The American Journal of Human Genetics, Volume *109*

Supplemental information

Harnessing tissue-specific genetic variation to dissect putative causal pathways between body mass index and cardiometabolic phenotypes

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Supplementary Figures

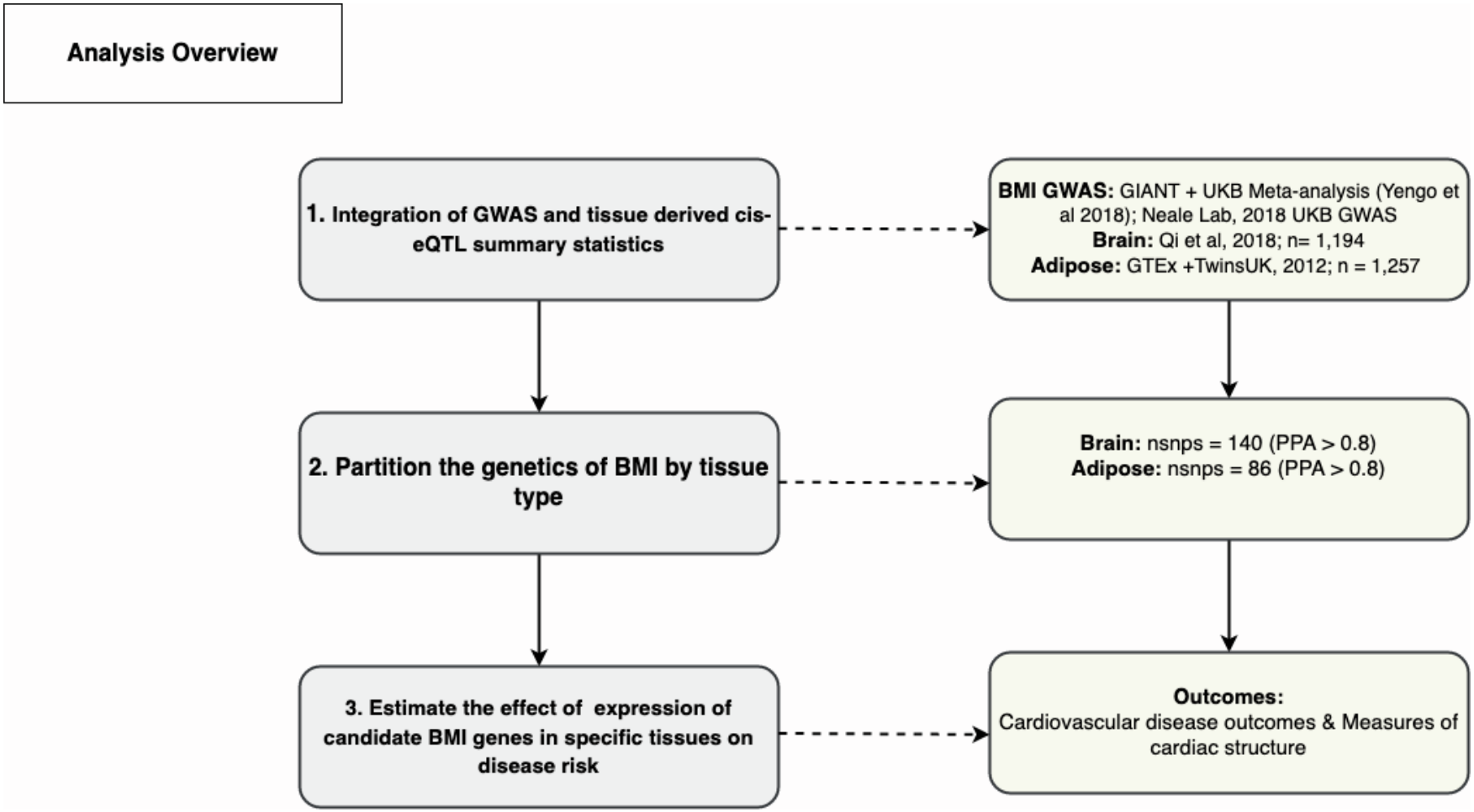

Figure S1 Analysis overview *Flowchart illustrates a summary flowchart of the analytical pipeline undertaken in this study (left panel), data integrated into analyses is summarized (right panel). GWAS – genome-wide association study, eQTL – expression quantitative trait loci, BMI – body mass index, UKB – UK Biobank, nsnps – number of single nucleotide polymorphisms, PPA – posterior probability of association,*

Supplementary Note 1:

Yengo et al:

SNPs were imputed with reference to the HRC imputation reference panel based on a quality score >0.3[1]. For each UKB participant, genotypes were called based on a posterior probability >0.9 and SNPs which survived >0.95 call rate, minor allele frequency >0.0001 and P-value for Hardy–Weinberg test >10-6 were retained for analysis:

UK Biobank only GWAS (to bolster SNP coverage):

Pre-imputation QC in the UK Biobank, along with phasing and imputation, are described elsewhere[2]. A graded filtering was applied for SNP selection with varying imputation quality for different allele frequency ranges. Therefore, rarer genetic variants are required to have a higher imputation INFO score (Info>0.3 for MAF >3%; Info>0.6 for MAF 1-3%; Info>0.8 for MAF 0.5-1%; Info>0.9 for MAF 0.1-0.5%) with MAF and info scores being determined using the 'European' subset. Genotyping rate > 0.015 and Hardy-Weinberg equilibrium p-value < 0.0001 were additionally applied.

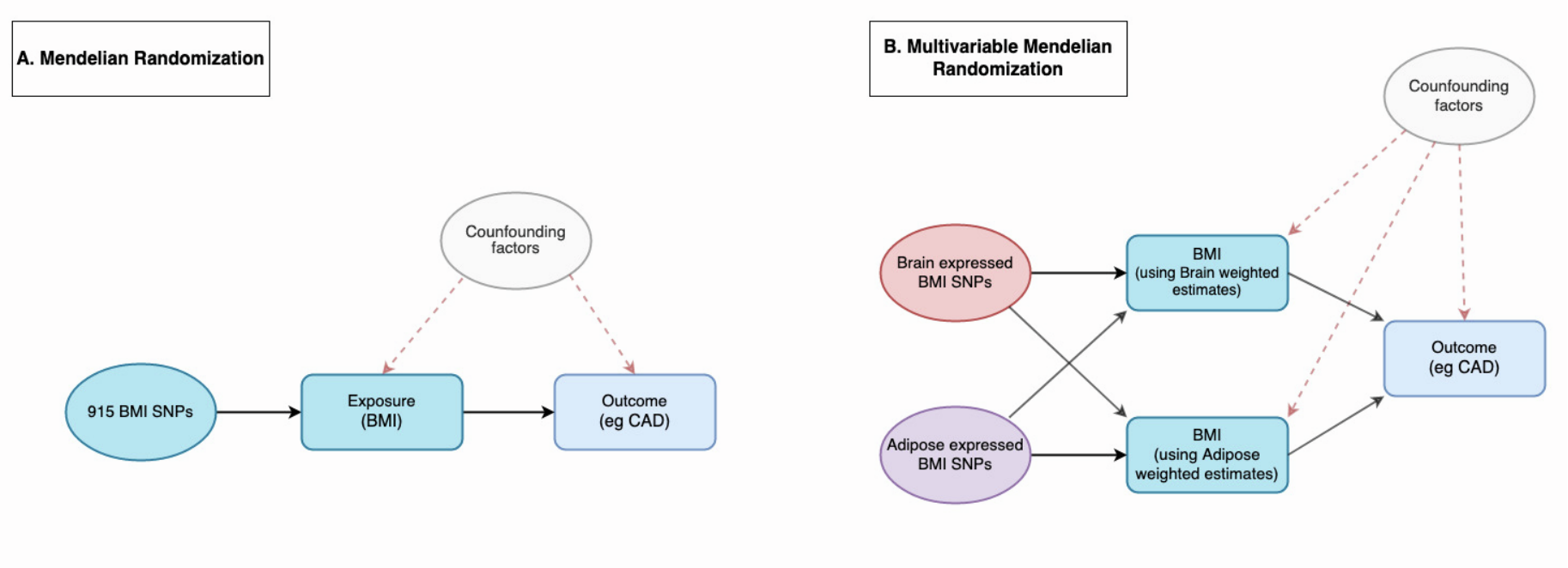

Figure S2 Summary of Mendelian randomization (MR) (A) and multivariable MR analyses (B) *The 'total' effect of BMI on disease outcomes eg. coronary artery disease (CAD) is estimated by instrumenting BMI using a genetic risk score (GRS) derived using the full set of 915 independent genome-wide significant BMI variants (A). BMI instrumented with a GRS derived from BMI variants identified by colocalization in adipose and brain tissue to estimate the 'independent' effect of BMI via gene expression in each tissue when taking into account their effect in the other tissue (B). BMI – body mass index, SNPs – single nucleotide polymorphisms, CAD – coronary artery disease*

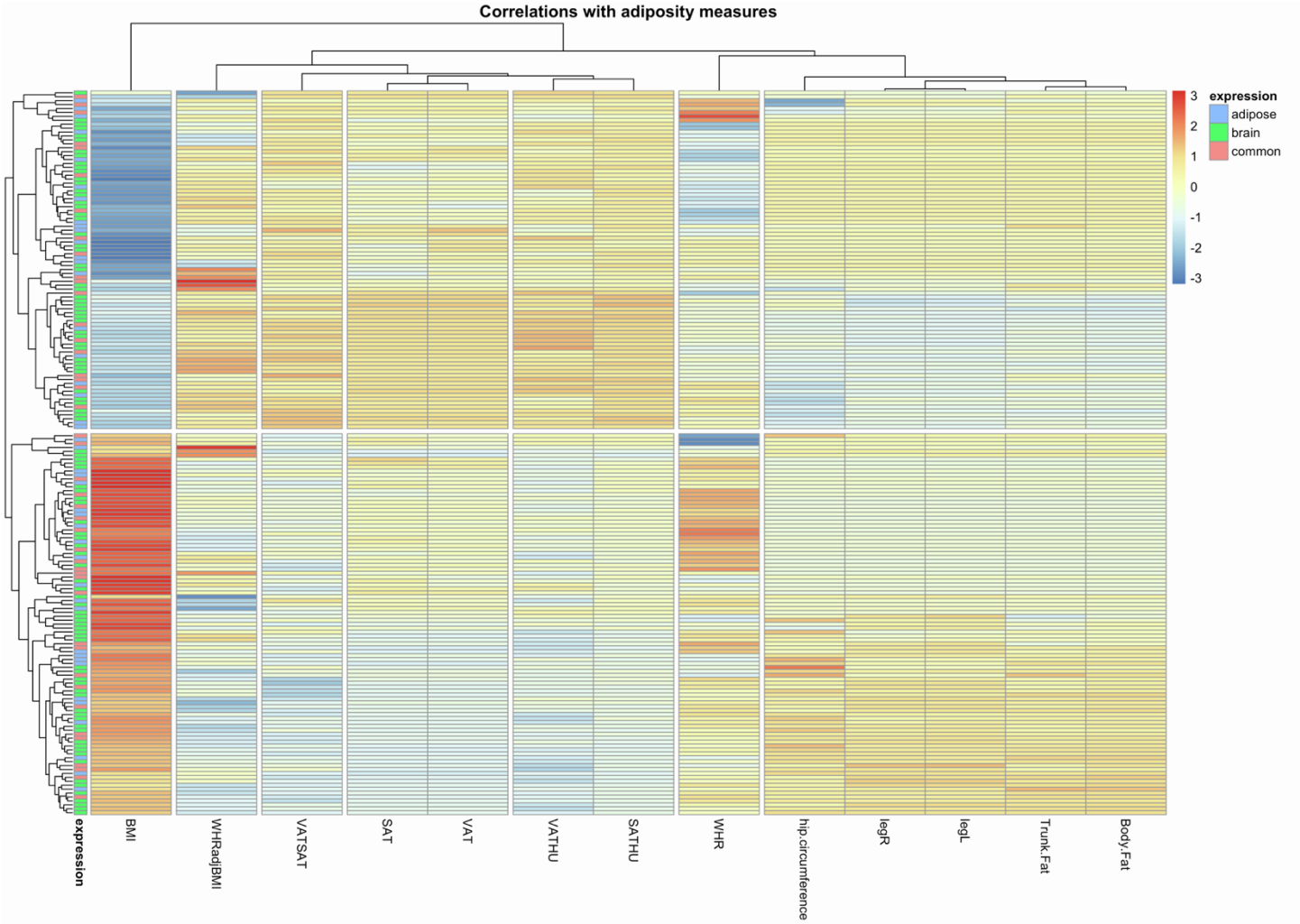

Figure S3 Heatmap based on hierarchical k-means clustering representing the relationship between adipose and brain tissue derived BMI instruments and measures of adiposity *Association between BMI SNPs identified in the colocalization analysis and various adiposity traits derived from publicly available GWAS summary statistics including: waist-to-hip ratio adjusted for BMI (WHRadjBMI), visceral adipose tissue volume (VAT) , subcutaneous adipose tissue volume (SAT), subcutaneous adipose tissue attenuation (SATHU), visceral adipose tissue attenuation (VATHU), ratio of visceral-to-subcutaneous adipose tissue volume (VASAT).waist-to-hip ratio (WHR), hip-circumference, leg-fat percentage (right and left), trunk-fat percentage, body-fat percentage, Pearson correlation coefficients were calculated to estimate the correlation each set of SNPs' estimates for BMI (calculated as Z scores (i.e. beta/standard error)) with each adiposity trait in turn*

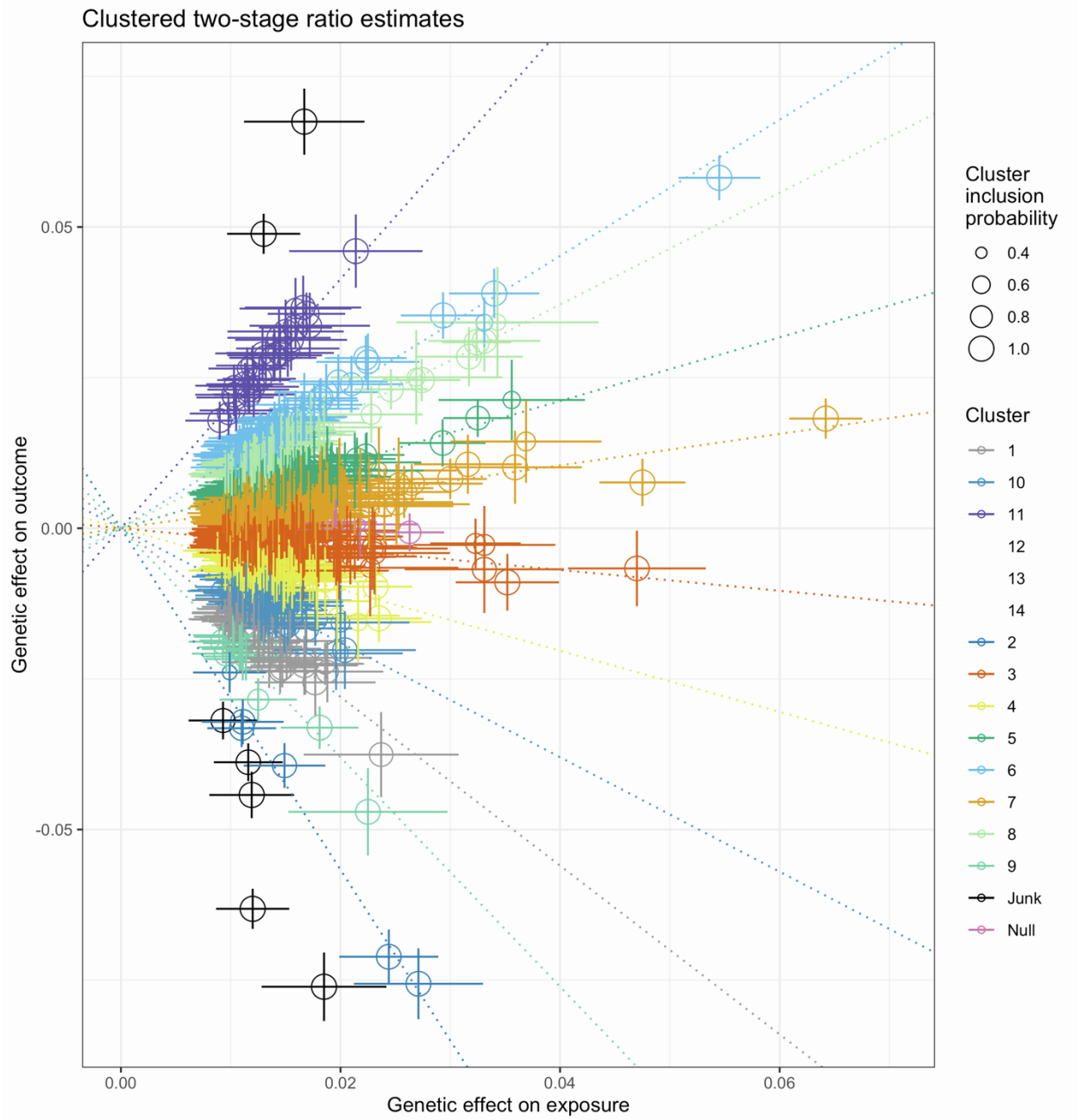

Figure S4 *MR-Clust analysis representing effect estimates between genetic effects between BMI (exposure) and coronary artery disease (outcome) Each point represents a genetic variant, error bars are 95% confidence intervals for each variant*

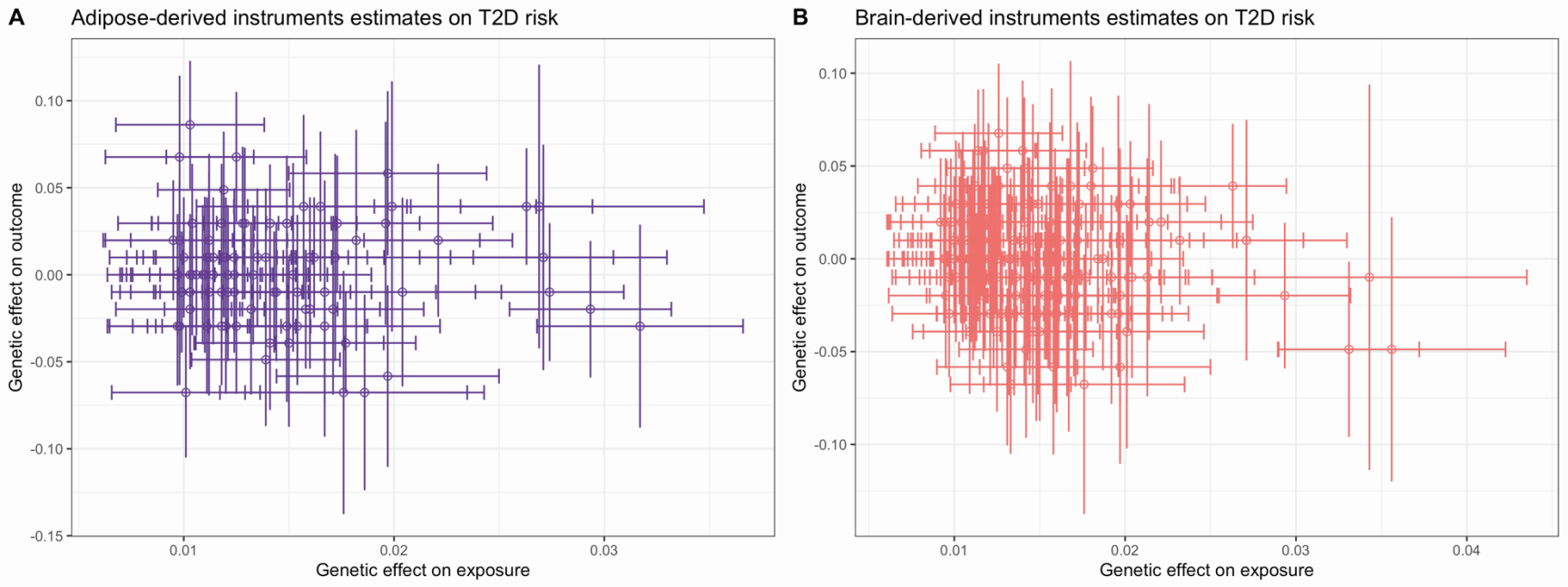

Figure S5 Comparison of effect estimates between adipose-tissue (purple, left) and brain-tissue (red, right) partitioned instruments on type 2 diabetes (T2D) risk *Each point represents a genetic variant, error bars are 95% confidence intervals for each variant's association.*

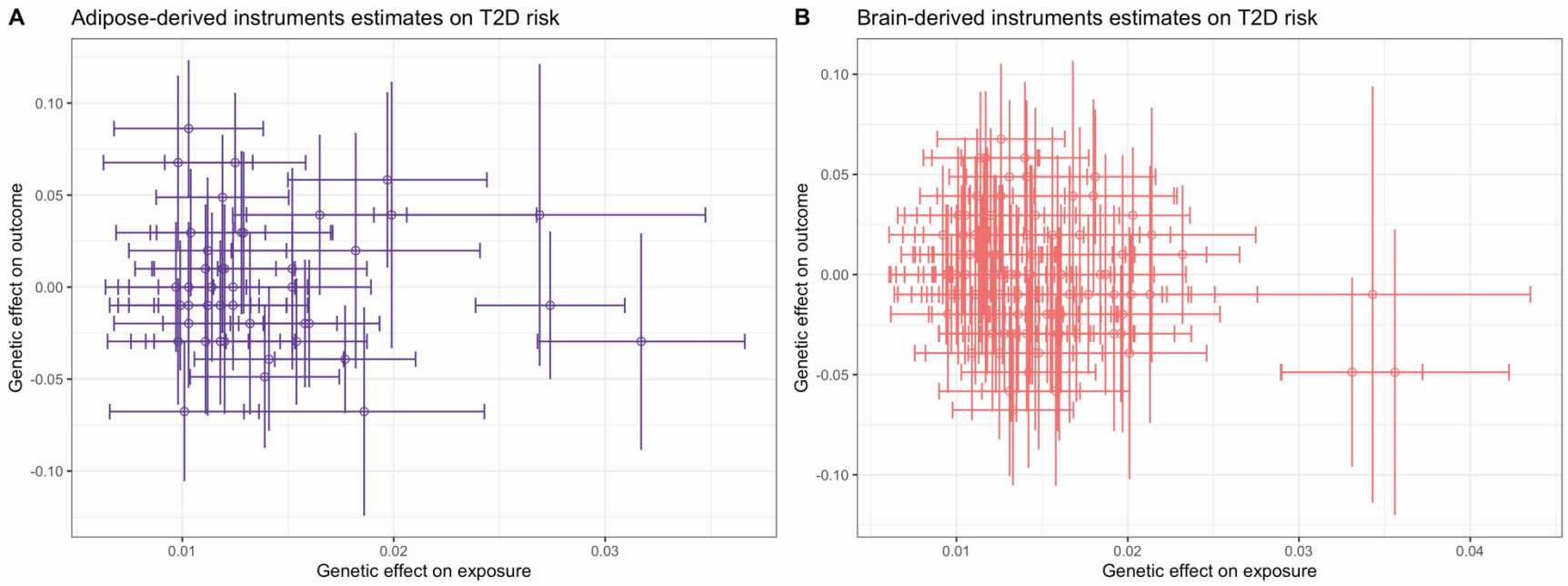

Figure S6 Comparison of effect estimates between adipose-tissue (purple, left) and brain-tissue (red, right) partitioned instruments on type 2 diabetes (T2D) risk after removing overlapping instruments between sets *Each point represents a genetic variant, error bars are 95% confidence intervals for each variant's association.*

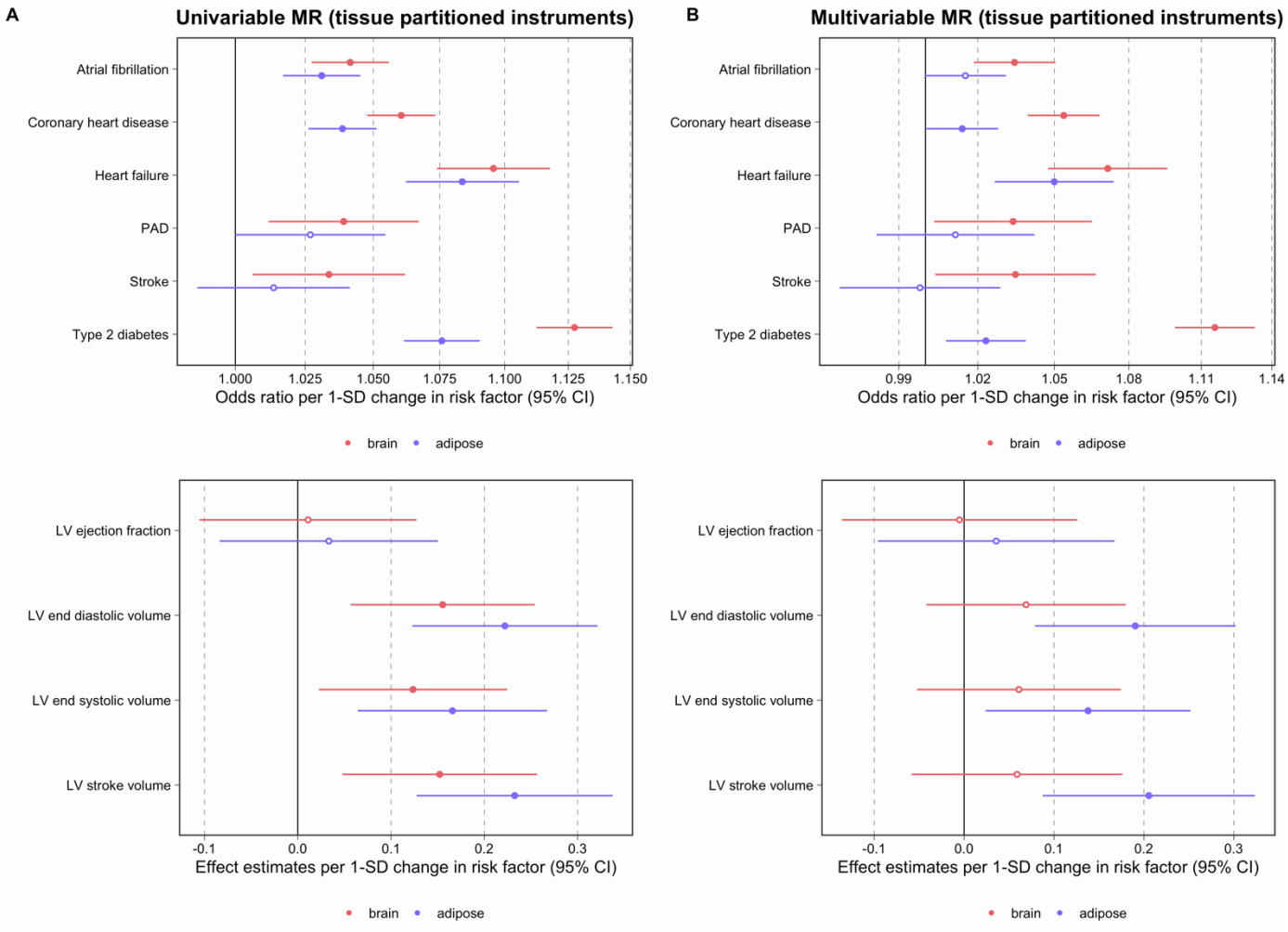

Figure S7 Mendelian randomization results for BMI instrumented using tissue-partitioned sets of variants in the univariable model (A) and in the multivariable model (B). *Forest plot illustrating the odds ratios per 1-standard deviation (SD) change in risk and 95% confidence intervals (CI) for each outcome analyzed in Mendelian randomization (MR) analyses using genetic risk scores (GRS) derived from adipose- and brain-tissue partitioned variants to instrument BMI. Circles representing central estimates are filled in when confidence intervals as illustrated by lines do not overlap with the null.*