

Dissecting COPD subtypes using multi-trait genetics

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Figures

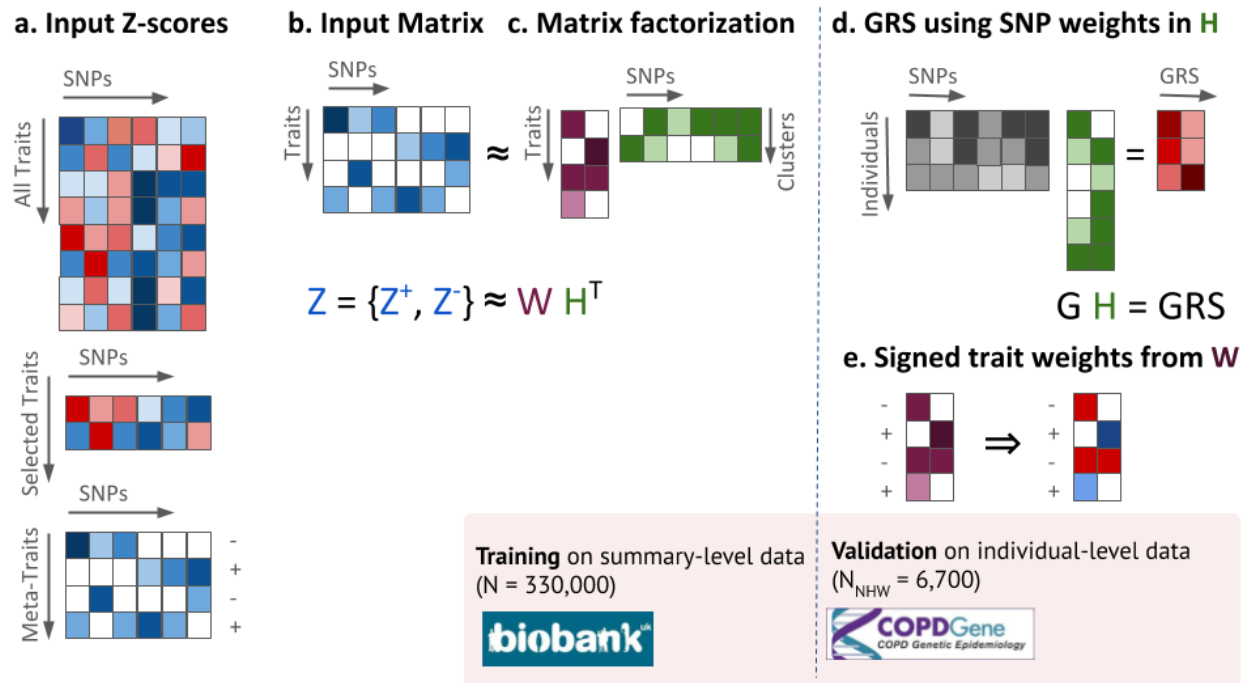


Figure 1: The analysis pipeline.

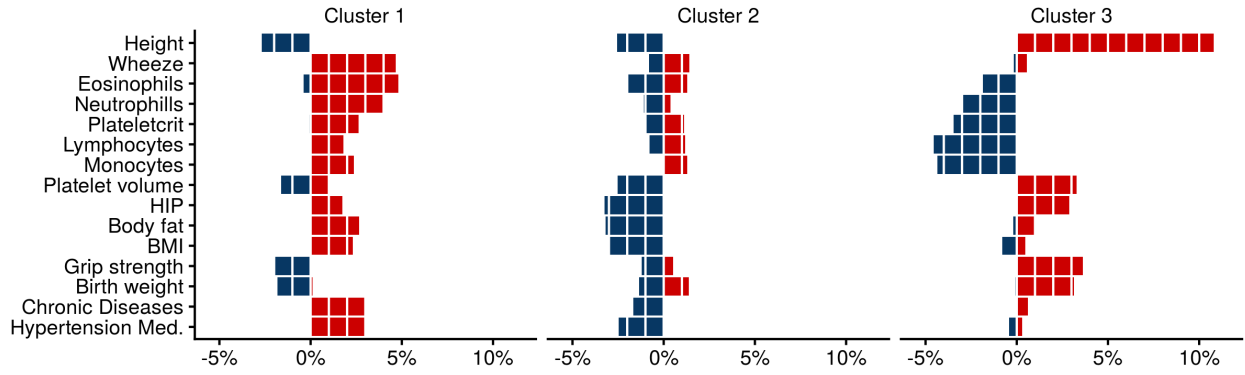


Figure 2: Top trait weights.

Top selected traits have trait weights at least 3% in any cluster. Three columns of weight matrix W from clustering $Z \approx WH^T$ were used to extract normalized weights (unit sum of column elements) for each of three clusters.

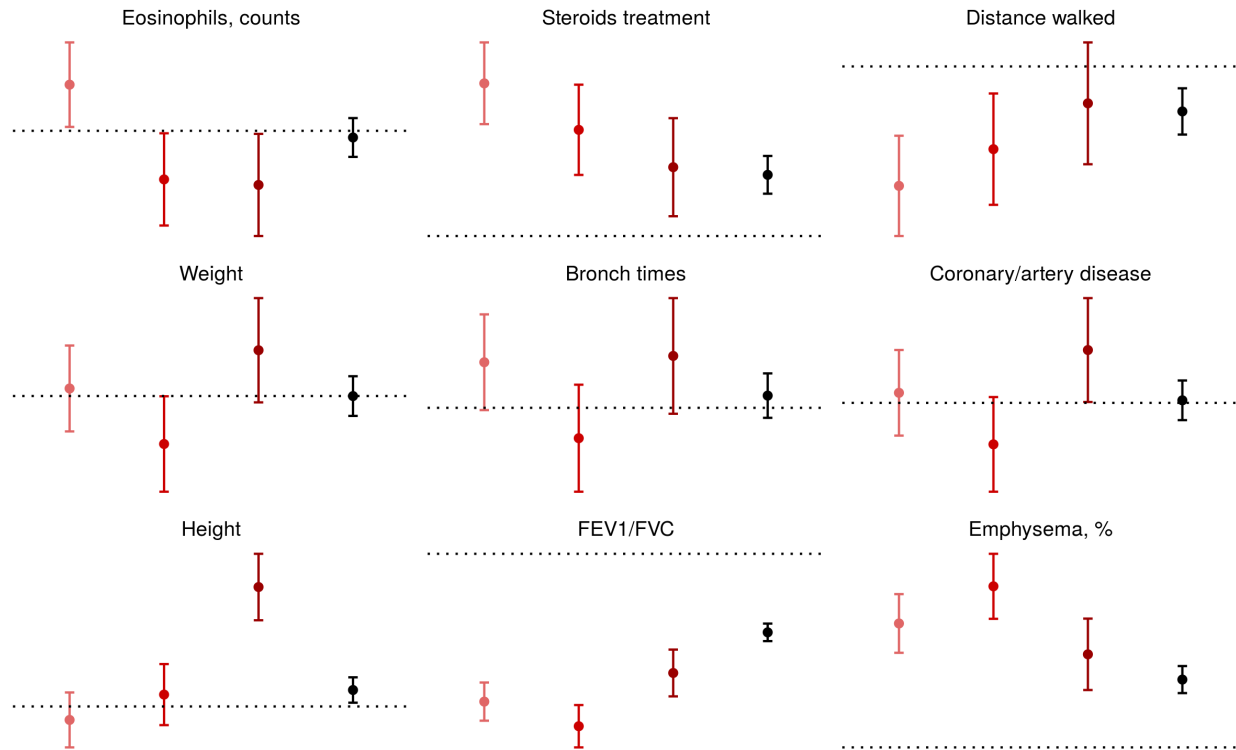


Figure 3: Marginal effects of GRSs on COPDGene traits.

Point estimates of effect sizes and their 95% confidence intervals are displayed for cluster-specific GRSs (GRS1-3; red) and unweighted GRS (GRS0; black). The horizontal dashed line corresponds to zero level.

Selected traits show a significant evidence of cluster-specific GRSs fitted in a joint model (all GRS0 and GRS1-3 are included; see Sup. Table S1).

Supplementary Figures

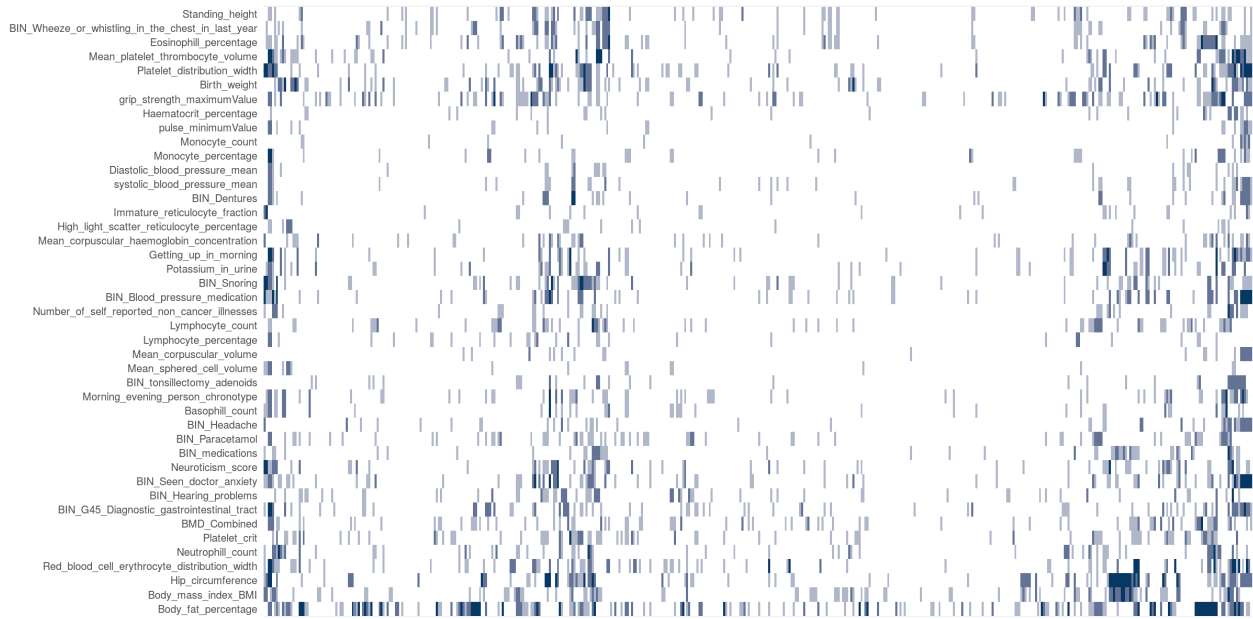


Figure S1: The heatmap of matrix of Z-scores of 44 traits and 482 SNPs, input to the NMF clustering algorithm.

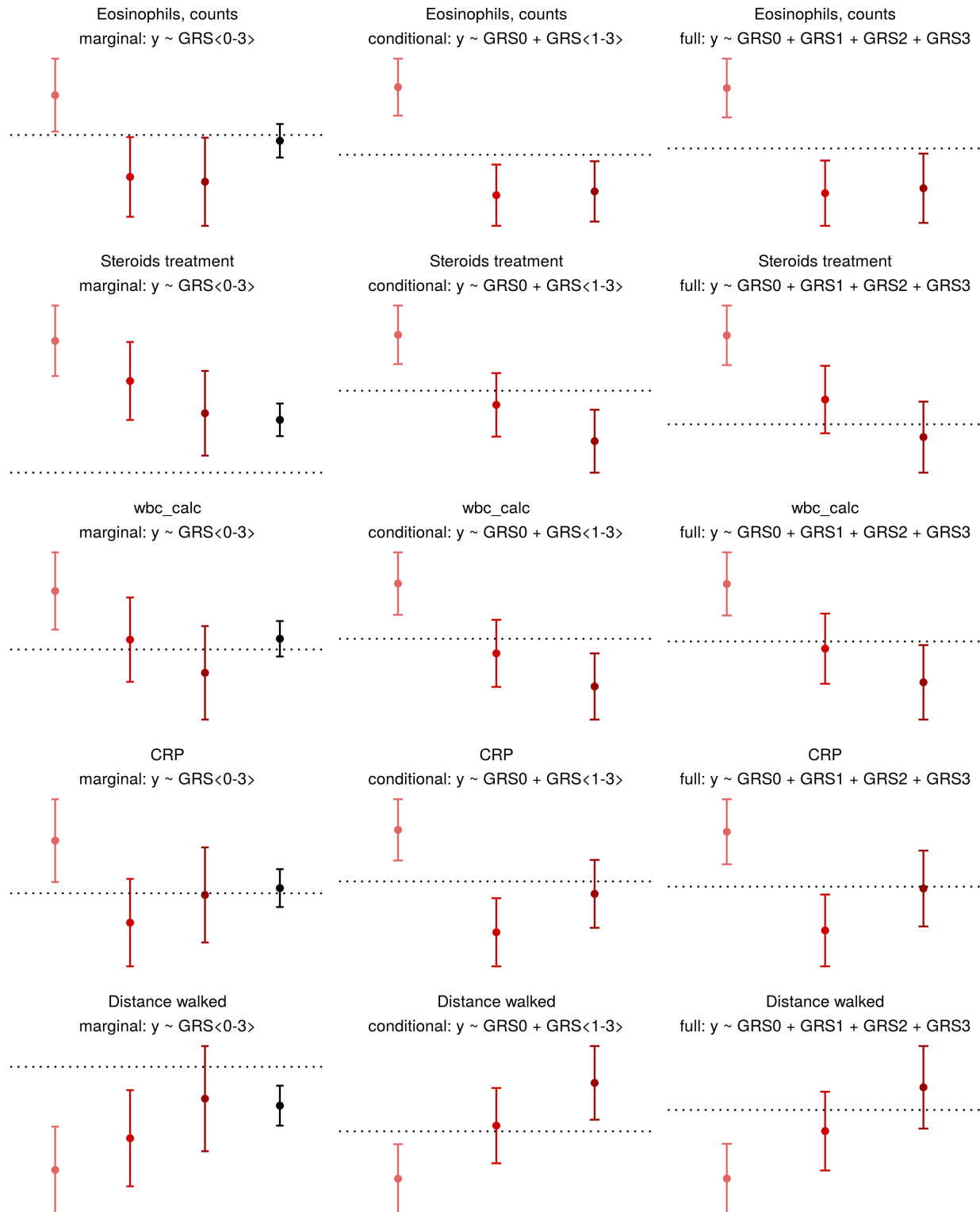


Figure S2: Marginal, conditional and join GRS effects for selected traits relevant to cluster 1.

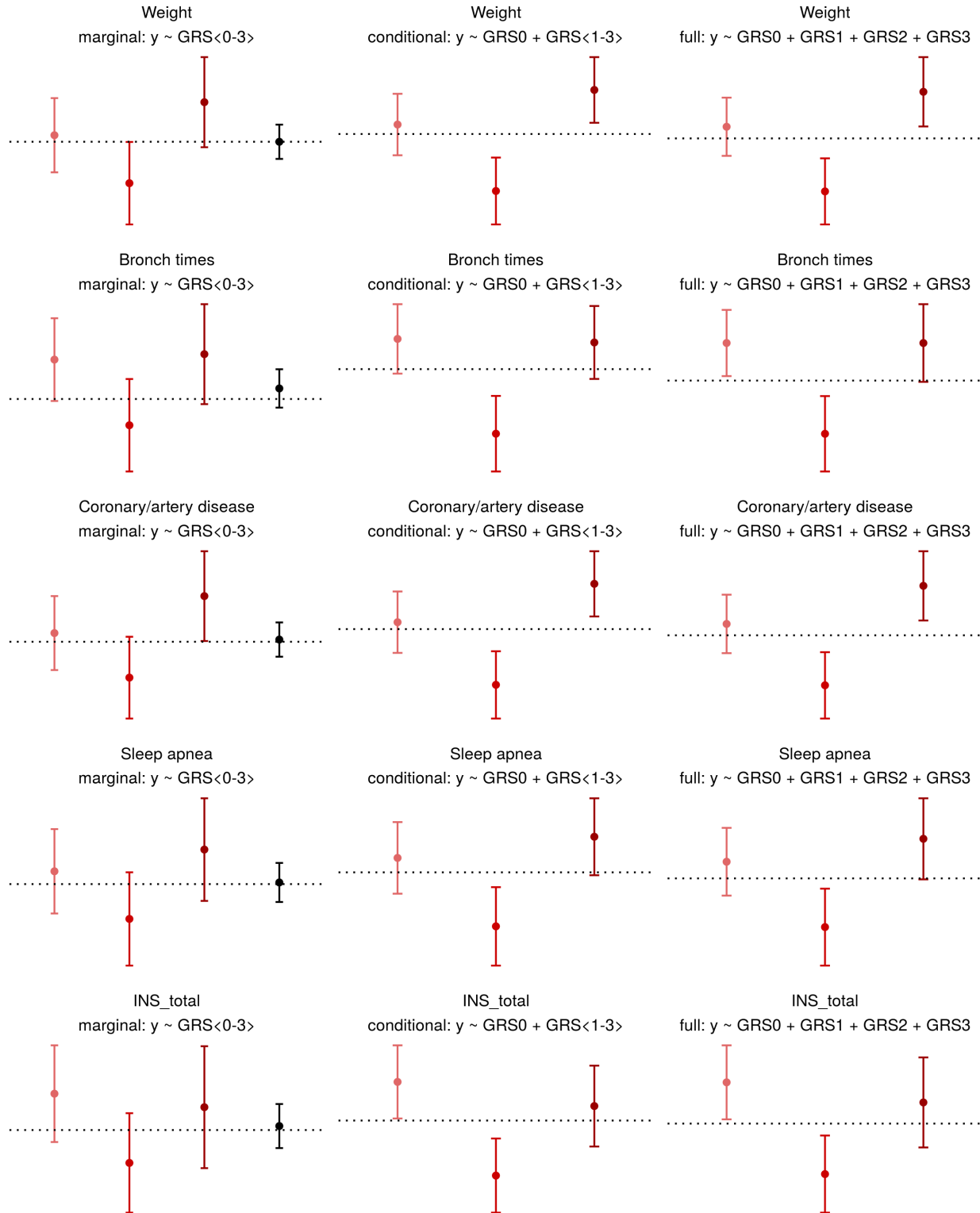


Figure S3: Marginal, conditional and join GRS effects for selected traits relevant to cluster 2.

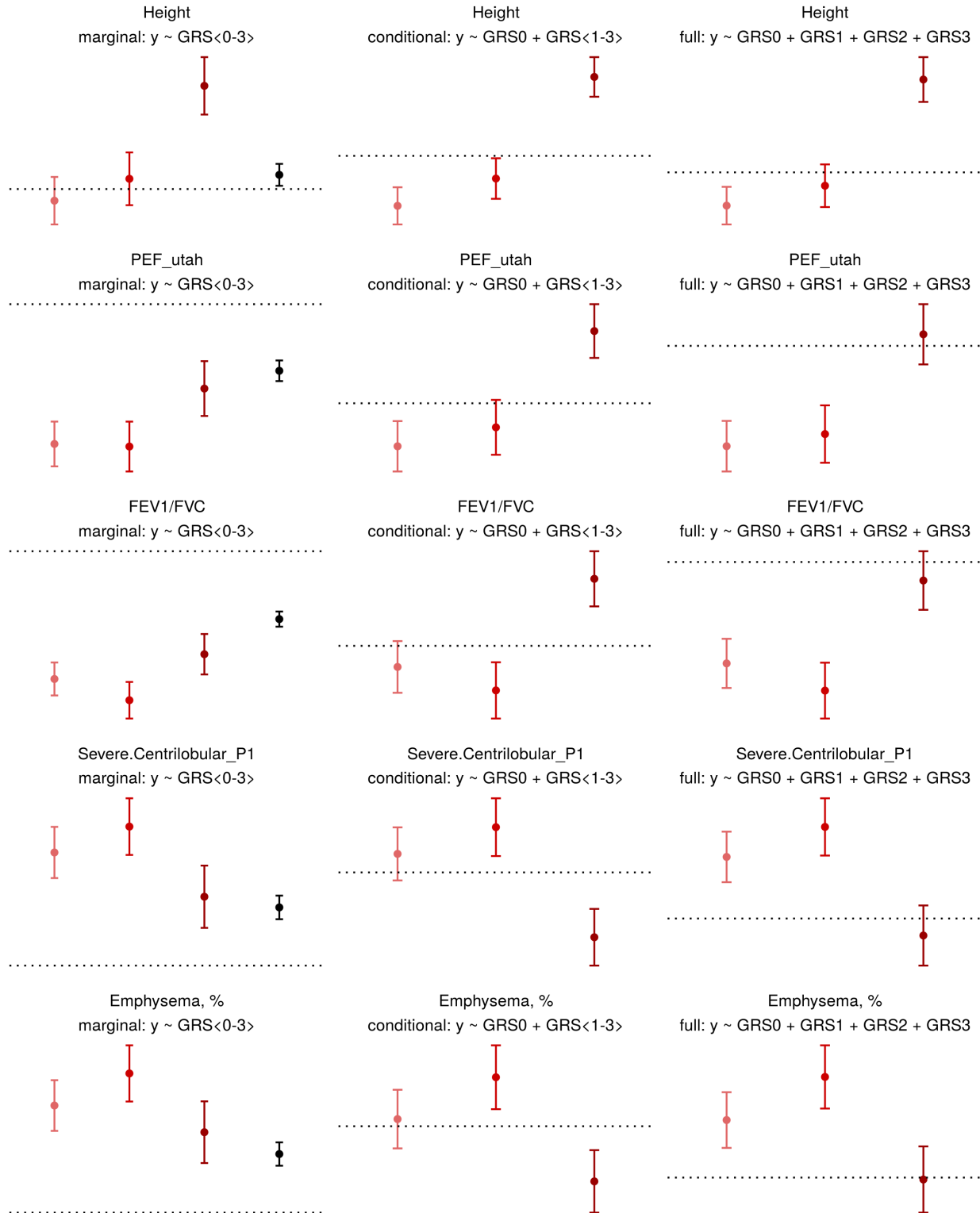


Figure S4: Marginal, conditional and joint GRS effects for selected traits relevant to cluster 3.

Supplementary Tables

Table S1: COPD Gene traits with evidence of cluster-specific GRS effect at FDR < 0.1

Trait	Group	Type	N	P(GRS0)	P(GRS1-3)	Q(GRS1-3)	Cluster
eosinphl_calc	Counts	num2inorm	3,866	0.5	1.9e-05	0.00057	1
TreatSteroids	Basic	bin01	6,677	1.7e-10	0.00039	0.0074	1
wbc_calc	Counts	num2inorm	3,866	0.24	0.0013	0.016	1
CRP	Biomarker_RBM	num	596	0.59	0.0017	0.016	1
eosinphl_pct_calc	Counts	num2inorm	3,866	0.21	0.0066	0.051	1
SELE	Biomarker_RBM	num	596	0.87	0.0076	0.054	1
distwalked	Basic	num2inorm	6,573	0.00014	0.011	0.071	1
neutrophl_calc	Counts	num2inorm	3,866	0.014	0.012	0.072	1
monocyt_calc	Counts	num2inorm	3,866	0.023	0.013	0.077	1
HGF	Biomarker_RBM	num	596	0.6	0.017	0.094	1
Weight_KG	Basic	num2inorm	6,681	1	0.0015	0.016	2
CoronaryArtery	Basic	bin01	6,678	0.8	0.0016	0.016	2
BronchTimes	Basic	num2inorm	3,165	0.28	0.0036	0.033	2
Insp_Below910_Slicer	Basic	num2inorm	6,307	7.4e-22	0.0038	0.033	2
INS_total	Biomarker_RBM	num2inorm	94	0.72	0.011	0.071	2
BMI	Basic	num2inorm	6,678	0.35	0.014	0.079	2
SleepApnea	Basic	bin01	5,869	0.87	0.019	0.1	2
Height_CM	Basic	num2inorm	6,681	0.011	2.7e-14	6.7e-12	3
PEF_utah	Basic	num2inorm	6,659	1.3e-36	8.2e-07	7.8e-05	3
pre_FEF2575	Basic	num2inorm	6,614	1.4e-73	1e-06	7.8e-05	3
FEF2575_utah	Basic	num2inorm	6,659	6.2e-66	1.3e-06	7.8e-05	3
FEV1_FVC_utah	Basic	num2inorm	6,659	4.1e-69	5.5e-06	0.00027	3
Emph_Extent_P1	Basic	num2inorm	5,205	7.7e-13	1.1e-05	0.00046	3
Severe.Centrilobular_P1	Basic	num2inorm	6,465	4e-22	1.8e-05	0.00057	3
pre_FEV1_FVC	Basic	num2inorm	6,614	1.7e-74	2.2e-05	6e-04	3
pctEmph_UpperThird_Slicer	Basic	num2inorm	6,201	8.2e-22	0.00011	0.0028	3
Panlobular_P1	Basic	num2inorm	6,465	1.2e-25	0.00039	0.0074	3
Slicer_15pctIn_Total	Basic	num2inorm	6,307	4.9e-22	0.00039	0.0074	3
pctEmph_Slicer	Basic	num2inorm	6,307	8.2e-23	0.00057	0.0093	3
Moderate.Centrilobular_P1	Basic	num2inorm	6,465	5e-20	0.00058	0.0093	3
Insp_Below950_Slicer	Basic	num2inorm	6,307	7.2e-22	0.00075	0.011	3
COPD_finalGold_P1	Basic	bin01	5,351	2.1e-57	0.00088	0.013	3
Normal_P1	Basic	num2inorm	6,464	3e-15	0.0014	0.016	3
UpperThird_LowerThird_Slicer	Basic	num2inorm	6,201	0.0019	0.0015	0.016	3
DLCOpp_P2	Basic	num2inorm	3,535	4.7e-06	0.0016	0.016	3
prm_emphysema	Basic	num2inorm	5,561	5.9e-24	0.0016	0.016	3
Slicer_15pctEx_Total	Basic	num2inorm	5,802	7.1e-30	0.0022	0.021	3
FumesJobEver	Basic	bin01	6,314	0.74	0.0052	0.043	3
prm_normal	Basic	num2inorm	5,561	7e-30	0.0058	0.047	3
Exp_Below856_Slicer	Basic	num2inorm	5,802	1.9e-30	0.007	0.051	3
pctGasTrap_Slicer	Basic	num2inorm	5,802	1.9e-30	0.007	0.051	3
Exp_Below910_Slicer	Basic	num2inorm	5,802	7.9e-29	0.0087	0.059	3
SGRQ_scoreImpact	Basic	num2inorm	6,677	4.5e-12	0.0088	0.059	3
SGRQ_scoreTotal	Basic	num2inorm	6,677	2.8e-12	0.011	0.071	3
CC_16_ng_mL	Biomarker_QBR	num2inorm	1,214	0.00011	0.017	0.094	3
Exp_Below950_Slicer	Basic	num2inorm	5,802	9.9e-26	0.018	0.098	3
prm_airtrapping	Basic	num2inorm	5,561	6e-28	0.019	0.099	3

Out of 312 tested COPDGene traits, 47 traits show a significant effect of three cluster-specific GRSs (GRS1-3) in addition to unweighted GRS (GRS0) cluster-specific GRS effects after multiple-testing correction.

Four types of nested models are compared by the Likelihood Ratio Test (LRT): (model 1) trait-specific covariates; (model 2) trait-specific covariates and unweighted GRS (GRS0); (model 3) trait-specific covariates, unweighted GRS (GRS0) and three cluster-specific GRS (GRS1-3); and (models 4) trait-specific covariates, unweighted GRS (GRS0) and a single cluster-specific GRS (either GRS1, GRS2 or GRS3).

Columns: $P(GRS0)$, p-value of comparison between models 1 and 2; $P(GRS1-3)$, (heterogeneity) p-value of comparison between models 2 and 3; and $Q(GRS1-3)$ (q-value) adjusted $P(GRS1-3)$ using the Benjamini-Hochberg (FDR) method with the number of comparisons equal to 312; *Cluster*, the cluster with the strongest marginal cluster-specific GRS assessed by p-value from comparison between model 2 and each model 4.