

SUPPLEMENTARY FIGURES

a

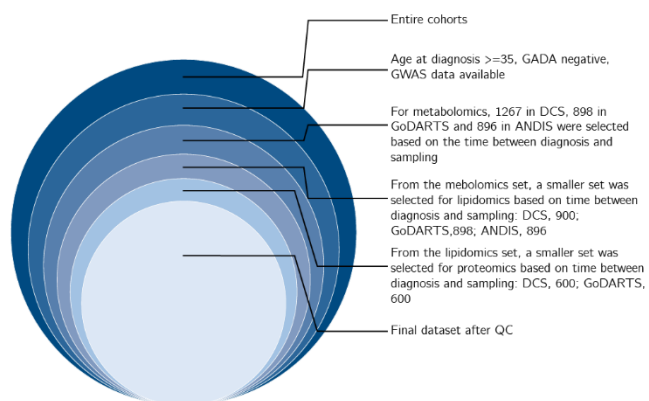


Figure S1. a. Selection of individuals in the study. In a subset of the cohorts, GWAS data was available. From this set, individuals were selected for metabolomics, lipidomics and proteomics. In those individuals which proteomics data also metabolomics and lipidomics data were available.

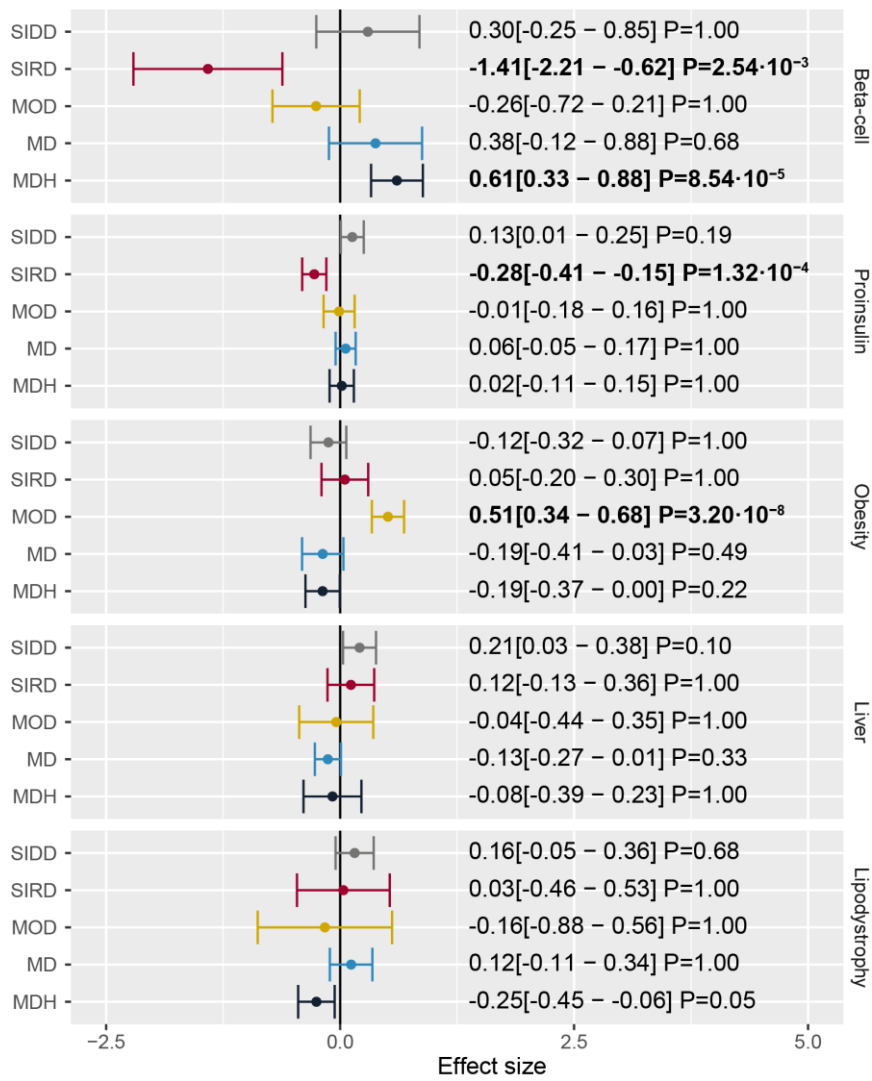


Figure S2. Meta-analysis of genetic risk scores from Udler et al.(1) across the different clusters. Numbers indicate effect size with 95% confidence intervals and the Bonferroni adjusted P-values.

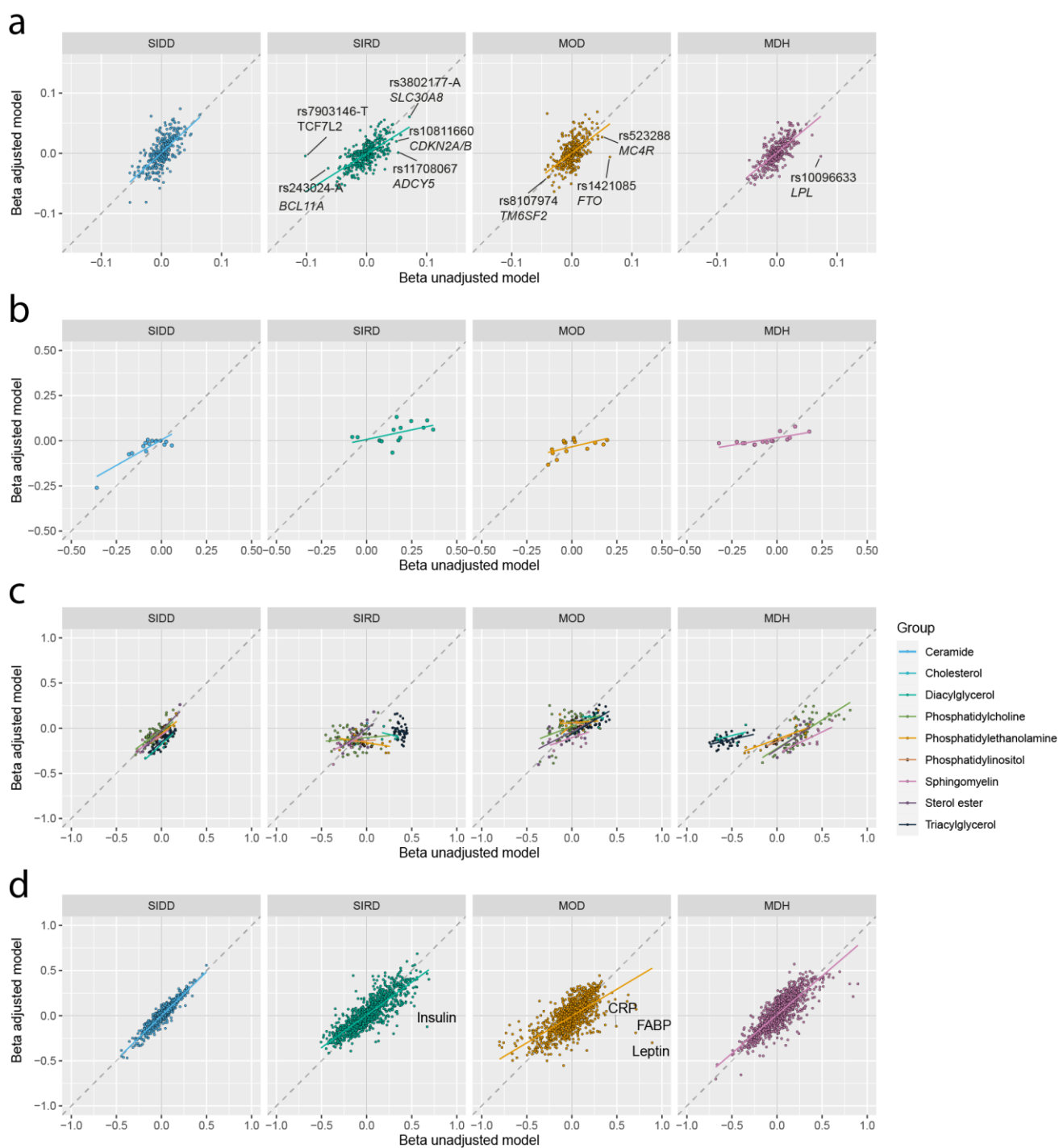


Figure S3. Comparison of effect sizes for genetic data (a), metabolite data (b), lipid data (c) and protein data (d). Effect sizes represent are on a log₁₀ SD scale. X-axis: unadjusted effect sizes. Y-axis: adjusted effect sizes. Models on SIDD were adjusted for HbA1c, SIRD for C-peptide, MOD or BMI and MDH for HDL.

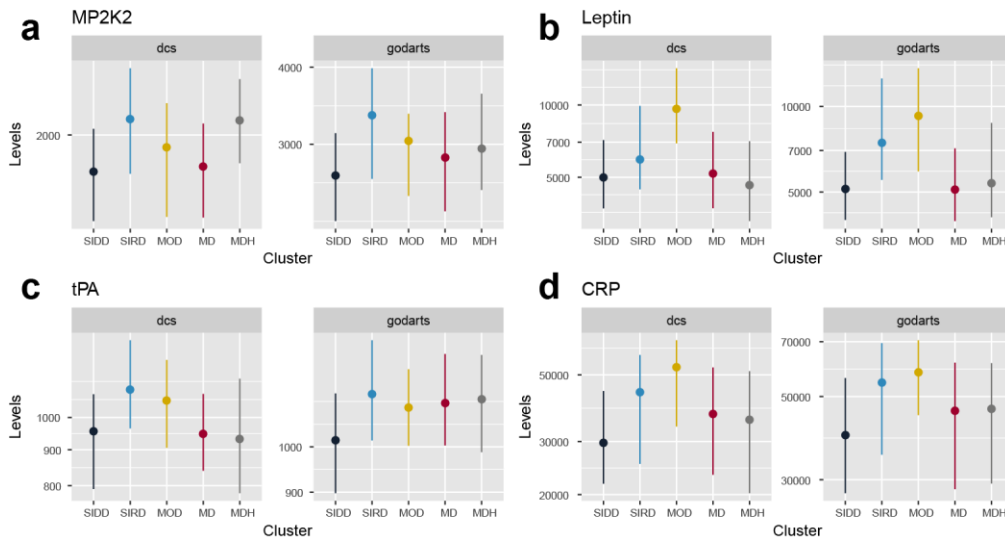


Figure S4. Protein levels in DCS and GoDARTS for MP2K2 (a), leptin (b), tPA (c), CRP (d). **MP2K2**, SIDD and SIRD $P_{FDR} \leq 0.05$; leptin, SIDD, SIRD, MOD, MD and MDH $P_{FDR} \leq 0.05$; tPA, SIDD and SIRD $P_{FDR} \leq 0.05$; CRP, SIDD, SIRD, MOD, MDH $P_{FDR} \leq 0.05$. Dots represent the median, the vertical line the interquartile range. X-axis, clusters; y-axis levels of protein.

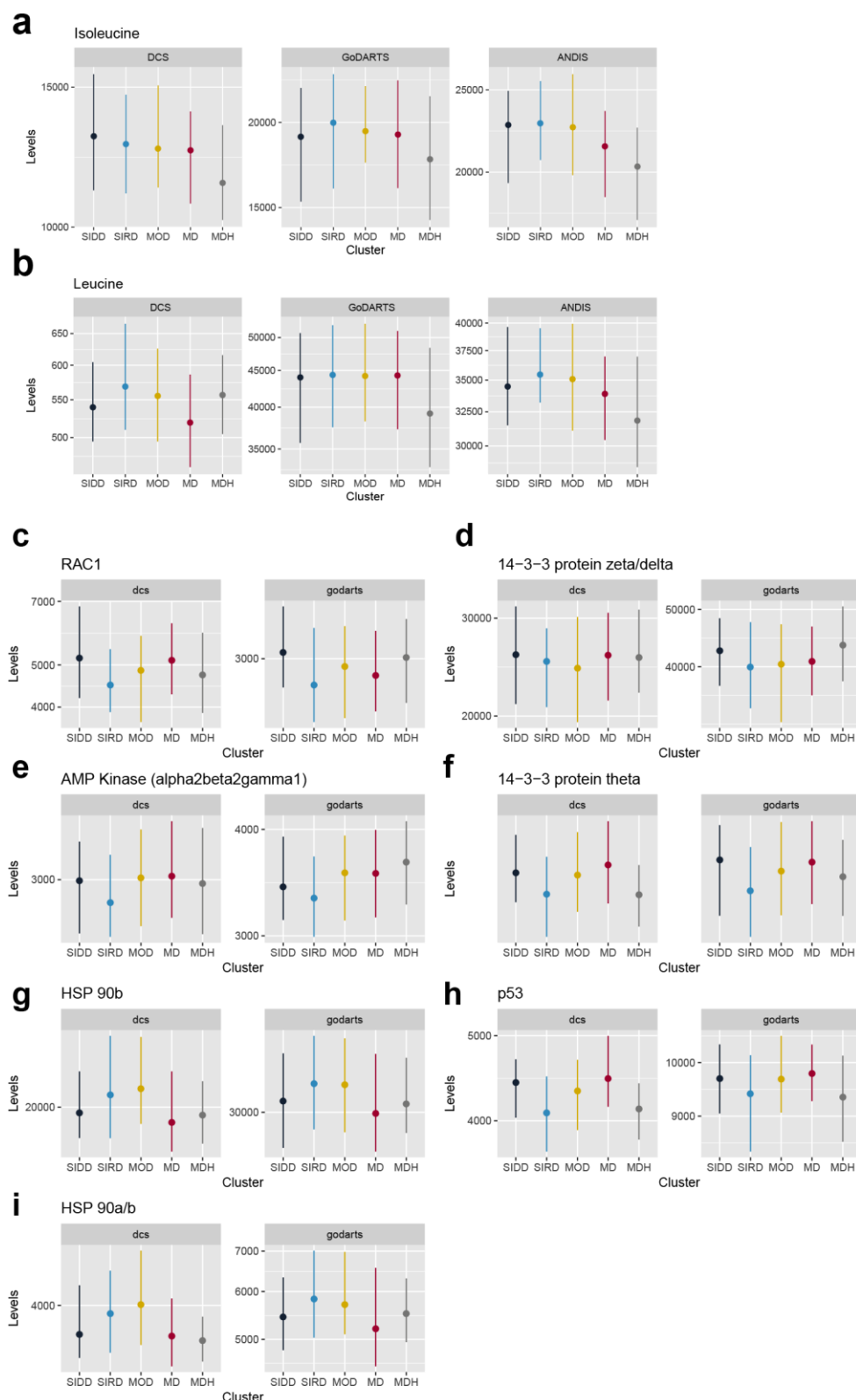


Figure S5. a-b Metabolite levels in DCS, GoDARTS and ANDIS of isoleucine (a) and leucine (b).

Isoleucine, SIRD, MOD and MDH $P_{FDR} \leq 0.05$; leucine, SIRD $P_{FDR} \leq 0.05$. Dots represent the median, the vertical line the interquartile range. **c-i**. Protein levels in DCS and GoDARTS for RAC1 (c), 14-3-3 protein zeta/delta (d), AMP kinase (e), 14-3-3 protein theta (f), HSP 90b (g), p53 (h), HSP 90 a/b (i). RAC1, SIRD $P_{FDR} \leq 0.05$; 14-3-3 protein zeta/delta, MDH $P_{FDR} \leq 0.05$; AMP kinase a2b2g1, SIRD $P_{FDR} \leq 0.05$; 14-3-3 protein theta, SIRD $P_{FDR} \leq 0.05$; HSP 90b, SIRD and MOD $P_{FDR} \leq 0.05$; p53 SIRD and MDH $P_{FDR} \leq 0.05$; HSP 90a/b, SIRD and MOD $P_{FDR} \leq 0.05$. X-axis, clusters; y-axis levels of protein.

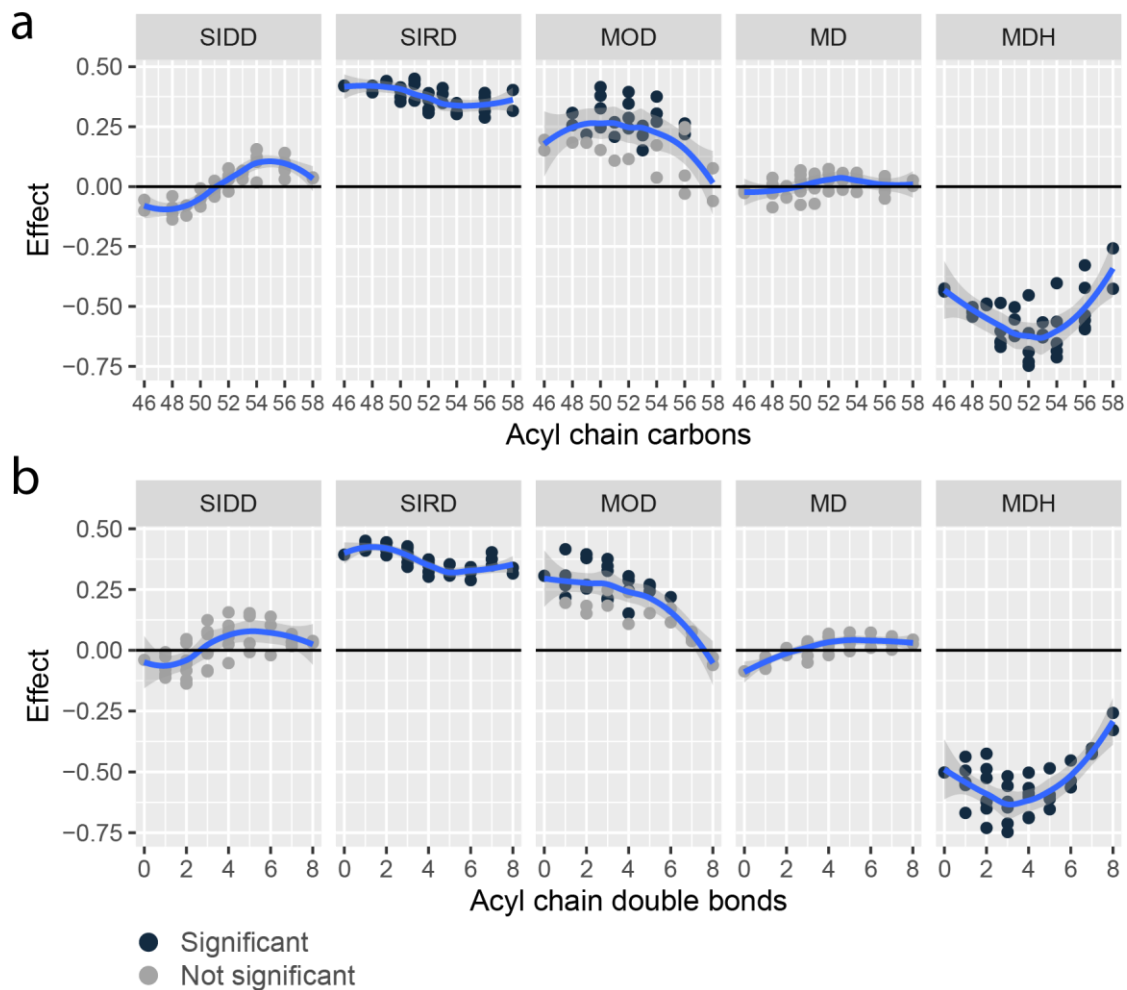


Figure S6. Influence of the number of acyl chain carbons and double bonds in TAGs on the effect size observed in each of the clusters. Relation between the observed effect size and the number acyl chain carbons (a) and double bonds (b). In blue the significant TAGs and in gray the non-significant TAGs.

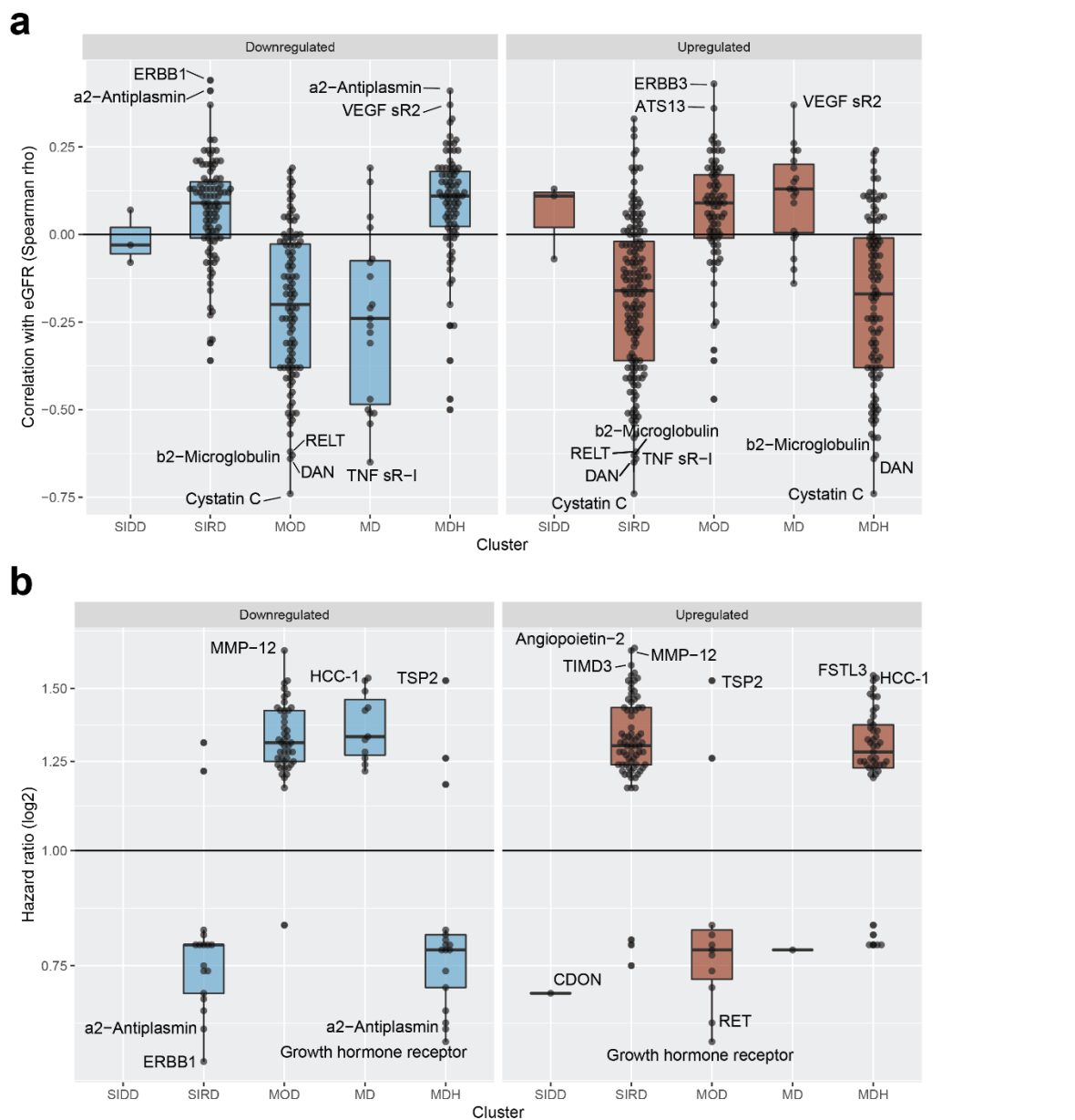


Figure S7 Overlap of identified proteins with proteins associated with eGFR (a) and CVD (b) in Yang et al. (2020). **a** Correlation between plasma protein levels and eGFR for each of the proteins identified in the respective clusters. **b** Hazard ratios of incident cardiovascular disease for the proteins identified in the clusters.

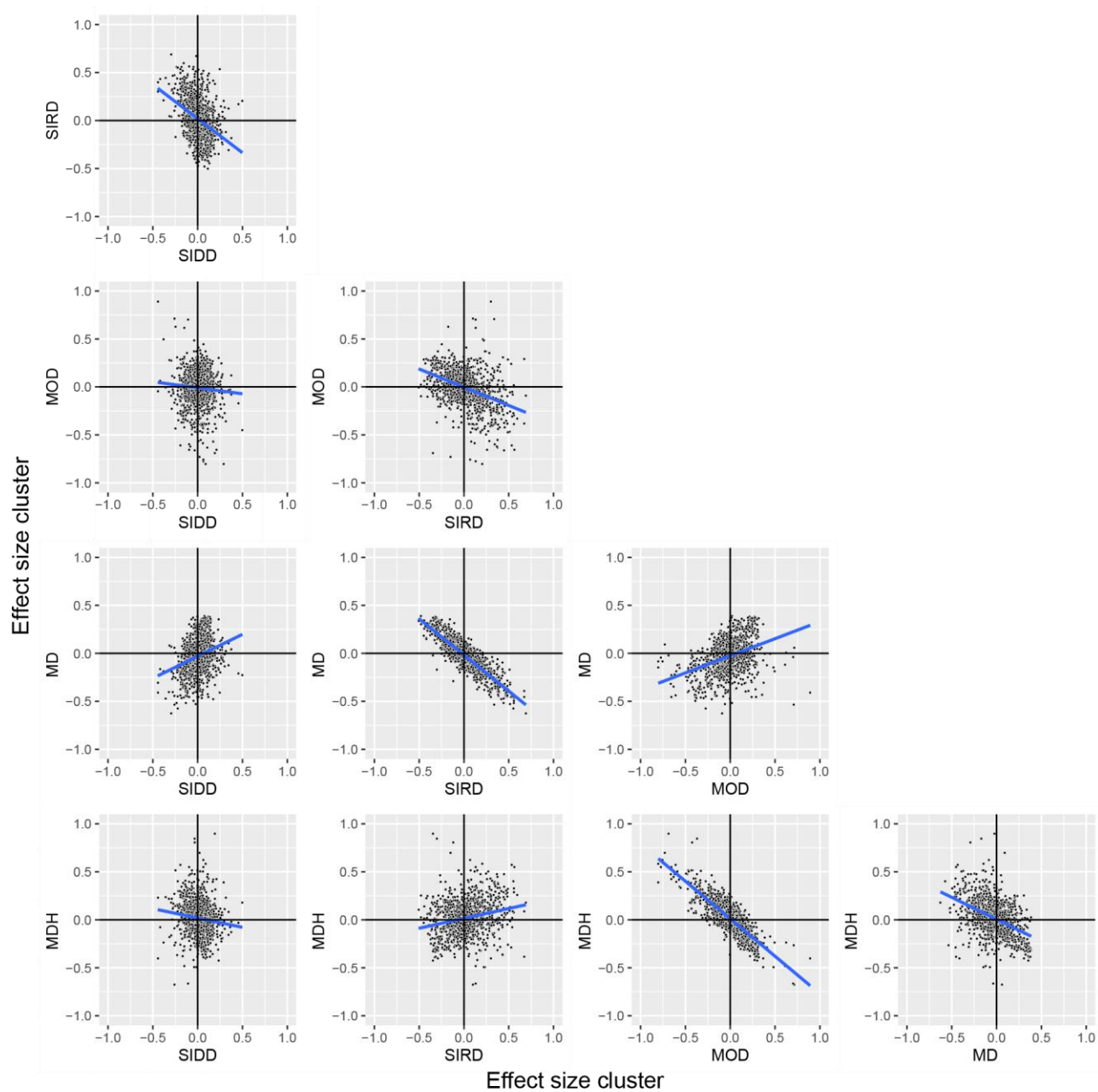


Figure S9. Pairwise comparison of effect sizes of proteins investigated. X-axis and y-axis on the log10 SD scale.

References

1. Udler MS, Kim J, von Grotthuss M, Bonàs-Guarch S, Mercader JM, Cole JB, et al. Clustering of Type 2 Diabetes Genetic Loci by Multi-Trait Associations Identifies Disease Mechanisms and Subtypes. 2018:319509.