
670 for each trait. Trait categories are colour coded, and outcomes are denoted with a circular or triangular point, according to whether they were coded as binary or
671 quantitative. *QC refers to spirometry passing ERS/ATS criteria.
672 **A.** Associations with respiratory traits.



673
674

B. Associations with all other traits.

675
676
677
678
679
680
681
682

Table 1: Genes implicated using gene expression data, protein level data and functional annotation

†Genes implicated by eQTL signals: Lung eQTL (n=1,111) and Blood eQTL (n=4,896) datasets and eleven GTEx (V7) tissues were screened: Artery Aorta (n=267), Artery Coronary (n=152), Artery Tibial (n=388), Colon Sigmoid (n=203), Colon Transverse (n=246), Esophagus Gastroesophageal Junction (n=213), Esophagus Muscularis (n=335), Lung (n=383), Small Intestine Terminal Ileum (n=122), Stomach (n=237), and Whole Blood (n=369); see **Supplementary Table 13** for direction of gene expression for the COPD (lung function reducing) risk allele.

‡Genes implicated by pQTL signals: pQTL look up in 3,600 plasma proteins (n up to 3,300).

*Genes implicated because they contain a deleterious variant (**Supplementary Table 11**).

“Other traits” column lists the other lung function traits for which the sentinel was associated at $P < 5 \times 10^{-9}$ in the meta-analysis of UK Biobank and SpiroMeta.

Gene	Phenotype	Other traits	Novel Tier/ Previous	Sentinel SNP	Position (b37)	COPD risk/alt	Functionally implicated genes
<i>DHDDS (intron)</i>	FVC	FEV ₁	Tier 2	rs9438626	1:26,775,367	G/C	<i>DHDDS</i> †, <i>DRAM2</i> †
<i>DHDDS (3' UTR)</i>	FEV ₁		Tier 1	rs12096239	1:26,796,922	C/G	<i>HMG2</i> †, <i>DHDDS</i> †
<i>NEXN (intron)</i>	FEV ₁ /FVC	FEV ₁	Tier 1	rs9661687	1:78,387,270	T/C	<i>NEXN</i> †
<i>DENND2D (intron)</i>	FEV ₁ /FVC		Tier 1	rs9970286	1:111,737,398	G/A	<i>CEPT1</i> †, <i>CHI3L2</i> †
<i>C1orf54 (intron)</i>	PEF	FVC	Tier 1	rs11205354	1:150,249,101	C/A	<i>MRPS21</i> †, <i>RPRD2</i> †, <i>ECM1</i> ‡
<i>KRTCAP2</i>	FEV ₁ /FVC		Tier 1	rs141942982	1:155,153,537	T/C	<i>THBS4</i> ‡
<i>RALGPS2 (intron)</i>	FEV ₁		Tier 1	rs4651005	1:178,719,306	C/T	<i>ANGPTL1</i> †
<i>LMOD1 (intron)</i>	FEV ₁ /FVC	FEV ₁	Tier 2	rs4309038	1:201,884,647	G/C	<i>SHISA4</i> †
<i>ATAD2B (intron)</i>	FVC	FEV ₁	Tier 2	rs13009582	2:24,018,480	G/A	<i>UBXN2A</i> †
<i>PKDCC</i>	FVC		Tier 1	rs4952564	2:42,243,850	A/G	<i>PKDCC</i> †
<i>ITGAV (intron)</i>	FEV ₁ /FVC		Tier 1	rs2084448	2:187,530,520	C/T	<i>ITGAV</i> †
<i>SPATS2L (intron)</i>	FEV ₁ /FVC		Tier 2	rs985256	2:201,208,692	C/A	<i>SPATS2L</i> †
<i>C2orf54</i>	FVC	FEV ₁	Tier 1	rs6437219	2:241,844,033	C/T	<i>C2orf54</i> †*
<i>MIR548G</i>	FVC		Tier 1	rs1610265	3:99,420,192	T/C	<i>FILIP1L</i> †
<i>BCHE (exon)</i>	FEV ₁ /FVC	FEV ₁	Tier 1	rs1799807	3:165,548,529	C/T	<i>BCHE</i> *
<i>BTC (intron)</i>	FEV ₁ /FVC	FEV ₁ /FVC	Tier 1	rs62316310	4:75,676,529	G/A	<i>BTC</i> *
<i>LOC100996325</i>	FEV ₁	FEV ₁ /FVC, PEF	Tier 1	rs11739847	5:609,661	A/G	<i>CEPT2</i> *
<i>RNU6-71P</i>	FEV ₁	FVC, PEF	Tier 1	rs2894837	6:56,336,406	G/A	<i>DST</i> *
<i>JAZF1 (intron)</i>	FEV ₁		Tier 1	rs1513272	7:28,200,097	C/T	<i>JAZF1</i> †
<i>MET (intron)</i>	FEV ₁ /FVC		Tier 2	rs193686	7:116,431,427	T/C	<i>MET</i> †
<i>IER5L</i>	FEV ₁		Tier 2	rs967497	9:131,943,843	G/A	<i>CRAT</i> †, <i>PPP2R4</i> †, <i>IER5L</i> *
<i>DOCK9</i>	FEV ₁ /FVC		Tier 1	rs11620380	13:99,665,512	A/C	<i>DOCK9</i> *
<i>CHAC1</i>	FVC		Tier 1	rs4924525	15:41,255,396	A/C	<i>INO80</i> †, <i>CHP1</i> †, <i>RAD51</i> †
<i>ATP2A3</i>	FEV ₁ /FVC		Tier 1	rs8082036	17:3,882,613	G/C	<i>ATP2A3</i> †
<i>PITPNM3</i>	FEV ₁		Tier 2	rs4796334	17:6,469,793	A/G	<i>KIAA0753</i> †*, <i>TXNDC17</i> †, <i>PITPNM3</i> †

Gene	Phenotype	Other traits	Novel Tier/ Previous	Sentinel SNP	Position (b37)	COPD risk/alt	Functionally implicated genes
<i>TNFSF12-TNFSF13</i>	FEV ₁		Tier 2	rs4968200	17:7,448,457	C/G	<i>TNFSF13</i> †, <i>SENP3</i> †
<i>NCOR1 (intron)</i>	FVC	FEV ₁	Tier 2	rs34351630	17:16,030,520	C/T	<i>ADORA2B</i> †, <i>TTC19</i> †
<i>ASPCR1 (intron)</i>	FVC	FEV ₁	Tier 1	rs59606152	17:79,952,944	C/T	<i>LRRC45</i> *
<i>C18orf8</i>	FVC		Tier 1	rs303752	18:21,074,255	A/G	<i>C18orf8</i> †
<i>ZFP82</i>	FVC	FVC, PEF	Tier 2	rs2967516	19:36,881,643	A/G	<i>ZFP14</i> †, <i>ZFP82</i> †
<i>MFAP2</i>	FEV ₁ /FVC	FEV ₁ , PEF	Previous	rs9435733	1:17,308,254	C/T	<i>MFAP2</i> †
<i>LOC101929516</i>	FEV ₁ /FVC		Previous	rs755249	1:39,995,074	T/C	<i>PABPC4</i> †
<i>TGFB2</i>	PEF	FEV ₁ /FVC	Previous	rs6604614	1:218,631,452	C/G	<i>TGFB2</i> †
<i>TRAF3IP1</i>	FEV ₁	FVC, FEV ₁ /FVC, PEF	Previous	rs6710301	2:239,441,308	C/A	<i>ASB1</i> *
<i>SLMAP (intron)</i>	FEV ₁	FEV ₁	Previous	rs6445932	3:57,879,611	T/G	<i>SLMAP</i> †
<i>RSRC1 (intron)</i>	FVC	FVC, FEV ₁ /FVC	Previous	rs12634907	3:158,226,886	G/A	<i>RSRC1</i> †
<i>GSTCD (intron)</i>	FEV ₁	FEV ₁ , FVC, PEF	Previous	rs11722225	4:106,766,430	T/C	<i>INTS12</i> †
<i>NPNT (intron)</i>	FEV ₁ /FVC		Previous	rs34712979	4:106,819,053	A/G	<i>NPNT</i> †‡
<i>AP3B1 (intron)</i>	FVC		Previous	rs425102	5:77,396,400	G/T	<i>AP3B1</i> †
<i>SPATA9</i>	FEV ₁ /FVC		Previous	rs987068	5:95,025,146	C/G	<i>RHOBTB3</i> †
<i>P4HA2-AS1</i>	FVC	FEV ₁ , PEF	Previous	rs3843503	5:131,466,629	A/T	<i>SLC22A5</i> †, <i>P4HA2</i> †, <i>C1QTNF5</i> †
<i>CYFIP2 (intron)</i>	FEV ₁ /FVC	FEV ₁ , PEF	Previous	rs11134766	5:156,908,317	T/C	<i>ADAM19</i> †
<i>ADAM19 (intron)</i>	FEV ₁ /FVC		Previous	rs11134789	5:156,944,199	A/C	<i>ADAM19</i> †*
<i>DSP (intron)</i>	FEV ₁ /FVC	FEV ₁	Previous	rs2076295	6:7,563,232	T/G	<i>DSP</i> †
<i>MIR588</i>	FVC	FVC, PEF	Previous	rs6918725	6:126,990,392	T/G	<i>CENPW</i> †
<i>GPR126 (exon)</i>	FEV ₁ /FVC		Previous	rs17280293	6:142,688,969	A/G	<i>GPR126</i> *
<i>C1GALT1 (intron)</i>	FEV ₁ /FVC	FEV ₁	Previous	rs4318980	7:7,256,490	A/G	<i>C1GALT1</i> †
<i>QSOX2 (3' UTR)</i>	FVC		Previous	rs7024579	9:139,100,413	T/C	<i>QSOX2</i> †
<i>DNLZ (intron)</i>	FVC	FEV ₁ , FVC, PEF	Previous	rs4073153	9:139,259,349	G/A	<i>SNAPC4</i> †, <i>CARD9</i> †, <i>INPP5E</i> †
<i>CDC123 (intron)</i>	FEV ₁ /FVC	FEV ₁	Previous	rs7090277	10:12,278,021	T/A	<i>NUDT5</i> †
<i>MYPN (intron)</i>	FVC	FVC	Previous	rs10998018	10:69,962,954	A/G	<i>MYPN</i> *
<i>EML3 (intron)</i>	FEV ₁	FEV ₁	Previous	rs71490394	11:62,370,155	G/A	<i>EEF1G</i> †, <i>ROM1</i> †*, <i>EML3</i> †*
<i>ARHGEF17 (intron)</i>	FEV ₁ /FVC		Previous	rs2027761	11:73,036,179	C/T	<i>FAM168A</i> †, <i>ARHGEF17</i> †*
<i>RAB5B (intron)</i>	FEV ₁	PEF	Previous	rs1689510	12:56,396,768	C/G	<i>CDK2</i> †
<i>LRP1 (intron)</i>	FEV ₁ /FVC		Previous	rs11172113	12:57,527,283	T/C	<i>LRP1</i> †
<i>FGD6 (intron)</i>	FEV ₁ /FVC		Previous	rs113745635	12:95,554,771	T/C	<i>FGD6</i> †
<i>RPAP1</i>	FEV ₁ /FVC		Previous	rs2012453	15:41,840,238	G/A	<i>ITPKA</i> †, <i>LTK</i> †, <i>TYRO3</i> †, <i>RPAP1</i> †

Gene	Phenotype	Other traits	Novel Tier/ Previous	Sentinel SNP	Position (b37)	COPD risk/alt	Functionally implicated genes
<i>AAGAB</i>	FVC	FEV ₁ , PEF	Previous	rs12917612	15:67,491,274	A/C	<i>AAGAB</i> [†] , <i>SMAD3</i> [†] , <i>IQCH</i> [†]
<i>THSD4</i> (intron)	FEV ₁ /FVC		Previous	rs1441358	15:71,612,514	G/T	<i>THSD4</i> [†]
<i>IL27</i>	FEV ₁		Previous	rs12446589	16:28,870,962	A/G	<i>SBK1</i> [†] , <i>TUFM</i> [†] , <i>CCDC101</i> [†] , <i>SULT1A1</i> [†] , <i>SULT1A2</i> ^{†*} , <i>SH2B1</i> [†] , <i>NPIP7</i> [†] , <i>CLN3</i> [†] , <i>ATXN2L</i> [†] , <i>EIF3C</i> [†]
<i>MMP15</i> (intron)	FEV ₁ /FVC	PEF	Previous	rs11648508	16:58,063,513	G/T	<i>MMP15</i> [†]
<i>SSH2</i> (intron)	FEV ₁ /FVC	FEV ₁	Previous	rs2244592	17:28,072,327	A/G	<i>EFCAB5</i> [†]
<i>FBXL20</i> (intron)	FVC	FVC, PEF	Previous	rs8069451	17:37,504,933	C/T	<i>CRKR5</i> [†] , <i>FBXL20</i> [†]
<i>MAPT-AS1</i>	FEV ₁		Previous	rs79412431	17:43,940,021	A/G	<i>LRR37A4</i> [†] , <i>MAPT</i> [*]
<i>TSEN54</i> (intron)	FEV ₁	PEF	Previous	rs9892893	17:73,525,670	G/T	<i>CASKIN2</i> [†] , <i>TSEN54</i> [*]
<i>LTBP4</i> (exon)	FEV ₁ /FVC		Previous	rs34093919	19:41,117,300	G/A	<i>LTBP4</i> [*]
<i>ABHD12</i> (intron)	FEV ₁	FEV ₁ , PEF	Previous	rs2236180	20:25,282,608	C/T	<i>PYGB</i> ^{†*}
<i>UQCC1</i> (5' UTR)	FVC	FEV ₁	Previous	rs143384	20:34,025,756	G/A	<i>UQCC1</i> [†] , <i>GDF5</i> [†]
<i>SLC2A4RG</i> (intron)	FVC	FEV ₁ /FVC	Previous	rs4809221	20:62,372,706	A/G	<i>LIME1</i> [†]
<i>SCARF2</i> (intron)	FEV ₁	FEV ₁	Previous	rs9610955	22:20,790,723	C/G	<i>SCARF2</i> ^{*‡}

684 References

- 685 1. Young, R.P., Hopkins, R. & Eaton, T.E. Forced expiratory volume in one second: not
686 just a lung function test but a marker of premature death from all causes. *Eur Respir J*
687 **30**, 616-22 (2007).
- 688 2. Lefaudeux, D. *et al.* U-BIOPRED clinical adult asthma clusters linked to a subset of
689 sputum omics. *J Allergy Clin Immunol* **139**, 1797-1807 (2017).
- 690 3. Hekking, P.P. *et al.* Pathway discovery using transcriptomic profiles in adult-onset
691 severe asthma. *J Allergy Clin Immunol* (2017).
- 692 4. Hobbs, B.D. *et al.* Genetic loci associated with chronic obstructive pulmonary disease
693 overlap with loci for lung function and pulmonary fibrosis. *Nat Genet* **49**, 426-432
694 (2017).
- 695 5. Salvi, S.S. & Barnes, P.J. Chronic obstructive pulmonary disease in non-smokers.
696 *Lancet* **374**, 733-43 (2009).
- 697 6. Nelson, M.R. *et al.* The support of human genetic evidence for approved drug
698 indications. *Nat Genet* **47**, 856-60 (2015).
- 699 7. Wilk, J.B. *et al.* A genome-wide association study of pulmonary function measures in
700 the Framingham Heart Study. *PLoS Genet* **5**, e1000429 (2009).
- 701 8. Repapi, E. *et al.* Genome-wide association study identifies five loci associated with
702 lung function. *Nat Genet* **42**, 36-44 (2010).
- 703 9. Hancock, D.B. *et al.* Meta-analyses of genome-wide association studies identify
704 multiple loci associated with pulmonary function. *Nat Genet* **42**, 45-52 (2010).
- 705 10. Soler Artigas, M. *et al.* Genome-wide association and large-scale follow up identifies
706 16 new loci influencing lung function. *Nat Genet* **43**, 1082-90 (2011).
- 707 11. Cho, M.H. *et al.* A genome-wide association study of COPD identifies a susceptibility
708 locus on chromosome 19q13. *Hum Mol Genet* **21**, 947-57 (2012).
- 709 12. Loth, D.W. *et al.* Genome-wide association analysis identifies six new loci associated
710 with forced vital capacity. **46**, 669-77 (2014).
- 711 13. Wain, L.V. *et al.* Novel insights into the genetics of smoking behaviour, lung
712 function, and chronic obstructive pulmonary disease (UK BiLEVE): a genetic
713 association study in UK Biobank. *Lancet Respir Med* **3**, 769-81 (2015).
- 714 14. Lutz, S.M. *et al.* A genome-wide association study identifies risk loci for spirometric
715 measures among smokers of European and African ancestry. *BMC Genet* **16**, 138
716 (2015).
- 717 15. Soler Artigas, M. *et al.* Sixteen new lung function signals identified through 1000
718 Genomes Project reference panel imputation. *Nat Commun* **6**, 8658 (2015).
- 719 16. Hobbs, B.D. *et al.* Exome Array Analysis Identifies a Common Variant in IL27
720 Associated with Chronic Obstructive Pulmonary Disease. **194**, 48-57 (2016).
- 721 17. Jackson, V. *et al.* Meta-analysis of exome array data identifies six novel genetic loci
722 for lung function [version 1; referees: 1 approved with reservations]. *Wellcome Open*
723 *Research* **3**(2018).
- 724 18. Wain, L.V. *et al.* Genome-wide association analyses for lung function and chronic
725 obstructive pulmonary disease identify new loci and potential druggable targets. *Nat*
726 *Genet* **49**, 416-425 (2017).
- 727 19. Wyss, A.B. *et al.* Multiethnic Meta-analysis Identifies New Loci for Pulmonary
728 Function. *bioRxiv* (2017).
- 729 20. Loh, P.R. *et al.* Efficient Bayesian mixed-model analysis increases association power
730 in large cohorts. *Nat Genet* **47**, 284-90 (2015).

- 731 21. Benyamin, B. *et al.* GWAS of butyrylcholinesterase activity identifies four novel loci,
732 independent effects within BCHE and secondary associations with metabolic risk
733 factors. *Hum Mol Genet* **20**, 4504-14 (2011).
- 734 22. Hammarsjo, A., Wang, Z., Vaz, R. & Taylan, F. Novel KIAA0753 mutations extend
735 the phenotype of skeletal ciliopathies. **7**, 15585 (2017).
- 736 23. Stephen, J. *et al.* Mutations in KIAA0753 cause Joubert syndrome associated with
737 growth hormone deficiency. *Hum Genet* **136**, 399-408 (2017).
- 738 24. Loukil, A., Tormanen, K. & Sütterlin, C. The daughter centriole controls ciliogenesis
739 by regulating Neurl-4 localization at the centrosome. *The Journal of Cell Biology*
740 (2017).
- 741 25. He, R. *et al.* LRRC45 is a centrosome linker component required for centrosome
742 cohesion. *Cell Rep* **4**, 1100-7 (2013).
- 743 26. Conkar, D. *et al.* The centriolar satellite protein CCDC66 interacts with CEP290 and
744 functions in cilium formation and trafficking. **130**, 1450-1462 (2017).
- 745 27. Uhlén, M. *et al.* Tissue-based map of the human proteome. *Science* **347**(2015).
- 746 28. Hao, K. *et al.* Lung eQTLs to help reveal the molecular underpinnings of asthma.
747 *PLoS Genet* **8**, e1003029 (2012).
- 748 29. Lamontagne, M. *et al.* Refining susceptibility loci of chronic obstructive pulmonary
749 disease with lung eqtls. *PLoS One* **8**, e70220 (2013).
- 750 30. Obeidat, M. *et al.* GSTCD and INTS12 regulation and expression in the human lung.
751 *PLoS One* **8**, e74630 (2013).
- 752 31. Westra, H.J. *et al.* Systematic identification of trans eQTLs as putative drivers of
753 known disease associations. *Nat Genet* **45**, 1238-1243 (2013).
- 754 32. Consortium, G. Human genomics. The Genotype-Tissue Expression (GTEx) pilot
755 analysis: multitissue gene regulation in humans. *Science* **348**, 648-60 (2015).
- 756 33. Kundaje, A. *et al.* Integrative analysis of 111 reference human epigenomes. *Nature*
757 **518**, 317-30 (2015).
- 758 34. Sun, B.B. *et al.* Genomic atlas of the human plasma proteome. *Nature* **558**, 73-79
759 (2018).
- 760 35. Dunham, I., Kulesha, E., Iotchkova, V., Morganella, S. & Birney, E. FORGE: A tool
761 to discover cell specific enrichments of GWAS associated SNPs in regulatory regions.
762 *F1000Research* **4**(2015).
- 763 36. Zhou, J. & Troyanskaya, O.G. Predicting effects of noncoding variants with deep
764 learning-based sequence model. *Nat Methods* **12**, 931-4 (2015).
- 765 37. Cotto, K.C. *et al.* DGIdb 3.0: a redesign and expansion of the drug-gene interaction
766 database. *Nucleic Acids Research*, gkx1143-gkx1143 (2017).
- 767 38. Slack, R. *et al.* P112 Discovery of a Novel, High Affinity, Small Molecule $\alpha\beta6$
768 Inhibitor for the Treatment of Idiopathic Pulmonary Fibrosis. *QJM: An International*
769 *Journal of Medicine* **109**, S60-S60 (2016).
- 770 39. Raab-Westphal, S., Marshall, J.F. & Goodman, S.L. Integrins as Therapeutic Targets:
771 Successes and Cancers. *Cancers (Basel)* **9**(2017).
- 772 40. Merrill, J.T. *et al.* Efficacy and Safety of Atacicept in Patients With Systemic Lupus
773 Erythematosus: Results of a Twenty-Four-Week, Multicenter, Randomized, Double-
774 Blind, Placebo-Controlled, Parallel-Arm, Phase IIb Study. *Arthritis Rheumatol* **70**,
775 266-276 (2018).
- 776 41. Aschard, H. *et al.* Evidence for large-scale gene-by-smoking interaction effects on
777 pulmonary function. *Int J Epidemiol* **46**, 894-904 (2017).
- 778 42. Pulley, J.M. *et al.* Accelerating Precision Drug Development and Drug Repurposing
779 by Leveraging Human Genetics. *ASSAY and Drug Development Technologies* **15**,
780 113-119 (2017).

- 781 43. Yengo, L. *et al.* Meta-analysis of genome-wide association studies for height and
782 body mass index in ~700,000 individuals of European ancestry. *bioRxiv* (2018).
- 783 44. Wain, L.V. *et al.* Whole exome re-sequencing implicates CCDC38 and cilia structure
784 and function in resistance to smoking related airflow obstruction. *PLoS Genet* **10**,
785 e1004314 (2014).
- 786 45. Black, P.N. *et al.* Changes in elastic fibres in the small airways and alveoli in COPD.
787 *Eur Respir J* **31**, 998-1004 (2008).
- 788 46. Løkke, A., Lange, P., Scharling, H., Fabricius, P. & Vestbo, J. Developing COPD: a
789 25 year follow up study of the general population. *Thorax* **61**, 935-939 (2006).
- 790 47. Pulit, S.L., With, S.A.J. & Bakker, P.I.W. Resetting the bar: Statistical significance in
791 whole-genome sequencing-based association studies of global populations. *Genetic*
792 *Epidemiology* **41**, 145-151 (2017).
- 793 48. Martinez, F.J. *et al.* A New Approach for Identifying Patients with Undiagnosed
794 Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* **195**, 748-756
795 (2017).
- 796 49. Strug, L.J. *et al.* Cystic fibrosis gene modifier SLC26A9 modulates airway response
797 to CFTR-directed therapeutics. *Hum Mol Genet* **25**, 4590-4600 (2016).
- 798 50. Pulit, S.L., de With, S.A. & de Bakker, P.I. Resetting the bar: Statistical significance
799 in whole-genome sequencing-based association studies of global populations. *Genet*
800 *Epidemiol* **41**, 145-151 (2017).
- 801 51. Bycroft, C. *et al.* Genome-wide genetic data on ~500,000 UK Biobank participants.
802 *bioRxiv* (2017).
- 803 52. Bulik-Sullivan, B.K. *et al.* LD Score regression distinguishes confounding from
804 polygenicity in genome-wide association studies. *Nature Genetics* **47**, 291 (2015).
- 805 53. The 1000 Genomes Project, C. A map of human genome variation from population-
806 scale sequencing. *Nature* **467**, 1061 (2010).
- 807 54. McCarthy, S. *et al.* A reference panel of 64,976 haplotypes for genotype imputation.
808 *Nature genetics* **48**, 1279-1283 (2016).
- 809 55. Yang, J., Lee, S.H., Goddard, M.E. & Visscher, P.M. GCTA: a tool for genome-wide
810 complex trait analysis. *Am J Hum Genet* **88**, 76-82 (2011).
- 811 56. Palmer, L.J. *et al.* Familial aggregation and heritability of adult lung function: results
812 from the Busselton Health Study. *Eur Respir J* **17**, 696-702 (2001).
- 813 57. Wilk, J.B. *et al.* Evidence for major genes influencing pulmonary function in the
814 NHLBI family heart study. *Genet Epidemiol* **19**, 81-94 (2000).
- 815 58. Wakefield, J. Reporting and interpretation in genome-wide association studies. *Int J*
816 *Epidemiol* **37**, 641-53 (2008).
- 817 59. van de Bunt, M., Cortes, A., Brown, M.A., Morris, A.P. & McCarthy, M.I. Evaluating
818 the Performance of Fine-Mapping Strategies at Common Variant GWAS Loci. *PLoS*
819 *Genet* **11**, e1005535 (2015).
- 820 60. Wang, K., Li, M. & Hakonarson, H. ANNOVAR: functional annotation of genetic
821 variants from high-throughput sequencing data. *Nucleic Acids Res* **38**, e164 (2010).
- 822 61. Shihab, H.A. *et al.* Predicting the functional, molecular, and phenotypic consequences
823 of amino acid substitutions using hidden Markov models. *Hum Mutat* **34**, 57-65
824 (2013).
- 825 62. Jansen, R. *et al.* Conditional eQTL analysis reveals allelic heterogeneity of gene
826 expression. *Hum Mol Genet* **26**, 1444-1451 (2017).
- 827 63. Battle, A., Brown, C.D., Engelhardt, B.E. & Montgomery, S.B. Genetic effects on
828 gene expression across human tissues. *Nature* **550**, 204-213 (2017).
- 829 64. Consortium, E.P. *et al.* An integrated encyclopedia of DNA elements in the human
830 genome. *Nature* **489**, 57-74 (2012).

- 831 65. MacArthur, J. *et al.* The new NHGRI-EBI Catalog of published genome-wide
832 association studies (GWAS Catalog). *Nucleic Acids Research* **45**, D896-D901 (2017).
833 66. Leslie, R., O'Donnell, C.J. & Johnson, A.D. GRASP: analysis of genotype-phenotype
834 results from 1390 genome-wide association studies and corresponding open access
835 database. *Bioinformatics* **30**, i185-94 (2014).

836

837 **URLs**

838 UK Biobank: <http://www.ukbiobank.ac.uk>

839 Variant Effect Predictor: <https://www.ensembl.org/vep>

840 Drug-Gene Interactions Database (DGIDB): <http://www.dgidb.org/data/>

841 ChEMBL: <https://www.ebi.ac.uk/chembl/drug/indications>

842 GWAS catalog: <https://www.ebi.ac.uk/gwas/>

843 GRASP: <https://grasp.nhlbi.nih.gov/Overview.aspx>

844

845 **Affiliations:**

- 846 1. Department of Health Sciences, University of Leicester, Leicester, LE1 7RH, UK
- 847 2. Population Health and Immunity Division, The Walter and Eliza Hall Institute of Medical
848 Research, 1G Royal Pde, 3052 Parkville, Australia
- 849 3. Department of Medical Biology, University of Melbourne, 3010 Parkville, Australia
- 850 4. Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, MA, USA
- 851 5. Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Boston, MA,
852 USA
- 853 6. Target Sciences, GlaxoSmithKline, Collegeville, PA, US
- 854 7. Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok,
855 Thailand
- 856 8. Division of Genetics, Genomics and Precision Medicine, Department of Medicine, University of
857 Arizona, Tucson AZ, USA
- 858 9. Nuffield Department of Population Health, University of Oxford, Oxford, OX3 7LF, UK
- 859 10. Medical Research Council Population Health Research Unit, University of Oxford, Oxford, OX3
860 7LF, UK
- 861 11. The University of British Columbia Centre for Heart Lung Innovation, St Paul's Hospital,
862 Vancouver, BC, Canada
- 863 12. MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, Cambridge, CB2
864 0QQ, UK
- 865 13. Department of Epidemiology and Biostatistics, MRC–PHE Centre for Environment & Health,
866 School of Public Health, Imperial College London, London, W2 1PG, UK
- 867 14. A list of contributors can be found in the Supplementary Appendix
- 868 15. Interfaculty Institute for Genetics and Functional Genomics, Department of Functional
869 Genomics, University Medicine Greifswald, 17475 Greifswald, Germany
- 870 16. Centre for Global Health Research, Usher Institute for Population Health Sciences and
871 Informatics, University of Edinburgh, Edinburgh, EH8 9AG, Scotland
- 872 17. Centre for Cardiovascular Sciences, Queen's Medical Research Institute, University of
873 Edinburgh, Edinburgh, EH16 4TJ, Scotland
- 874 18. Department of Biostatistics, University of Liverpool, Liverpool L69 3GL, UK
- 875 19. MRC/BHF Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care,
876 University of Cambridge, Cambridge CB1 8RN, UK
- 877 20. Flatiron Institute, Simons Foundation, New York, New York, USA
- 878 21. Busselton Population Medical Research Institute, Sir Charles Gairdner Hospital, Nedlands WA
879 6009, Australia
- 880 22. School of Population Health, The University of Western Australia, Crawley WA 6009, Australia
- 881 23. PathWest Laboratory Medicine of WA, Sir Charles Gairdner Hospital, Crawley WA 6009,
882 Australia
- 883 24. School of Pathology and Laboratory Medicine, The University of Western Australia, Crawley WA
884 6009, Australia
- 885 25. Institute of Epidemiology, Helmholtz Zentrum Muenchen – German Research Center for
886 Environmental Health, Neuherberg, Germany
- 887 26. Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, Ludwig-
888 Maximilians-Universität, Munich, Germany

- 889 27. Comprehensive Pneumology Center Munich (CPC-M), Member of the German Center for Lung
890 Research (DZL), Neuherberg, Germany
- 891 28. Swiss Tropical and Public Health Institute, Basel, Switzerland
- 892 29. University of Basel, Switzerland
- 893 30. Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh
894 EH8 9JZ, UK
- 895 31. Medical Genetics Section, Centre for Genomic and Experimental Medicine, Institute of Genetics
896 and Molecular Medicine, University of Edinburgh, Edinburgh, EH4 2XU, UK
- 897 32. Medical Research Council Human Genetics Unit, Institute of Genetics and Molecular Medicine,
898 University of Edinburgh, Edinburgh EH4 2XU, UK
- 899 33. Department of Immunology, Genetics and Pathology, Uppsala Universitet, Science for Life
900 Laboratory, Husargatan 3, Uppsala, SE-75108, Sweden
- 901 34. Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Helsinki, Finland
- 902 35. The National Institute for Health and Welfare (THL), Helsinki, Finland
- 903 36. Department of Clinical Chemistry, Fimlab Laboratories, and Finnish Cardiovascular Research
904 Center - Tampere, Faculty of Medicine and Life Sciences, University of Tampere, Tampere 33520,
905 Finland
- 906 37. Department of Clinical Science, University of Bergen, Norway
- 907 38. Department of Epidemiology, Johns Hopkins University School of Public Health, Baltimore, M.D.,
908 USA 21205
- 909 39. Department of Molecular Medicine, Laval University, Québec, Canada
- 910 40. Institut Universitaire de Cardiologie et de Pneumologie de Québec, Laval University, Québec,
911 Canada
- 912 41. University of Groningen, University Medical Center Groningen, Department of Pathology and
913 Medical Biology, GRIAC Research Institute, University of Groningen, Groningen, The Netherlands
- 914 42. National Jewish Health, Denver, CO, USA
- 915 43. Division of Pulmonary, Critical Care and Sleep Medicine, National Jewish Health, Denver, CO,
916 USA
- 917 44. British Heart Foundation Cambridge Centre of Excellence, Division of Cardiovascular Medicine,
918 Addenbrooke's Hospital, Cambridge CB2 0QQ, UK
- 919 45. Department of Human Genetics, Wellcome Trust Sanger Institute, Wellcome Trust Genome
920 Campus, Hinxton, Cambridge CB10 1RQ, UK
- 921 46. NIHR Blood and Transplant Research Unit in Donor Health and Genomics, Department of Public
922 Health and Primary Care, University of Cambridge, Cambridge CB1 8RN, UK
- 923 47. Department of Internal Medicine B - Cardiology, Intensive Care, Pulmonary Medicine and
924 Infectious Diseases, University Medicine Greifswald, 17475 Greifswald, Germany
- 925 48. Department of Molecular Epidemiology, Institute of Epidemiology II, Helmholtz Zentrum
926 Muenchen – German Research Center for Environmental Health, Neuherberg, Germany
- 927 49. UK Small Area Health Statistics Unit, MRC-PHE Centre for Environment and Health, School of
928 Public Health, Imperial College London, London, UK
- 929 50. Imperial College Healthcare NHS Trust, St Mary's Hospital, Paddington, London, UK
- 930 51. Icahn Institute of Genomics and Multiscale Biology, Icahn School of Medicine at Mount Sinai,
931 New York, NY, USA
- 932 52. Department of Epidemiology, University of Colorado Anschutz Medical Campus, Aurora,
933 Colorado, USA

- 934 53. Department of Molecular Biology, Medical Biochemistry, and Pathology, Laval University,
935 Québec, Canada
- 936 54. Department of Epidemiology & Biostatistics, Peking University Health Science Centre, Peking
937 University, Beijing 100191, China
- 938 55. Department of Medical Sciences, Cardiovascular Epidemiology, Uppsala University, Uppsala 751
939 85, Sweden
- 940 56. GSK R&D, Collegeville, PA, US
- 941 57. Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford OX3 7BN, UK
- 942 58. MRL, Merck & Co., Inc., Kenilworth, New Jersey, USA
- 943 59. The Institute of Medical Sciences, Aberdeen Biomedical Imaging Centre, University of Aberdeen,
944 Aberdeen AB25 2ZD, UK
- 945 60. Merck Research Laboratories, Genetics and Pharmacogenomics, Boston, MA, USA
- 946 61. Centre for Genomic and Experimental Medicine, Institute of Genetics & Molecular Medicine,
947 University of Edinburgh, Western General Hospital, Edinburgh EH4 2XU, UK
- 948 62. Centre for Cognitive Ageing and Cognitive Epidemiology, Department of Psychology, The
949 University of Edinburgh, 7 George Square, Edinburgh, EH8 9JZ, UK
- 950 63. Division of Respiratory Medicine and NIHR-Nottingham Biomedical Research Centre, University
951 of Nottingham
- 952 64. Respiratory Division, Department of Medicine, University of British Columbia, Vancouver, BC,
953 Canada
- 954 65. Division of Population Health Sciences, Ninewells Hospital and Medical School, University of
955 Dundee, Dundee DD1 9SY, UK
- 956 66. Psychiatric Genetics Unit, Group of Psychiatry, Mental Health and Addiction, Vall d'Hebron
957 Research Institute (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain
- 958 67. Department of Psychiatry, Hospital Universitari Vall d'Hebron, Barcelona, Spain
- 959 68. Biomedical Network Research Centre on Mental Health (CIBERSAM), Instituto de Salud Carlos
960 III, Barcelona, Spain
- 961 69. VA Boston Healthcare System, Boston, MA, USA
- 962 70. Department of Medicine, Boston University School of Medicine, Boston, MA USA
- 963 71. University of Groningen, University Medical Center Groningen, Department of Pulmonology,
964 GRIAC Research Institute, University of Groningen, Groningen, The Netherlands
- 965 72. Target Sciences - R&D, GSK Medicines Research Centre, Gunnels Wood Road, Stevenage,
966 Hertfordshire, SG1 2NY, UK
- 967 73. UCSF Pulmonary, Critical Care, Allergy and Sleep Medicine, University of California San
968 Francisco, USA
- 969 74. Department of Computer Science, Princeton University, Princeton, New Jersey, USA
- 970 75. Lewis-Sigler Institute for Integrative Genomics, Princeton University, Princeton, New Jersey,
971 USA
- 972 76. Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital, Turku
973 20521, Finland
- 974 77. Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku
975 20520, Finland
- 976 78. Department of Clinical Physiology, Tampere University Hospital, and Finnish Cardiovascular
977 Research Center - Tampere, Faculty of Medicine and Life Sciences, University of Tampere, Tampere
978 33521, Finland

- 979 79. University of Split School of Medicine, Split, Croatia
980 80. Centre for Global Health Research, Usher Institute for Population Health Sciences and
981 Informatics, University of Edinburgh, Edinburgh, Scotland
982 81. Department of Psychology, University of Edinburgh, Edinburgh, EH8 9JZ, UK
983 82. Department of Pulmonary Physiology and Sleep Medicine, Sir Charles Gairdner Hospital,
984 Nedlands WA 6009, Australia
985 83. School of Medicine and Pharmacology, The University of Western Australia, Crawley 6009,
986 Australia
987 84. MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of
988 Edinburgh, Western General Hospital, Crewe Road, Edinburgh, EH4 2XU, Scotland
989 85. Wellcome Trust Sanger Institute, Hinxton, CB10 1SA, UK
990 86. Center for Life Course Health Research, Faculty of Medicine, University of Oulu, 90014 Oulu,
991 Finland
992 87. Biocenter Oulu, University of Oulu, Finland
993 88. Unit of Primary Care, Oulu University Hospital, Kajaanintie 50, P.O. Box 20, FI-90220 Oulu 90029
994 OYS, Finland
995 89. MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of
996 Edinburgh, Western General Hospital, Edinburgh EH42 XU, UK
997 90. Division of Genetics, Genomics and Precision Medicine, University of Arizona, Tucson AZ, USA
998 91. Population Health Research Institute, St George's, University of London, London SW17 0RE, UK
999 92. National Institute for Health Research, Leicester Respiratory Biomedical Research Centre,
1000 Glenfield Hospital, Leicester, LE3 9QP, UK

1001 **Study contributions:**

1002 All authors critically reviewed the manuscript prior to submission.

1003 Contributed to the conception and design of the study: K.S., U.S.S.G., S.K., S.M.K., T.L., P.S.B., T.H.B.,
1004 E.R.B., Y.B., Z.C., J.D.C., J.D., D.L.D., C.G., A.G., K.H., J.D.H., J.Hokanson, P.J., C.L., L.Li, N.L., J.C.M.,
1005 H.R., I.Sayers, D.D.S., R. T-S., J.C.W., P.W., L.M.Y., O.T.R., M.K., O.P., U.G., I.R., I.J.D., N.M.P., H.S.,
1006 A.L.J., J.F.W., E.Z., M.J., N.W., A.S.B., R.A.S., D.A.M., M.H.C., D.P.S., I.P.H., M.D.T., L.V.W.

1007 Undertook data analysis: N.S., A.L.G., A.M.E., V.E.J., B.D.H., C.M., C.Batini, K.A.F., K.S., P.S., Xingnan
1008 Li, R.B., N.F.R., M.O., J.Zhao, M.W., S.W., K.A.K., J.P.C., B.B.S., J.Zhou, J.Hui, M.I., S.E.H., J.M., S.E.,
1009 I.Surakka, V.V., T.L., R.J.A., C.Brandsmas, F.D., J.D.H., P.K.J., Xuan Li, A.Mahajan, J.C.M., D.C.N.,
1010 M.M.P., D.Prokopenko, D.Q., R.R., H.R., D.S., P.R.H.J.T., M.V., L.M.Y., O.G.T., N.M.P., N.W., E.K.S.,
1011 C.H., A.P.M., A.S.B., R.A.S., M.H.C., D.P.S., M.D.T., L.V.W.

1012 Contributed to data acquisition and/or interpretation: N.S., A.L.G., A.M.E., V.E.J., C.M., C.Batini,
1013 K.A.F., K.S., P.S., Xingnan Li, N.F.R., M.O., M.W., K.A.K., B.B.S., S.K., M.I., R.J.A., J.D., F.D., R.E., C.G.,
1014 A.G., A.L.H., J.D.H., G.H., P.K.J., C.L., Xuan Li, K.L., L.Lind, J.L., J.C.M., A.Murray, R.P., M.M.P., M.L.P.,
1015 D.Porteous, D.Prokopenko, D.Q., R.R., H.R., I.Sayers, B.H.S., M.S., L.M.Y., O.G.T., N.M.P., H.S., J.F.W.,
1016 B.S., M.J., N.W., C.H., A.P.M., A.S.B., R.A.S., R.G.W., M.H.C., D.P.S., I.P.H., M.D.T., L.V.W.

1017 Drafted the manuscript: N.S., A.L.G., A.M.E., I.P.H., M.D.T., L.V.W.

1018 **Funding and Acknowledgments:**

1019

1020 **The following authors report specific personal funding from the following grants:**

1021 B.D.H.: NIH K08 HL136928, Parker B. Francis Research Opportunity Award

1022 M.W.: EU Horizon2020 (633212 ALEC)

1023 U.S.S.G.: Economic and Social Research Council (ES/H029745/1)

1024 B.B.S.: Cambridge School of Clinical Medicine MB-PhD programme and MRC/Sackler Prize PhD
1025 Studentship (MR/K50127X/1).

1026 J.D.: J.D. is a BHF Professor, European Research Council Senior Investigator, and NIHR Senior
1027 Investigator.

1028 I.Sayers: MRC (G1000861)

1029 D.S.: D.S. is supported by a VA Research Career Scientist award.

1030 E.Z.: Wellcome Trust (WT098051)

1031 A.P.M.: Wellcome Trust (WT098017 & WT064890)

1032 M.H.C.: This work was supported by NHLBI grants R01HL113264, R01HL137927 (M.H.C. and E.K.S.),
1033 R01HL135142 (M.H.C.). The content is solely the responsibility of the authors and does not
1034 necessarily represent the official views of the NIH. The funding body has no role in the design of the
1035 study and collection, analysis, and interpretation of data and in writing the manuscript.

1036 I.P.H.: The research was partially supported by the NIHR Nottingham Biomedical Research Centre;
1037 the views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the
1038 Department of Health.

1039 M.D.T.: M.D. Tobin is supported by a Wellcome Trust Investigator Award (WT202849/Z/16/Z). M.D.
1040 Tobin and L.V. Wain have been supported by the MRC (MR/N011317/1). The research was partially

1041 supported by the NIHR Leicester Biomedical Research Centre; the views expressed are those of the
1042 author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

1043 L.V.W.: L.V. Wain holds a GSK/British Lung Foundation Chair in Respiratory Research.

1044

1045 **Funding and acknowledgment statements from individual cohorts:**

1046 China Kadoorie Biobank: Kadoorie Charitable Foundation in Hong Kong; the UK Wellcome Trust
1047 (grant numbers 202922/Z/16/Z, 088158/Z/09/Z, 104085/Z/14/Z); Chinese Ministry of Science and
1048 Technology (grant number 2011BAI09B01); National Natural Science Foundation of China (Grant
1049 numbers 81390540, 81390541, 81390544); UK Medical Research Council (grant numbers
1050 MC_PC_13049, MC_PC_14135); GlaxoSmithKline; BHF Centre of Research Excellence, Oxford (grant
1051 number RE/13/1/30181); British Heart Foundation; and Cancer Research UK: The China Kadoorie
1052 Biobank participants; CKB project staff based at Beijing, Oxford and the 10 regional centres; the
1053 China National Centre for Disease Control and Prevention (CDC) and its regional offices for assisting
1054 with the fieldwork. We acknowledge the assistance of BGI (Shenzhen, China) for conducting DNA
1055 extraction and genotyping

1056 COPDGene: See Supplementary Note.

1057 ECLIPSE: The ECLIPSE study (NCT00292552; GSK code SCO104960) was funded by GSK.

1058 GenKOLS: The Norway GenKOLS study (Genetics of Chronic Obstructive Lung Disease, GSK code
1059 RES11080) was funded by GSK.

1060 NETTNAS: The National Emphysema Treatment Trial was supported by the NHLBI N01HR76101,
1061 N01HR76102, N01HR76103, N01HR76104, N01HR76105, N01HR76106, N01HR76107, N01HR76108,
1062 N01HR76109, N01HR76110, N01HR76111, N01HR76112, N01HR76113, N01HR76114, N01HR76115,
1063 N01HR76116, N01HR76118 and N01HR76119, the Centers for Medicare and Medicaid Services and
1064 the Agency for Healthcare Research and Quality. The Normative Aging Study is supported by the
1065 Cooperative Studies Program/ERIC of the US Department of Veterans Affairs and is a component of
1066 the Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC).

1067 SPIROMICS: NIH/NHLBI grants: HHSN268200900013C, HHSN268200900014C, HHSN268200900015C,
1068 HHSN268200900016C, HHSN268200900017C, HHSN268200900018C, HHSN268200900019C (Eugene
1069 Bleecker), HHSN268200900020C. Supplemented by contributions made through the Foundation for
1070 the NIH from AstraZeneca; Bellerophon Pharmaceuticals; Boehringer-Ingelheim Pharmaceuticals,
1071 Inc; Chiesi Farmaceutici SpA; Forest Research Institute, Inc; GSK; Grifols Therapeutics, Inc; Ikaria, Inc;
1072 Nycomed GmbH; Takeda Pharmaceutical Company; Novartis Pharmaceuticals Corporation;
1073 Regeneron Pharmaceuticals, Inc; and Sanofi. The authors thank the SPIROMICS participants and
1074 participating physicians, investigators and staff for making this research possible. More information
1075 about the study and how to access SPIROMICS data is at www.spiromics.org. We would like to
1076 acknowledge the following current and former investigators of the SPIROMICS sites and reading
1077 centers: Neil E Alexis, PhD; Wayne H Anderson, PhD; R Graham Barr, MD, DrPH; Eugene R Bleecker,
1078 MD; Richard C Boucher, MD; Russell P Bowler, MD, PhD; Elizabeth E Carretta, MPH; Stephanie A
1079 Christenson, MD; Alejandro P Comellas, MD; Christopher B Cooper, MD, PhD; David J Couper, PhD;
1080 Gerard J Criner, MD; Ronald G Crystal, MD; Jeffrey L Curtis, MD; Claire M Doerschuk, MD; Mark T
1081 Dransfield, MD; Christine M Freeman, PhD; MeiLan K Han, MD, MS; Nadia N Hansel, MD, MPH;
1082 Annette T Hastie, PhD; Eric A Hoffman, PhD; Robert J Kaner, MD; Richard E Kanner, MD; Eric C

1083 Kleeerup, MD; Jerry A Krishnan, MD, PhD; Lisa M LaVange, PhD; Stephen C Lazarus, MD; Fernando J
1084 Martinez, MD, MS; Deborah A Meyers, PhD; John D Newell Jr, MD; Elizabeth C Oelsner, MD, MPH;
1085 Wanda K O’Neal, PhD; Robert Paine, III, MD; Nirupama Putcha, MD, MHS; Stephen I. Rennard, MD;
1086 Donald P Tashkin, MD; Mary Beth Scholand, MD; J Michael Wells, MD; Robert A Wise, MD; and
1087 Prescott G Woodruff, MD, MPH. The project officers from the Lung Division of the National Heart,
1088 Lung, and Blood Institute were Lisa Postow, PhD, and Thomas Croxton, PhD, MD.

1089 DeepSEA: The DeepSEA project was primarily supported by US National Institutes of Health (NIH)
1090 grants R01 GM071966 to O.G.T and supported in part by US NIH grant P50 GM071508. O.G.T. is a
1091 senior fellow of the Genetic Networks program of the Canadian Institute for Advanced Research
1092 (CIFAR). Jian Zhou and Olga G Troyanskaya carried out SNV effect prediction analyses in an updated
1093 version of DeepSEA (deepsea.princeton.edu), which contained more lung-related cell lines than the
1094 original version published in Nature Methods in August 2015
1095 (www.nature.com/articles/nmeth.3547).

1096 GSK: This research has been conducted using the UK Biobank Resource under application number
1097 26041.

1098 B58C: Genotyping for the B58C-WTCCC subset was funded by the Wellcome Trust (076113/B/04/Z).
1099 The B58C-T1DGC genotyping utilized resources provided by the Type 1 Diabetes Genetics
1100 Consortium, a collaborative clinical study sponsored by the National Institute of Diabetes and
1101 Digestive and Kidney Diseases (NIDDK), National Institute of Allergy and Infectious Diseases (NIAID),
1102 National Human Genome Research Institute (NHGRI), National Institute of Child Health and Human
1103 Development (NICHD), and Juvenile Diabetes Research Foundation International (JDRF) and
1104 supported by U01 DK062418. B58C-T1DGC GWAS data were deposited by the Diabetes and
1105 Inflammation Laboratory, Cambridge Institute for Medical Research (CIMR), University of
1106 Cambridge, which is funded by Juvenile Diabetes Research Foundation International, the Wellcome
1107 Trust and the National Institute for Health Research Cambridge Biomedical Research Centre; the
1108 CIMR is in receipt of a Wellcome Trust Strategic Award (079895). The B58C-GABRIEL genotyping was
1109 supported by a contract from the European Commission Framework Programme 6 (018996) and
1110 grants from the French Ministry of Research.

1111 BHS: Generous support for the 1994/5 follow-up study from Healthway, Western Australia, and
1112 support from The Great Wine Estates of the Margaret River region of Western Australia. The study
1113 also acknowledges the numerous Busselton community volunteers who assisted with data collection
1114 and the study participants from the Shire of Busselton.

1115 CROATIA-Korcula/Split/Vis: MRC, the Ministry of Science, Education and Sport in the Republic of
1116 Croatia (216-1080315-0302) and the Croatian Science Foundation (grant 8875) (funding to I. Rudan,
1117 C. Hayward, S.M. Kerr, O. Polasek, V. Vitart, and J. Marten).

1118 H2000: Medical Research Fund of the Tampere University Hospital.

1119 KORA F4 and KORA S3: The KORA study was initiated and financed by the Helmholtz Zentrum
1120 München – German Research Center for Environmental Health, which is funded by the German
1121 Federal Ministry of Education and Research (BMBF) and by the State of Bavaria. Furthermore, KORA
1122 research was supported within the Munich Center of Health Sciences (MC-Health), Ludwig-
1123 Maximilians-Universität, as part of LMUinnovativ and by the Competence Network Asthma and

- 1124 COPD (ASCONET), network COSYCONET (subproject 2, BMBF FKZ 01GI0882) funded by the German
1125 Federal Ministry of Education and Research (BMBF):
- 1126 LBC1936: Phenotype collection in the Lothian Birth Cohort 1936 was supported by Age UK (The
1127 Disconnected Mind project). Genotyping was funded by the Biotechnology and Biological Sciences
1128 Research Council (BBSRC). The work was undertaken by The University of Edinburgh Centre for
1129 Cognitive Ageing and Cognitive Epidemiology, part of the cross council Lifelong Health and Wellbeing
1130 Initiative (MR/K026992/1). Funding from the BBSRC and MRC is gratefully acknowledged.
- 1131 NSPHS: Swedish Medical Research Council (K2007-66X-20270-01-3, 2011-5252, 2012-2884 and
1132 2011-2354), the Foundation for Strategic Research (SSF). NSPHS as part of European Special
1133 Populations Research Network (EUROSPAN) was also supported by the European Commission FP6
1134 STRP (01947, LSHG-CT-2006-01947).
- 1135 ORCADES: Supported by the Chief Scientist Office of the Scottish Government (CZB/4/276,
1136 CZB/4/710), the Royal Society, the MRC Human Genetics Unit, Arthritis Research UK and the
1137 European Union framework program 6 EUROSPAN project (contract no. LSHG-CT-2006-018947).
1138 ORCADES DNA extractions were performed at the Wellcome Trust Clinical Research Facility in
1139 Edinburgh.
- 1140 SAPALDIA: Swiss National Science Foundation (33CS30-148470/1&2, 33CSCO-134276/1, 33CSCO-
1141 108796, 324730_135673, 3247BO-104283, 3247BO-104288, 3247BO-104284, 3247-065896, 3100-
1142 059302, 3200-052720, 3200-042532, 4026-028099, PMPDP3_129021/1, PMPDP3_141671/1), the
1143 Federal Office for the Environment, the Federal Office of Public Health, the Federal Office of Roads
1144 and Transport, the canton's government of Aargau, Basel-Stadt, Basel-Land, Geneva, Luzern, Ticino,
1145 Valais, and Zürich, the Swiss Lung League, the canton's Lung League of Basel Stadt/ Basel Landschaft,
1146 Geneva, Ticino, Valais, Graubünden and Zurich, Stiftung ehemals Bündner Heilstätten, SUVA,
1147 Freiwillige Akademische Gesellschaft, UBS Wealth Foundation, Talecris Biotherapeutics GmbH,
1148 Abbott Diagnostics, European Commission 018996 (GABRIEL) and the Wellcome Trust (WT
1149 084703MA). The SAPALDIA study could not have been done without the help of the study
1150 participants, technical and administrative support and the medical teams and field workers at the
1151 local study sites. Local fieldworkers : Aarau: S Brun, G Giger, M Sperisen, M Stahel, Basel: C Bürli, C
1152 Dahler, N Oertli, I Harreh, F Karrer, G Novicic, N Wyttenbacher, Davos: A Saner, P Senn, R Winzeler,
1153 Geneva: F Bonfils, B Blicharz, C Landolt, J Rochat, Lugano: S Boccia, E Gehrig, MT Mandia, G Solari, B
1154 Viscardi, Montana: AP Bieri, C Darioly, M Maire, Payerne: F Ding, P Danieli A Vonnez, Wald: D
1155 Bodmer, E Hochstrasser, R Kunz, C Meier, J Rakic, U Schafroth, A Walder.
- 1156 YFS: The Young Finns Study has been financially supported by the Academy of Finland: grants
1157 286284, 134309 (Eye), 126925, 121584, 124282, 129378 (Salve), 117787 (Gendi), and 41071 (Skidi);
1158 the Social Insurance Institution of Finland; Competitive State Research Financing of the Expert
1159 Responsibility area of Kuopio, Tampere and Turku University Hospitals (grant X51001); Juho Vainio
1160 Foundation; Paavo Nurmi Foundation; Finnish Foundation for Cardiovascular Research ; Finnish
1161 Cultural Foundation; Tampere Tuberculosis Foundation; Emil Aaltonen Foundation; Yrjö Jahnsson
1162 Foundation; Signe and Ane Gyllenberg Foundation; Diabetes Research Foundation of Finnish
1163 Diabetes Association; and EU Horizon 2020 (grant 755320 for TAXINOMISIS).
- 1164 EPIC: Cancer Research UK and the MRC. The authors thank the participants, General Practitioners
1165 and staff of the EPIC-Norfolk study team, and collaborators for their contribution.

1166

1167 Generation Scotland: Chief Scientist Office of the Scottish Government Health Directorate
1168 (CZD/16/6), the Scottish Funding Council (HR03006), Medical Research Council UK, and a Wellcome
1169 Trust Strategic Award 'Stratifying Resilience and Depression Longitudinally'
1170 (104036/Z/14/Z)(STRADL). Genotyping of the GS:SFHS samples was carried out by the Edinburgh
1171 Clinical Research Facility, University of Edinburgh. We are grateful to all the families who took part in
1172 the Generation Scotland: Scottish Family Health Study, the general practitioners and Scottish School
1173 of Primary Care for their help in recruiting them, and the whole Generation Scotland team, which
1174 includes academic researchers, IT staff, laboratory technicians, statisticians and research managers.

1175 NFBC1966: received financial support from the Academy of Finland (project grants 104781, 120315,
1176 129269, 1114194, 24300796, Center of Excellence in Complex Disease Genetics and SALVE),
1177 University Hospital Oulu, Biocenter, University of Oulu, Finland (75617), NHLBI grant 5R01HL087679-
1178 02 through the STAMPEED program (1RL1MH083268-01), NIH/NIMH (5R01MH63706:02), ENGAGE
1179 project and grant agreement HEALTH-F4-2007-201413, EU FP7 EurHEALTHAgeing -277849, the
1180 Medical Research Council, UK (G0500539, G0600705, G1002319, PrevMetSyn/SALVE) and the MRC,
1181 Centenary Early Career Award. The program is currently being funded by the H2020-633595
1182 DynaHEALTH action, academy of Finland EGEA-project (285547) and EU H2020 ALEC project (Grant
1183 Agreement 633212).

1184 NFBC1986: received financial support from EU QLGI-CT-2000-01643 (EUROBLCS) Grant no. E51560,
1185 NorFA Grant no. 731, 20056, 30167, USA / NIH 2000 G DF682 Grant no. 50945.

1186 PIVUS: Swedish Research Council, Swedish Heart-Lung Foundation, Swedish Diabetes Foundation
1187 and Uppsala University. Genotyping and analysis was funded by the Wellcome Trust under awards
1188 WT064890 and WT098017. The PIVUS investigators express their deepest gratitude to the study
1189 participants.

1190 SHIP / SHIP-Trend: Federal Ministry of Education and Research (01ZZ9603, 01ZZ0103, 01ZZ0403,
1191 03ZIK012), and the German Research Foundation (GR 1912/5-1).

1192 UKHLS: Economic and Social Research Council (ES/H029745/1). These data are from Understanding
1193 Society: The UK Household Longitudinal Study, which is led by the Institute for Social and Economic
1194 Research at the University of Essex and funded by the Economic and Social Research Council. The
1195 data were collected by NatCen and the genome wide scan data were analysed by the Wellcome
1196 Trust Sanger Institute. The Understanding Society DAC have an application system for genetics data
1197 and all use of the data should be approved by them. The application form is at:
1198 <https://www.understandingsociety.ac.uk/about/health/data>. A full list of authors is available in the
1199 Supplementary Note.

1200 VIKING: Supported by a MRC Human Genetics Unit quinquennial programme grant "QTL in Health
1201 and Disease". VIKING DNA extractions and genotyping were performed at the Edinburgh Clinical
1202 Research Facility, University of Edinburgh.

1203 pQTL: The INTERVAL study: NHSBT (11-01-GEN) and the NIHR-BTRU in Donor Health and Genomics
1204 (NIHR BTRU-2014-10024) at the University of Cambridge in partnership with NHSBT. This study was
1205 partially funded by Merck. The views expressed are those of the authors and not necessarily those of
1206 the NHS, the NIHR, the Department of Health of England, or NHSBT. The Cardiovascular
1207 Epidemiology Unit at the University of Cambridge: UK MRC (G0800270), BHF (SP/09/002), UK NIHR

1208 Cambridge Biomedical Research Centre, ERC (268834), and European Commission Framework
1209 Programme 7 (HEALTH-F2-2012-279233):

1210 **Competing interests:**

1211 The following authors report potential competing interests:

1212

1213 L.V.W.: Louise V. Wain has received grant support from GSK.

1214

1215 M.D.T.: Martin D. Tobin has received grant support from GSK.

1216

1217 I.P.H.: Ian P. Hall has received support from GSK and BI.

1218

1219 K.S.: Kijoung Song is an employee of GlaxoSmithKline and may own company stock.

1220

1221 J.D.: John Danesh reports personal fees and non-financial support from Merck Sharp & Dohme
1222 (MSD) and Novartis, and grants from British Heart Foundation, European Research Council, MSD,
1223 NIHR, NHS Blood and Transplant, Novartis, Pfizer, UK MRC, Wellcome Trust, and AstraZeneca.

1224

1225 J.D.H.: Josh D. Hoffman is an employee of GlaxoSmithKline and may own company stock.

1226

1227 N.L.: Nick Locantore is an employee of GlaxoSmithKline and may own company stock.

1228

1229 J.C.M.: Joseph. C. Maranville was a Merck employee during this study, and is now a Celgene
1230 employee.

1231

1232 H.R.: Heiko Runz was a Merck employee during this study, and is now a Biogen employee.

1233

1234 R. T-S.: Ruth Tal-Singer is an employee of GlaxoSmithKline and owns company stock.

1235

1236 J.C.W.: John C. Whittaker is an employee of GlaxoSmithKline and may own company stock.

1237

1238 L.M.Y.: Laura M. Yerges Armstrong is an employee of GlaxoSmithKline and may own company stock.

1239

1240 E.K.S.: In the past three years, Edwin K. Silverman received honoraria from Novartis for Continuing
1241 Medical Education Seminars and grant and travel support from GlaxoSmithKline

1242

1243 A.S.B.: Adam S. Butterworth reports grants from Merck, Pfizer, Novartis, Biogen and Bioverativ and
1244 personal fees from Novartis

1245

1246 R.A.S.: Robert A. Scott is an employee of GlaxoSmithKline and may own company stock.

1247

1248 M.H.C.: Michael H. Cho has received grant support from GSK.