

Running title: HERITABILITY OF DIABETES COMPLICATIONS

**Systematic heritability and heritability enrichment analysis  
for diabetes complications in UK Biobank and ACCORD Studies**

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**Abstract (199 < 200 words)**

Diabetes-related complications reflect longstanding damage to small and large vessels throughout the body. In addition to the duration of diabetes and poor glycemic control, genetic factors are important contributors to the variability in the development of vascular complications. Early heritability studies found strong familial clustering of both macrovascular and microvascular complications. However, they were limited by small sample sizes and large phenotypic heterogeneity, leading to less accurate estimates. We take advantage of two independent studies—UK Biobank and the Action to Control Cardiovascular Risk in Diabetes trial to survey the SNP-heritability for diabetes microvascular (diabetic kidney disease and diabetic retinopathy) and macrovascular (cardiovascular events) complications. Heritability for diabetic kidney disease was estimated at 29%. Heritability estimates for microalbuminuria ranged from 24% to 60% and was 41% for macroalbuminuria. Heritability estimates of diabetic retinopathy ranged from 6% to 33%, depending on the phenotype definition. More severe diabetes retinopathy possessed higher genetic contributions. We show, for the first time, that rare variants account for much of the heritability of diabetic retinopathy. This study suggests that a large portion of the genetic risk of diabetes complications is yet to be discovered and emphasizes the need for additional genetic studies of diabetes complications.

## Introduction (3991 < 4000 words)

Genome-wide association studies (GWAS) have identified >300 genetic loci associated with type 2 diabetes. Together these top GWAS signals explain >19% of the phenotypic variance in risk for the type 2 diabetes risk (1). Genetic exploration underlying type 1 diabetes has been heavily focused on the human leukocyte antigen (HLA) region, although GWAS has identified >50 regions contributing to type 1 diabetes risk thus far (2-4). The area under the receiver operating characteristic curve of a genetic risk score for type 1 diabetes generated using top GWAS loci was estimated as high as 0.9 (5; 6). Although there is strong inheritance of risk of developing diabetes, less is known about the heritability of diabetes complications. Poor glycemic control and duration of diabetes are two major risk factors for vascular injury (7; 8). The progression of diabetes to the development of diabetes complications is heterogeneous even in individuals with comparable glucose control and diabetes duration (9). This heterogeneity greatly complicates the prediction of risk and personalization of diabetes therapy.

Among other diabetes-associated diseases, diabetic kidney disease (DKD) has been extensively studied in family studies. Diabetic siblings of probands with DKD had approximately 2-4 times the risk of developing DKD than diabetic siblings of probands free of DKD (10-12). A heritability analysis of renal complications in type 1 diabetes estimated that 34–59% (adjusted for sex, diabetes duration, and age at diabetes onset; 24–42% unadjusted) of the variance was explained by common genetic variants, depending on the stages or phenotype definitions of DKD (13). A similar unadjusted analysis of DKD in individuals with type 2 diabetes estimated SNP heritability to be 8-12%, probably because of the phenotypic heterogeneity of kidney disease in the type 2 diabetes (14).

Early family and twin studies suggested high concordance of diabetic retinopathy between family members (15; 16). Of note, genetic components for the risk of diabetic retinopathy appear more closely related to the severity of retinopathy, rather than to the simple presence or absence of retinopathy (15; 17). Heritability estimates from family studies range from 18% to 52% (18-20), while SNP heritability of severe diabetic retinopathy due to common genetic variants is estimated at 7% (21).

Little is known about the genetic contributions to CVD heritability among individuals with diabetes. The heritability of coronary artery disease in the general population is estimated to be between 40% and 60% in family and twin studies (22-24) and around 30% in studies of unrelated individuals using common genetic variants (25). However, the only heritability-based studies for CVD in diabetes populations come from small family studies of quantitative traits, including coronary artery calcification (26) and carotid intima-media thickness (27).

As the rising prevalence of diabetes has led to more people at risk for serious complications, elucidating the genetic contribution (i.e., heritability) to the development and progression of complications takes on greater urgency. A deeper understanding of these genetic connections with diabetes complications may identify those most in need of aggressive interventions, uncover new target pathways and ultimately enhance our ability to use precision medicine for a tailored disease prevention/treatment. In the present study, we conducted a comprehensive heritability analysis using two well-characterized cohorts—the UK Biobank (UKB) study and the Action to Control Cardiovascular Risk in Diabetes trial (ACCORD)—to investigate genetic components involved in the development and progression of diabetes complications. Our results highlight the importance of the genetic contribution, whether alone or in conjunction with environmental perturbations, to the development and progression of diabetes complications.

## Research design

### ***Study design and participants***

The UKB study recruited during the years 2006-2010 approximately 500,000 individuals aged 40-69 from the general population across the United Kingdom. Participants answered detailed demographic, socioeconomic, and health-related questions. Historical and follow-up information is provided by linking to health and medical records. Genome-wide genotype data have been collected on all participants, permitting study of the genetic basis of complex traits (28; 29). This large-scale cohort study with linked health and longitudinal medical records enables use of a prospective study design to study incident diabetes complications.

From the UKB, we curated a diabetes cohort using the following sources: (A) baseline information (2006-2010) and subsequent assessments (2012-2013) at UKB assessment centers including questionnaires, physical exam measurements, and biological samples, and (B) health-related records which include hospital visits, a death registry, algorithmically-defined event outcomes, first occurrences of medical conditions, and ongoing primary care data. Diabetes mellitus cases were ascertained according to the following criteria: (A) the first occurrence of any of the following: International Classification of Disease, Ninth and Tenth Revision (ICD-9 and ICD-10) codes for type 1, type 2, and unspecified diabetes mellitus; self-report of diabetes mellitus at a UKB Assessment center visit along with the interpolated date from the age of diagnosis; or a limited number of primary care codes mapped to the three-digit ICD10 code: E10, E11, and E14; (B) the first occurrence of a more extensive list of diabetes-related primary care codes. Pregnancy or malnutrition-related diabetes was excluded. After excluding individuals with non-European ancestry, a total of 26,387 non-Hispanic white (NHW) diabetes patients were identified between the ages of 49 and 82 years as of 2020. We refer to this group of individuals as the UKB-NHW-

Diabetes cohort (Supplemental Figure 1). Among the UKB-NHW-Diabetes cohort, we defined the first recorded diagnosis of diabetes as the index date and any incident vascular complication “case” to be the first occurrence of the event after the index date.

The ACCORD study was a double-blind, two-by-two factorial, randomized controlled, parallel treatment trial with 10,251 participants (30; 31). The glucose-lowering component of the ACCORD study was to evaluate the effectiveness of a more aggressive treatment target to reduce the rate of macrovascular and microvascular complications (32). The ACCORD study included type 2 diabetes participants with HbA1c concentrations of 7.5% (58.5 mmol/mol) or more, and who were aged 40-79 years with a history of cardiovascular disease or 55-79 years with evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two risk factors for cardiovascular disease (dyslipidemia, hypertension, smoking, or obesity). As with the UKB analysis, we excluded individuals with non-European ancestry from the ACCORD because having people of different ancestral groups can inflate heritability estimates. Analyses for other ethnic groups were not conducted because of their small sample sizes. For example, the next biggest ethnic group in the ACCORD was African Americans with a sample size of 935 after data preprocessing steps. Details of the design and principal results of the ACCORD trial were reported previously (30; 31).

### ***Outcome definitions***

In the UKB-NHW-Diabetes cohort, we defined incident cases as the first occurrence of the event after the first diabetes diagnosis. For each type of incident case, we excluded individuals with documented occurrences of the event before the diagnosis of diabetes. For the control cases of DKD, we additionally required them to have no event of interest during the entire observation period with at least five years of follow-up. Key phenotypes are detailed in Table 1. A complete

list of codes and data fields used in the definition of diabetes mellitus, diabetes complications, and their date of the first occurrence are presented in the Supplemental Material.

In the ACCORD trial, all outcomes were pre-specified and adjudicated by the outcome committee. The pre-specified ACCORD primary cardiovascular (CVD) outcome was the first occurrence of nonfatal myocardial infarction (MI) or nonfatal stroke or death from cardiovascular causes. We expanded this primary CVD outcome by including individual outcomes of new or worsening congestive heart failure (CHF), total stroke, and major coronary heart disease (CHD). For microvascular complications, taking advantage of the adjudicated broad combination of microvascular outcomes (illustrated in Table 1), we analyzed a spectrum of outcomes ranging from severe microvascular complications (e.g., Neph3 and Retin1) to less advanced conditions. A detailed description of the pre-specification of the ACCORD outcomes was documented previously (30; 31).

#### ***Genotyping and imputation in UKB and ACCORD***

We analyzed the genotyping and imputation (version 3) data released by the UKB in 2017. Details on genotyping and imputation have been extensively described elsewhere (29). In summary, genome-wide genotyping was performed on all UKB participants using the UKB Axiom array. Around 850,000 variants were directly genotyped, and more than 90 million variants were imputed using the merged UK10K and 1000 Genomes Phase 3 (33) reference panels. Only autosomal SNPs were included for all analyses. In the analyses involving imputation data, we discarded SNPs with imputation info score  $> 0.3$ , missing genotype rate  $> 0.05$ , Hardy-Weinberg equilibrium test  $p < 1 \times 10^{-6}$  and MAF  $< 0.0001$ , yielding a total of 33,932,888 autosomal SNPs.

Detailed accounts on DNA extraction, genotyping, and quality control (QC) procedures in ACCORD were reported previously (34). After retrieving the ACCORD genetic study data from

dbGap, we used genetic variants genotyped on Affymetrix Axiom Biobank chips from the University of North Carolina and merged data under two different institutional review board (IRB) protocols—HMB-IRB (73941) and DS-CDKD-IRB (73944). There were 6,291 (2,335 females and 3,956 males) with 546,800 SNPs in the merged dataset. Based on self-reported ethnicity, there were 4,369 NHW, 935 African-Americans, 381 Hispanics, and 606 others. After pre-imputation QC steps, imputation was performed on the genotype data using a two-step approach: pre-phasing genotype calls (35) and imputation (36). After discarding imputed SNPs with  $R^2 < 0.3$  and MAF<0.0003, the total number of SNPs was 25,667,109. Additional details are provided in Supplemental Material.

### ***Data and Resource Availability***

The data that support the findings of this study are available from open access repositories. ACCORD study data is available in the biologic Specimen and Data Repository Information Coordinating Center (BioLinc), <https://biolincc.nhlbi.nih.gov/>, with the permission of BioLinc. The UK Biobank data are retrieved under Project ID: 48152. Data are available at <https://www.ukbiobank.ac.uk>, with the permission of UK Biobank.

### **Statistical Analysis**

#### ***Overview of Methods***

We use three different methods to compute heritability: single-component GREML (GREML-SC), GREML-LDMS-I, and Stratified LD Score Regression (S-LDSC). GREML-SC is a single component variance component approach that is typically applied to common SNPs (MAF  $\geq 0.01$ ) (37). GREML-LDMS-I is a multiple variance components approach that bins imputed SNPs by their MAF and individual levels of linkage disequilibrium (LD) (37; 38). Compared to GREML-SC, GREML-LDMS-I can attenuate the bias arising from a mismatch between the MAF

distribution of the causal variants and that of the SNPs used to generate the genetic relationship matrix (GRM) (39). We selected GREML-LDMS-I approach over other multicomponent approaches such as GREML-LDMS-R, which allocates SNPs by the MAF and regional LD, since GREML-LDMS-I was shown to be the least biased method (40). While both GREML-SC and GREML-LDMS-I require individual-level genotypes and phenotypes data, S-LDSC relies only on GWAS summary statistics. S-LDSC partitions SNP heritability by functional genomic annotations, as opposed to SNP properties such as MAF or LD in GREML-LDMS-I. For a survey of heritability estimation methods, see Evans et al. (40).

We first computed a GRM from all autosomal SNPs in genotype data using the Relatedness Estimation in Admixed Populations (REAP) approach (41). We then selectively excluded one of any pair of individuals with an estimated kinship greater than the separation between full and half-siblings (estimated kinship  $> (1/2)^{5/2}=0.1768$ ) to maximize the remaining sample size (42). This step was done to avoid inflation caused by cryptic relatedness. After the pruning step, we estimated heritability in the NHW cohort. Based on the GRM constructed from the REAP, heritability was computed using the GREML-SC approach via the software package Genome-wide Complex Trait Analysis (GCTA) (43). For the UKB data, the following covariates were accounted for: sex, age in 2010, and the top ten principal components. For the ACCORD data, we adjusted for sex, age at baseline, history of CVD at baseline, and the top five principal components. Within the UKB-NHW-Diabetes cohort, sensitivity analysis was also conducted by additionally adjusting for systolic blood pressure for the DKD outcome. In ACCORD, analysis was also conducted by excluding subjects with CVD history at baseline.

To calculate the narrow-sense heritability of diabetes complications from imputed datasets, we first applied GREML-LDMS-I. Following Evans et al. (40), we first calculated segment-based

LD scores using the default settings in the GCTA software and stratified SNPs into high and low LD score groups using the median as a threshold. In each LD group, SNPs were further partitioned into four MAF bins. Then GRMs were computed for each of the eight groups. Finally, we estimated the heritability of each binary phenotype with fixed covariates.

Next, we applied S-LDSC (44; 45). After acquiring statistics from logistic regression, we performed an analysis with 53 overlapping functional categories used in Finucane et al. (44) and a tissue-specific heritability enrichment analysis. In the tissue-specific analysis, we used the specifically expressed gene annotations generated by Finucane et al. (45) with the Genotype-Tissue Expression (GTEx) project (46). For all S-LDSC analyses, we used 1000 Genomes Project Phase 3 (33) European population SNPs as an LD reference panel. For more details on methods, see Supplemental Material.

Note that our heritability estimates do not take population prevalence/incidence into account. We display estimates without population ascertainment correction because the UKB and ACCORD reflect longitudinal and prospective intervention designs, respectively, rather than ascertained case-control studies. In the latter design, the proportion of cases are often overrepresented. In fact, our sample proportion of cases agree with the prevalence/incidence reported in the literature. For example, the proportion of DKD cases in the UKB-NHW-Diabetes cohort is 0.256, which is similar to the prevalence of any diabetic kidney disease among US adults with diabetes (0.262; 95% CI, 0.226-0.299) reported in Afkarian et al. (47). The proportions of incident cases for the primary CVD outcome and total stroke in the ACCORD group are 0.106 and 0.018, respectively, while the hospital discharge record in 2016 reported the proportion of cases to be 0.0753 and 0.0136 (48).

## Results

Characteristics of the NHW samples used in the UKB and ACCORD analyses are presented in Tables 2 and 3, respectively. Supplemental Figures 1 and 2 show participant flow in the UKB and ACCORD analyses, respectively.

### ***Heritability***

We computed the heritability of phenotypes from the SNPs on the genotyping array using the GREML-SC approach (37). After pruning related individuals and extracting NHW samples, there remained 26,387 samples for the UKB and 4,318 samples for the ACCORD.

Heritability estimates from the UKB genotype data are illustrated in Table 4 and as purple bars in **Error! Reference source not found..A**. Interestingly, estimates of the UKB phenotypes are smaller in magnitude than those of the ACCORD. While the composite CVD phenotype from the ACCORD (primary) is 0.248 (SE 0.093), the composite CVD outcome from UKB is 0.081 (SE 0.028). Heritability estimates for the ACCORD data are displayed in Table 5 and as purple bars in **Error! Reference source not found..A**. The estimate for the composite nephropathy outcome among type 2 diabetes (Neph4) is 0.129 (SE 0.091), which is comparable with estimates from a similar analysis (0.12 for chronic kidney disease and 0.08 for diabetic kidney disease among type 2 diabetes subjects) (14). We also ran an additional GREML-SC analysis that includes interaction with the intensive glycemic treatment arm (Supplemental Figure 3). Interestingly, variance component for the gene-treatment interaction appears to explain a large part of phenotypic variance in microalbuminuria (Neph5). Heritability estimates from the UKB genotype data tend to have smaller error bars than those from the ACCORD genotype data due to the larger sample size in the UKB-NHW-Diabetes cohort.

Heritability estimates using imputed datasets and GREML-LDMS-I method are provided as green bars in Figures 1.A and 2.A for the UKB and ACCORD, respectively (also see Tables 4 and 5). In UKB, the heritability of diabetic kidney disease is estimated to be 0.29 (SE 0.20). Microalbuminuria estimates range from 0.25 (SE 0.12) to 0.60 (SE 0.25), while macroalbuminuria estimates are up to 0.41 (SE 0.20). In ACCORD, heritability estimates of diabetic retinopathy range from 0.06 (SE 0.17) to 0.33 (SE 0.17), depending on the definition of phenotype. Although still less than family study estimates for broad-sense heritability—0.27 for diabetic retinopathy (20) and as high as 0.52 (SE 0.31) for proliferative retinopathy among adults with type 1 diabetes (19), our estimates are close to pedigree heritability estimates.

Of note, we observed higher estimates with more advanced retinopathy: 0.29 and 0.33 for Retin1 (retinal photocoagulation or vitrectomy) and Retin4 (severe vision loss), respectively, as opposed to 0.06 and around 0 for Retin2 (cataract extraction) and Retin3 (three-line change in visual acuity), respectively. On the other hand, diabetic nephropathy phenotypes do not exhibit such a pattern. While the heritability of macroalbuminuria phenotype within ACCORD is estimated at 0.41, that of microalbuminuria from ACCORD is at 0.60, respectively. Estimates for either Neph1 or Neph3 are unavailable despite larger sample sizes (4,318 for both Neph1 and Neph3; 3,866 and 2,912 for Neph2 and Neph5, respectively). This pattern or lack thereof is consistent with earlier heritability studies that implicated genetic components in the severity of diabetic retinopathy and the presence/absence of diabetic nephropathy (15; 17). Although we cannot confirm the trend of diabetic retinopathy in the UKB data (due to the absence of more granular outcome definitions for diabetic retinopathy), when restricting the analysis to T2D participants in UKB only, we found the heritability of DR reduces to 0.029 (0.199) from 0.166

(0.130) (Table 4). As DR recorded in primary care data tends to be less severe, it is consistent with the observations from ACCORD.

Heritability analyses using imputed data reveal a substantial contribution of low-frequency/rare variants to the predisposition for complications. While the heritability of severe diabetic retinopathy from common genetic variants among individuals with type 2 diabetes was estimated to be 0.07 in a previous study (21) and up to 0.14 in our analysis (see GREML-SC results of Retin1 and Retin4 in Table 5), heritability estimates of advanced diabetic retinopathy among type 2 diabetes individuals were higher (0.29 and 0.33 for Retin1 and Retin4 in ACCORD) when calculated from directly typed plus imputed genetic markers. The distribution of heritability across the MAF spectrum for other complication phenotypes, including retinopathy, is found in Figures 1.B and 2.B. Notably, the UKB results (**Error! Reference source not found..B**) show a more pronounced contribution pattern with small error bars and heritability heavily concentrated in very rare variants ( $0.0003 \leq \text{MAF} < 0.0025$ ).

To corroborate our results, we applied the same set of phenotyping rules to a sample of 26,387 individuals with no diabetes in the UKB to estimate heritability of chronic kidney and cardiovascular disease using the definition outlined above. This group was randomly sampled from 296,315 individuals with no diabetes in the UKB to match the sample size of the diabetes group and ease the computational burden. We also computed estimates after combining diabetes and non-diabetes groups and adjusting for diabetes status as a covariate. These results can be found in Table 4. Overall, heritability shows higher estimates for kidney disease in the non-diabetes group, i.e., 0.291 (SE 0.196) in diabetes vs 0.453 (SE 0.15) in non-diabetes, while the heritability estimate for microalbuminuria is higher than that in the non-diabetes group, i.e., 0.250 (SE 0.119) in diabetes vs 0.155 (SE 0.201) in non-diabetes.

## GWAS

Association results identified multiple significant peaks ( $p < 5 \times 10^{-8}$ ) in the UKB-NHW-Diabetes cohort. For macrovascular complications in the UKB-NHW-Diabetes cohort (CVD and MI), variants on chromosome 9p21 reached genome-wide significance. Association of the regions on chromosome 9p21 with T2D and progression of CVD was reported previously (49). For DR in UKB-NHW-Diabetes cohort, 22 variants on 6p21 reached genome-wide significance ( $p < 5 \times 10^{-8}$ ) with rs9273367 ( $p = 1.23 \times 10^{-9}$ , OR=1.18) being the most significant SNP. These variants were in or near HLA regions, whose previous associations with T1D have been well-documented (50). For DKD, 17 variants had  $p < 5 \times 10^{-8}$ . Eleven of these SNPs were on chromosome 3q26.31, and six were in *UMOD* and *PDLT* genes (lead SNP rs77924615 with  $p = 7.82 \times 10^{-9}$ , OR = 0.75) on chromosome 16p12.3. *UMOD* was previously reported to be associated with eGFR in the meta-analysis combining type 1 and type 2 diabetes patients of European and Asian ancestry (14). Although some variants were below the genome-wide significance threshold in the ACCORD cohort, they were not as prominent as in the UKB-NHW-Diabetes cohort.

Supplemental Data 1 reports all genome-wide significant GWAS loci for diabetes complications. Supplemental Figures 4-7 show Manhattan and QQ plots for GWAS.

### ***Heritability enrichment by functional annotations***

We applied S-LDSC to identify disease-relevant tissues and cell types. Results for the selected ACCORD phenotypes are illustrated in **Error! Reference source not found.** (also see Supplemental Figures 8-9). Renal failure or ESRD phenotype (Neph3) exhibit skin-specific (sun-exposed skin  $p = 4.82 \times 10^{-4}$ ; non-sun-exposed skin  $p = 4.29 \times 10^{-3}$ ) and brain-specific enrichments (brain cerebellar hemisphere  $p = 1.99 \times 10^{-3}$ ). The skin-specific enrichment captures dermatologic manifestations of ESRD (51). Macrovascular complications (primary and major CHD) show

enrichments in EBV transformed lymphocytes ( $p=1.38 \times 10^{-3}$  and  $p=2.25 \times 10^{-3}$ , respectively). This finding reflects the mechanism of macrovascular complications involving inflammatory cells (e.g., monotypes and T lymphocytes) (52). Despite the larger sample size, no tissues were enriched for the heritability of diabetic complications from the UKB (Supplemental Figures 10-11).

Results from the S-LDSC analysis partitioning heritability into 53 (overlapping) categories used in Finucane et al. (44) are illustrated in Supplemental Figure 12. In the UKB data, only the coding region shows Bonferroni-corrected ( $0.05/53=9.43 \times 10^{-4}$ ) significant enrichment in DKD ( $p=6.55 \times 10^{-4}$ ). Though only nominally significant, H3K9ac is enriched in the microalbuminuria phenotype ( $p=0.04$ ). H3K9ac enrichment agrees with the findings from Salem et al. (53) that the top signal (TAMM41) for microalbuminuria is close to the histone marks—H3K27ac, H3K9ac, H3k4me1. In the ACCORD data, none of the categories for any phenotype passed the Bonferroni significance threshold ( $0.05/53=9.43 \times 10^{-4}$ ), given the small sample size. Some categories are still noteworthy, however. Promoter region showed enrichment in the retinopathy phenotype (Retin1;  $p=2.82 \times 10^{-2}$ ) and H3K27ac showed enrichment in the composite nephropathy phenotype (Neph4;  $p=4.64 \times 10^{-2}$ ).

## Discussion

In this paper, we have provided a comprehensive assessment of SNP heritability for diabetes microvascular and macrovascular complications. Estimates from the imputed data revealed a substantial contribution of low-frequency/rare variants in low LD with neighboring variants for variation of diabetes complications. Our estimates are higher than those obtained from common SNPs in GWAS but approach pedigree heritability. Our findings imply that a large portion of the genetic risk of diabetes complications is yet to be discovered. Additional sensitivity analyses adjusting for the common risk factor (blood pressure measures at baseline) and excluding

participants with CVD history in ACCORD cohort did not change the heritability estimates in our studies.

We have used two independent studies to estimate the heritability for diabetes complications. Although a meta-analysis from the two studies would have increased the sample size, we conducted two separate analyses to reduce the risk of phenotypic heterogeneity. Our analyses show some discordance in findings between the two data sets. Heritability estimates obtained using imputed datasets tend to be larger in the ACCORD study than in the UKB study despite a larger sample size in the UKB-NHW-Diabetes cohort. Additionally, no tissue enrichment is observed in the UKB-NHW-Diabetes cohort. Differences in study designs and potential biases may provide a basis for such discordant findings. First, the ACCORD is a clinical trial that offers adjudicated outcomes in a well-controlled clinical trial setting. In contrast, the UKB reflects a cohort in “real world” scenarios and is based on electronic medical records, which typically have high noise-to-signal ratio and many possible sources of bias. Second, there is an underlying risk of sampling or selection bias of the two research studies. While the ACCORD cohort consisted of adults at increased risk for CVD with a longer duration of diabetes and higher glycated hemoglobin level (Table 2), the UKB participants were younger and relatively healthy (Table 1). We have also shown that genetic contributions to chronic kidney disease are larger in the non-diabetes group than in the diabetes group, while heritability for macrovascular complications stay similar between two groups. Several reasons may explain the differences: (1) outcome misclassifications due to EHR-based phenotyping; (2) un-accounted confounders, such as medications; (3) higher heritability of kidney diseases among the general population than that of DKD among diabetes (54). The heritability of macrovascular complications was similar between diabetes and non-

diabetes groups. It may be because GWAS hits for CVD among the diabetes population tend to coincide with those in the general population (55).

This heritability analysis represents the first systematic investigation of SNP heritability for diabetes complications in the white subset of UKB and ACCORD cohorts. It adds to the existing heritability information derived primarily from family or small cohort studies and supports the need for further genetic investigation of diabetes complications, both for general disease outcomes and for specific phenotypes. Replication studies will be instrumental in strengthening conclusions in this area.

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Dr. Jin J Zhou is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The authors have no conflicts of interest to declare.



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Running title: HERITABILITY OF DIABETES COMPLICATIONS

## Figures

Figure 1. Heritability estimates and standard errors of diabetes complication outcomes using the UKB data. (Panel A) Estimates from genotype and imputed data are obtained using the GREML-SC and GREML-LDMS-I approaches, respectively. We adjusted for sex, age in 2010, and the top ten genetic principal components. (Panel B) GREML-LDMS estimates with 8 bins (2 LD bins for each of the 4 MAF bins). For each phenotype, the sum of estimates from the 8 bins of MAF shown in panel B is equal to the estimate represented as the green bar on panel A.

Figure 2. Heritability estimates and standard errors of diabetes complications using the ACCORD data. (Panel A) Estimates from genotype and imputed data are obtained using the GREML-SC and GREML-LDMS-I approaches, respectively. We adjusted for sex, age at baseline, CVD history at baseline, and the top five genetic principal components. (Panel B) GREML-LDMS estimates with 8 bins (2 LD bins for each of the 4 MAF bins). For each phenotype, the sum of estimates from the 8 bins of MAF shown in panel B is equal to the estimate represented as the green bar on panel A.

Figure 3. Enrichment of the selected ACCORD phenotypes in tissue-specific gene expression annotations used in Finucane et al. (45). The black dashed lines indicate the Bonferroni significance threshold ( $p < 0.05/53$ ).

## Running title: HERITABILITY OF DIABETES COMPLICATIONS

**Tables**

	Outcome	Definition
UKB	DR	Composite for diabetic eye disease in self-reported, primary care, or hospital admission records
	DKD	Chronic/diabetic kidney disease in self-reported, primary care, hospital or death records
	Macroalbuminuria	UACR > 33.9 mg/mmol at either UKB visit
	Microalbuminuria	UACR > 3.4 mg/mmol at either UKB visit
	CVD	Composite for CVD. Either MI, Ischemic stroke, unstable angina, or percutaneous coronary intervention
	MI	Myocardial infarction from self-report, primary care, hospital admissions, or death records. Controls were required to have no evidence of certain cardiovascular diseases
	Stroke any	Either ischemic, hemorrhagic, or unspecified stroke
	Stroke infarct	Ischemic stroke
	Retin1	Retinal photocoagulation or vitrectomy to treat retinopathy
	Retin2	Eye surgery for cataract extraction
ACCORD	Retin3	Three-line change in visual acuity
	Retin4	Severe vision loss (Snellen fraction < 20/200)
	Neph1	Doubling of baseline serum creatinine or > 20 mL/min per 1.73 m <sup>2</sup> decrease in estimated GFR
	Neph2	Development of macroalbuminuria. Urine Albumin:Creatinine ratio (UACR) ≥ 33.9 mg/mmol
	Neph3	End-stage renal disease (ESRD, i.e., initiation of dialysis or a rise of serum creatinine to 3.3 mg per deciliter (292 μ mol/L))
	Neph4	Development of Neph1, Neph2, or Neph3
	Neph5	Development of microalbuminuria. UACR ≥ 3.4 mg/mmol
	Primary	Composite for CVD. Either nonfatal MI, nonfatal/total stroke, death from cardiovascular causes, new/worsening congestive heart failure, or major coronary heart disease
	Nonfatal MI	Nonfatal myocardial infarction
	Major CHD	Major coronary heart disease
	Total mortality	All-cause mortality
	CVD mortality	Mortality from cardiovascular causes
	Nonfatal stroke	Nonfatal stroke
	Total stroke	Total stroke

Table 1. Outcome definitions for UKB and ACCORD.

Characteristics	N=26,387
Age in 2010, years*	60.9 ± 7.0
Age at first DM diagnosis, years*	56.4 ± 12.4
BMI*	31.5 ± 5.7
Lipids at baseline, mmol/L*	
High density lipoprotein	1.2 ± 0.3
Low density lipoprotein	3.0 ± 0.9
Triglycerides	2.3 ± 1.3
Blood pressure at baseline, mmHg*	
Systolic blood pressure	143.5 ± 18.8
Diastolic blood pressure	83.3 ± 10.9
HbA1c at initial visit, mmol/mol*	48.8 ± 13.3
HbA1c at repeat visit, mmol/mol*	48.6 ± 11.1
Sex, %	
Male	61.4
Female	38.6
Current/former smoking, %	
Yes	56.1
No	43.4
Missing	0.5
DM Type, %	
Type 1	2.9
Type 2	69.0
Unspecified	28.1

Table 2. Characteristics of the non-Hispanic white participants used in the UKB analyses. The initial visit occurred between 2006 to 2010, depending on the individual. \* Denotes mean ± standard deviation. DM, Diabetes mellitus.

Characteristics	N=4,318
Age at baseline, years*	63.2 ± 6.4
Years since diabetes diagnosis*	10.7 ± 7.4
Lipids at baseline, mg/dL*	
High density lipoprotein	40.2 ± 10.6
Low density lipoprotein	102.8 ± 33.1
Triglycerides	208.7 ± 158.4
Blood pressure at baseline, mmHg*	
Systolic blood pressure	135.2 ± 17.3
Diastolic blood pressure	74.2 ± 10.8
HbA1c at baseline, %*	8.2 ± 1.0
Sex, %	
Female	34.4
Male	65.6
Smoked cigarettes in last 30 days, %	
Yes	12.4
No	87.6
Smoked >100 cigarettes during lifetime, %	
Yes	50.4
No	37.9
NA	11.7
CVD history at baseline, %	
Yes	36.1
No	63.9
Glycemic treatment arm, %	
Intensive	49.8
Standard	50.2

Table 3. Characteristics of the non-Hispanic white participants used in the ACCORD analyses. \* Denotes mean ± standard deviation.

## Running title: HERITABILITY OF DIABETES COMPLICATIONS

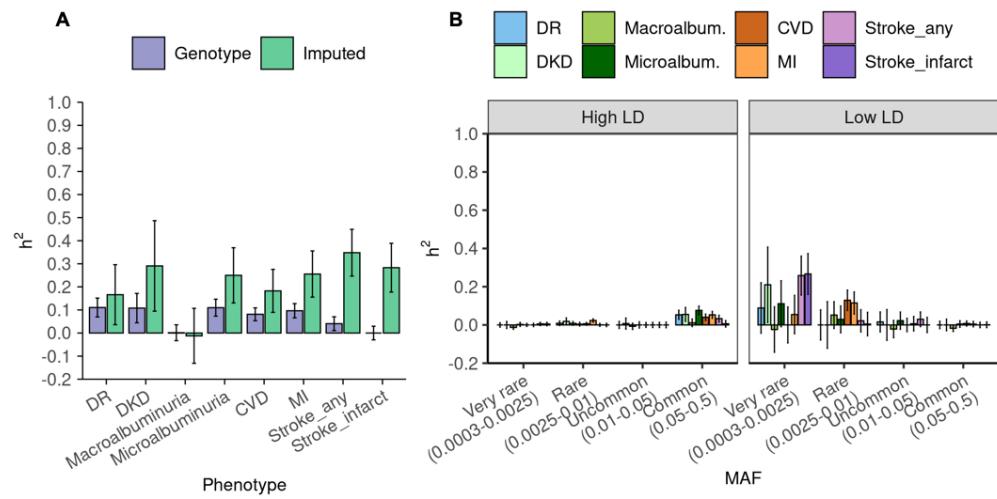
Phenotype	Diabetes (N = 26,387)				Diabetes – Type 2 only (N = 18,198)				Non-diabetes (N = 26,387)	Diabetes and non-diabetes (N = 52,774)
	Proportion of cases	n	V(G)/V(p) (SE)		Proportion of cases	n	V(G)/V(p) (SE)		V(G)/V(p) (SE)	V(G)/V(p) (SE)
			GREML- SC	GREML- LDMS			GREML- LDMS	GREML- LDMS	GREML- LDMS	GREML- LDMS
DR	0.541	11739	0.110 (0.041)	0.166 (0.130)	0.514	7516	0.029 (0.199)	NA	NA	NA
DKD	0.256	7707	0.108 (0.064)	0.291 (0.196)	0.259	4969	0.237 (0.300)	0.453 (0.15)	0.217 (0.089)	
Macroalbumuria	0.029	13246	0.001 (0.034)	0.000 (0.119)	0.026	9332	NA	NA	0.026 (0.085)	
Microalbumuria	0.238	13246	0.110 (0.037)	0.250 (0.119)	0.230	9332	0.214 (0.163)	0.155 (0.201)	0.226 (0.079)	
CVD	0.159	17540	0.081 (0.028)	0.183 (0.093)	0.170	11506	0.208 (0.139)	0.176 (0.069)	0.085 (0.041)	
MI	0.094	16310	0.097 (0.031)	0.256 (0.100)	0.099	10610	0.192 (0.149)	0.278 (0.072)	0.141 (0.043)	
Stroke any	0.087	16002	0.041 (0.030)	0.348 (0.101)	0.095	10434	0.590 (0.151)	NA	0.199 (0.044)	
Stroke infarct	0.042	15429	0.000 (0.029)	0.283 (0.106)	0.047	10030	0.330 (0.158)	0.141 (0.073)	0.167 (0.045)	

Table 4. GREML-SC estimates for individuals with diabetes using the UKB genotype data and GREML-LDMS estimates for individuals with 1) diabetes (both type 1 and type 2), 2) type 2 diabetes only, 3) without diabetes, and 4) diabetes and non-diabetes groups combined using the UKB imputed data. Non-diabetes individuals (N=26,387) in this table were randomly sampled from a pool of 296,315 individuals with no diabetes in the UKB data. Estimates for the last column were obtained from combining diabetes and non-diabetes groups (n=52,774). N, number of total samples in the group. n, number of samples without missing phenotype. V(G)/V(p), proportion of phenotypic variance explained by genotypes, i.e., heritability, as observed in the study population. SE, standard error. MI, myocardial infarction. DR, diabetic retinopathy.

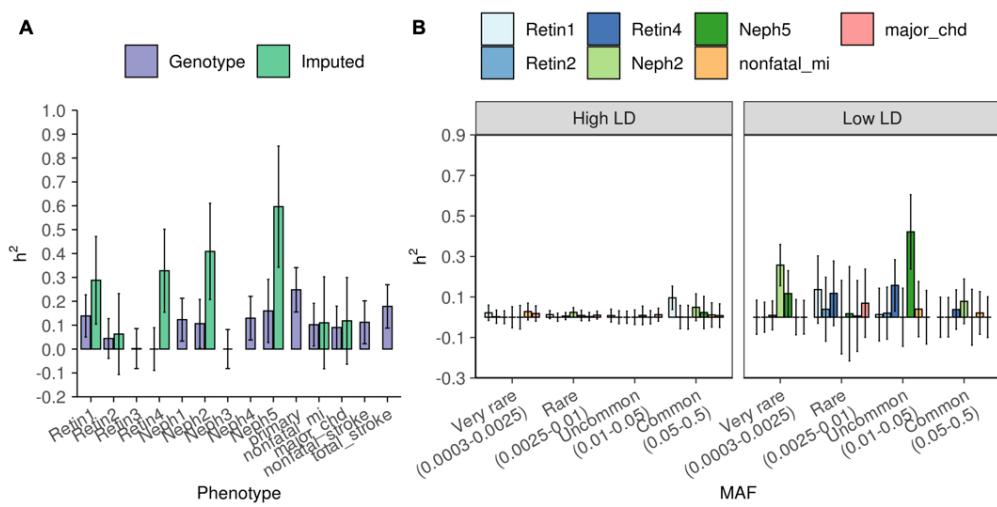
## Running title: HERITABILITY OF DIABETES COMPLICATIONS

Phenotype	Proportion of cases in the sample	n	V(G)/V(p) (SE)	
			GREML-SC	GREML-LDMS
Retin1	0.084	4318	0.139 (0.088)	0.288 (0.183)
Retin2	0.158	4318	0.044 (0.083)	0.063 (0.169)
Retin3	0.360	4318	0.002 (0.084)	NA
Retin4	0.068	4318	0.000 (0.089)	0.328 (0.174)
Neph1	0.591	4318	0.123 (0.090)	NA
Neph2	0.070	3866	0.106 (0.101)	0.409 (0.201)
Neph3	0.028	4318	0.000 (0.082)	NA
Neph4	0.616	4318	0.129 (0.091)	NA
Neph5	0.241	2912	0.160 (0.132)	0.596 (0.254)
Primary	0.106	4318	0.248 (0.093)	NA
Nonfatal MI	0.071	4318	0.102 (0.090)	0.110 (0.192)
Major CHD	0.129	4318	0.090 (0.089)	0.118 (0.181)
Total mortality	0.066	4318	0.013 (0.088)	NA
CVD mortality	0.028	4318	0.094 (0.089)	NA
Nonfatal stroke	0.015	4318	0.112 (0.090)	NA
Total stroke	0.018	4318	0.179 (0.091)	NA

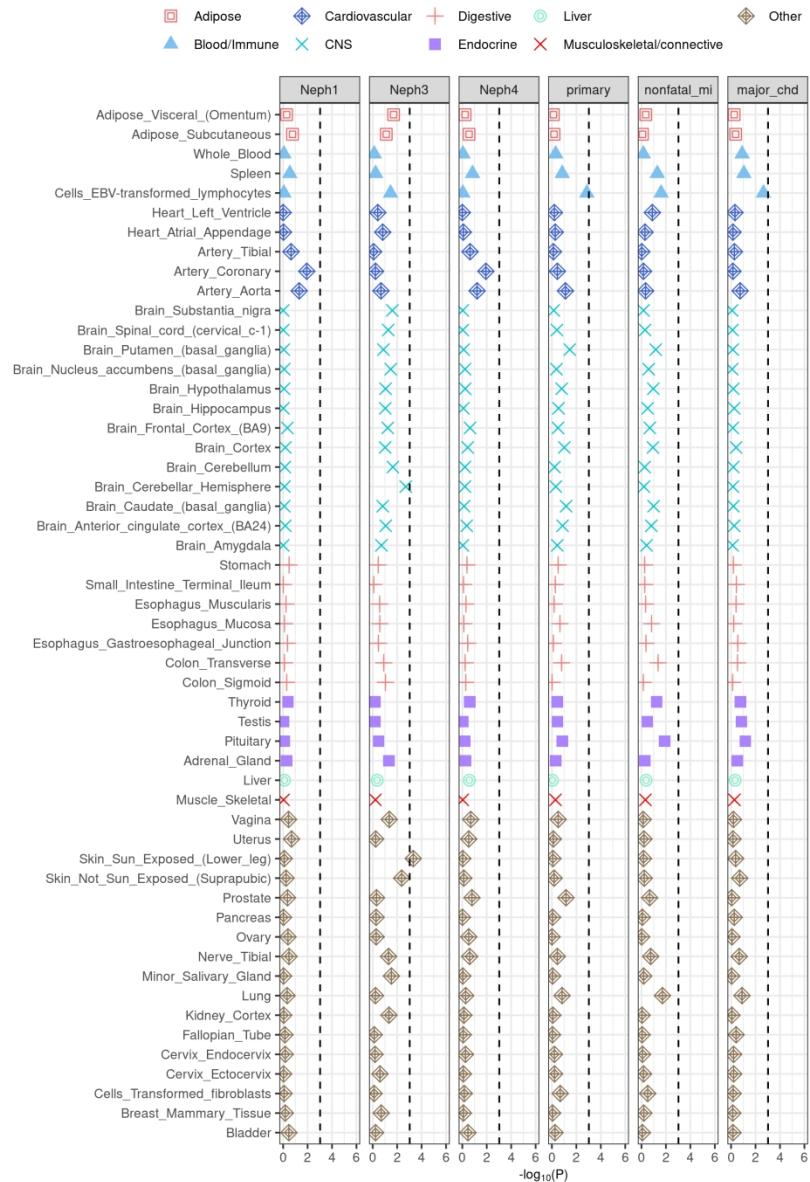
Table 5. GREML-SC and GREML-LDMS estimates using the ACCORD genotype and imputed data, respectively. NA under GREML-LDMS, the GREML analysis failed to run due to the small sample size. n, number of samples without missing phenotype. V(G)/V(p), proportion of phenotypic variance explained by genotypes, i.e., heritability, as observed in the study population. SE, standard error.



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180x89mm (150 x 150 DPI)



457x660mm (118 x 118 DPI)

## Supplemental Material

### Systematic heritability and heritability enrichment analysis for diabetes complications in ACCORD and UK Biobank Studies

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## UKB phenotype definition

**Myocardial infarction (MI).** Cases of MI were identified by the International Classification of Disease, Ninth and Tenth Revision (ICD-10) code families I21, I22, and I23 (Acute, subsequent, and complications of MI). The primary source was UKB's fields 131298, 131300, and 131302 (Date I21/I22/I23 first reported, respectively). These fields gather information from hospital admissions, death records, primary care, and self-reported outcomes from surveys taken at UK Biobank assessment centers at initiation into the study and map them to three-digit ICD-10 categories. To obtain the most up-to-date information, we also gathered these ICD-10 code families directly from hospital admission and death records. We also included cases of MI identified through UKB's algorithmically defined outcome (field 42000). Controls were required to have no evidence of certain cardiovascular diseases.

**Unstable angina.** Cases of unstable angina were identified by the ICD-10 code I20.0, extracted from hospital admissions and death records.

**Ischemic stroke (Stroke infarct).** Cases of ischemic stroke were identified in a manner similar to MI, using a combination of UKB's first occurrence field 131366 (Date I63 first reported (cerebral infarction), the algorithmically defined outcome for ischemic stroke (field 42008), and the ICD-10 code I63 in hospital admission or death records. Controls were required to have no evidence of cerebrovascular disease (ICD10 codes I6\*, G45\*, G46\*).

**Stroke (Stroke any).** Stroke was taken to be the first occurrence of either ischemic or hemorrhagic stroke, or of unspecified stroke via UKB fields 42006 (algorithmically defined stroke), 131368 (unspecified stroke), or ICD10 code I64. Controls were required to have no evidence of cerebrovascular disease (ICD10 codes I6\*, G45\*, G46\*).

**Percutaneous coronary intervention (PCI).** Cases of PCI were identified through OPCS4 codes K40, K41, K42, K43, K44, K45, K46, K483, K49, K501, K75, K76, and UKB self-report codes 1070 (coronary angioplasty) and 1095 (coronary bypass grafts). Controls were not to have self-reported any non-coronary revascularization procedures.

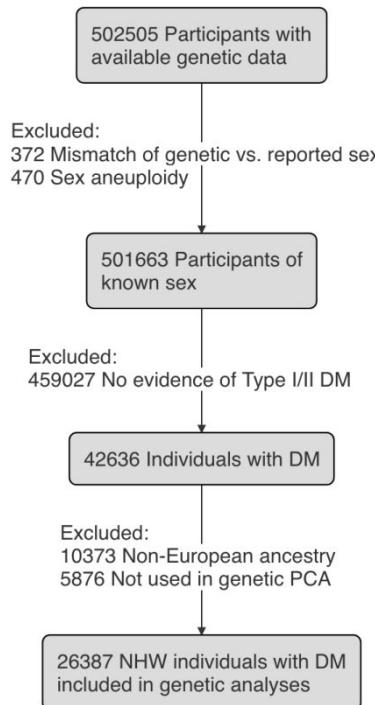
**Composite CVD (CVD).** A composite CVD event consisted of either MI, ischemic stroke, unstable angina, or PCI. The first date of CVD was taken as the first date of any of these events. Controls were required to satisfy all the conditions for each component outcome.

**Macroalbuminuria/Microalbuminuria.** Urine Albumin:Creatinine ratio (UACR) was calculated using UKB fields 30700 (urine creatinine), 30500 (urine microalbumin), and 30505 (reason for missing urine microalbumin). UACR above 33.9 was considered macroalbuminuria, while above 3.4 was considered microalbuminuria. In cases where urine microalbumin was below detectable levels, albuminuria status was inferred from urine creatinine where possible.

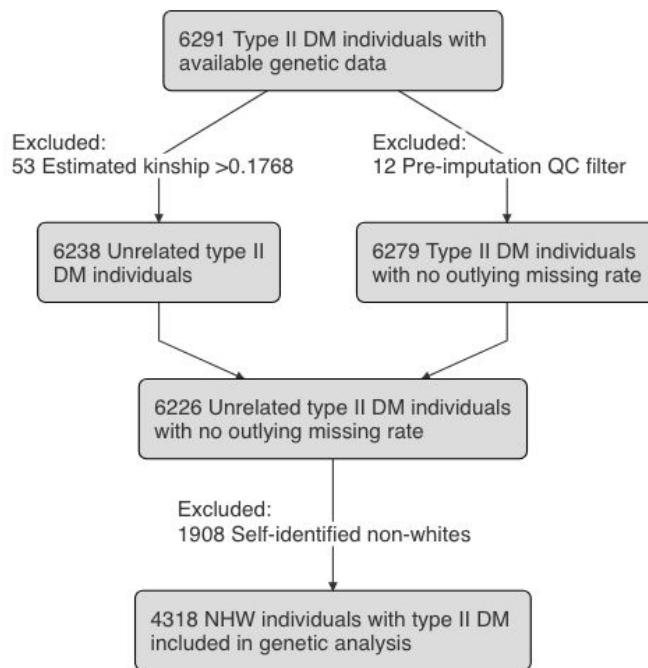
**Chronic/Diabetic kidney disease (DKD).** DKD was identified through UKB's algorithmically defined end-stage renal disease (field 42026, previously described), ICD10 codes E1\*.2 (diabetes mellitus with renal complications), E18[0345] (chronic kidney disease stage 3-5, end-stage), N08.3 (glomerular disorders in diabetes mellitus) in hospital or death records, self-reported diabetic kidney disease, two or more consecutive eGFR (EPI creatinine)  $< 60 \text{ mL/min}/1.73\text{m}^2$  measured 90+ days apart from either UK Biobank Assessment Center or primary care data. The date of the first DKD was taken as the first occurrence of any of the previous codes/events. Controls were required not to have micro/macroalbuminuria or a list of exclusion codes. Controls were required to have at least five years of follow-up since their diabetes diagnosis, and cases were required to have more than five years between their date of diabetes diagnosis and first DKD.

**Diabetic eye disease (DR).** DR was determined using the ICD10 codes E1\*.3 (diabetes mellitus with ophthalmic complications), H36.0 (diabetic retinopathy), and H28.0 (Diabetic Cataract), as well as a set of primary care codes. Since most cases were identified through primary care data, controls were required to have this data available in order to reduce misclassification. Controls were also required not to have glaucoma, cataract, or non-diabetic/unspecified retinopathy.

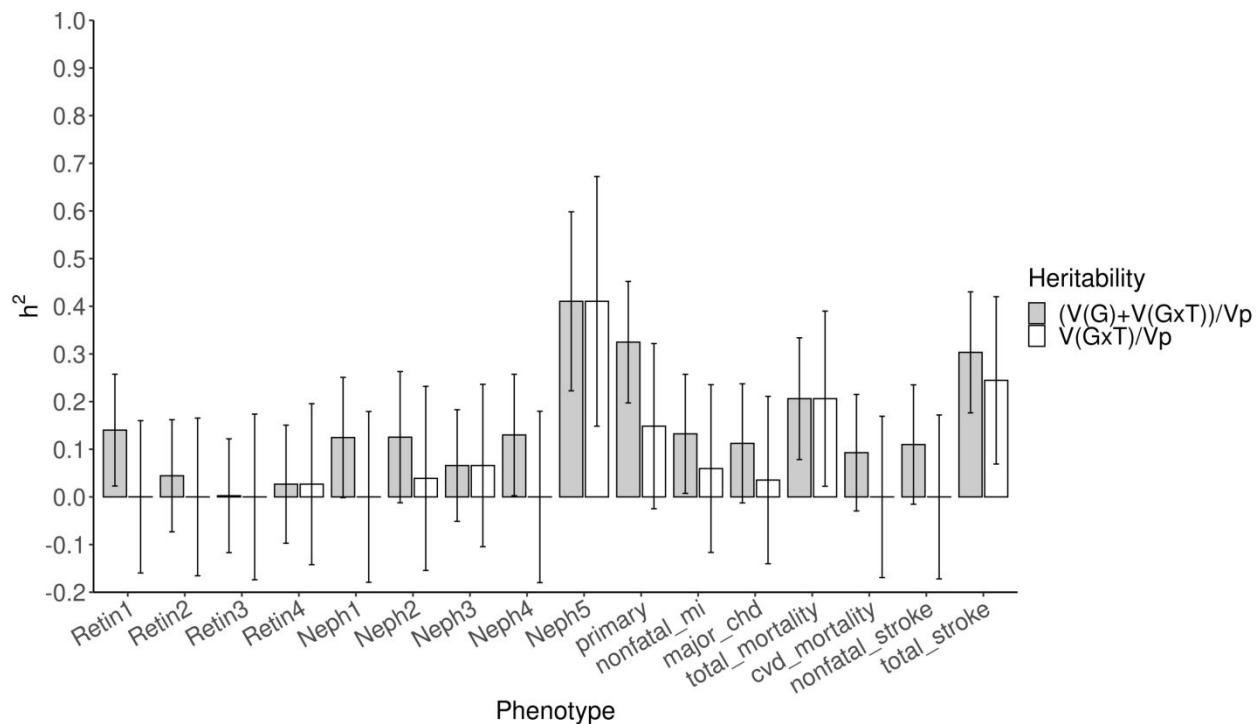
## Additional figures and tables



Supplemental Figure 1. Diagram depicting a flow of participants used in the UKB analyses. DM, diabetes mellitus. NHW, non-Hispanic white.

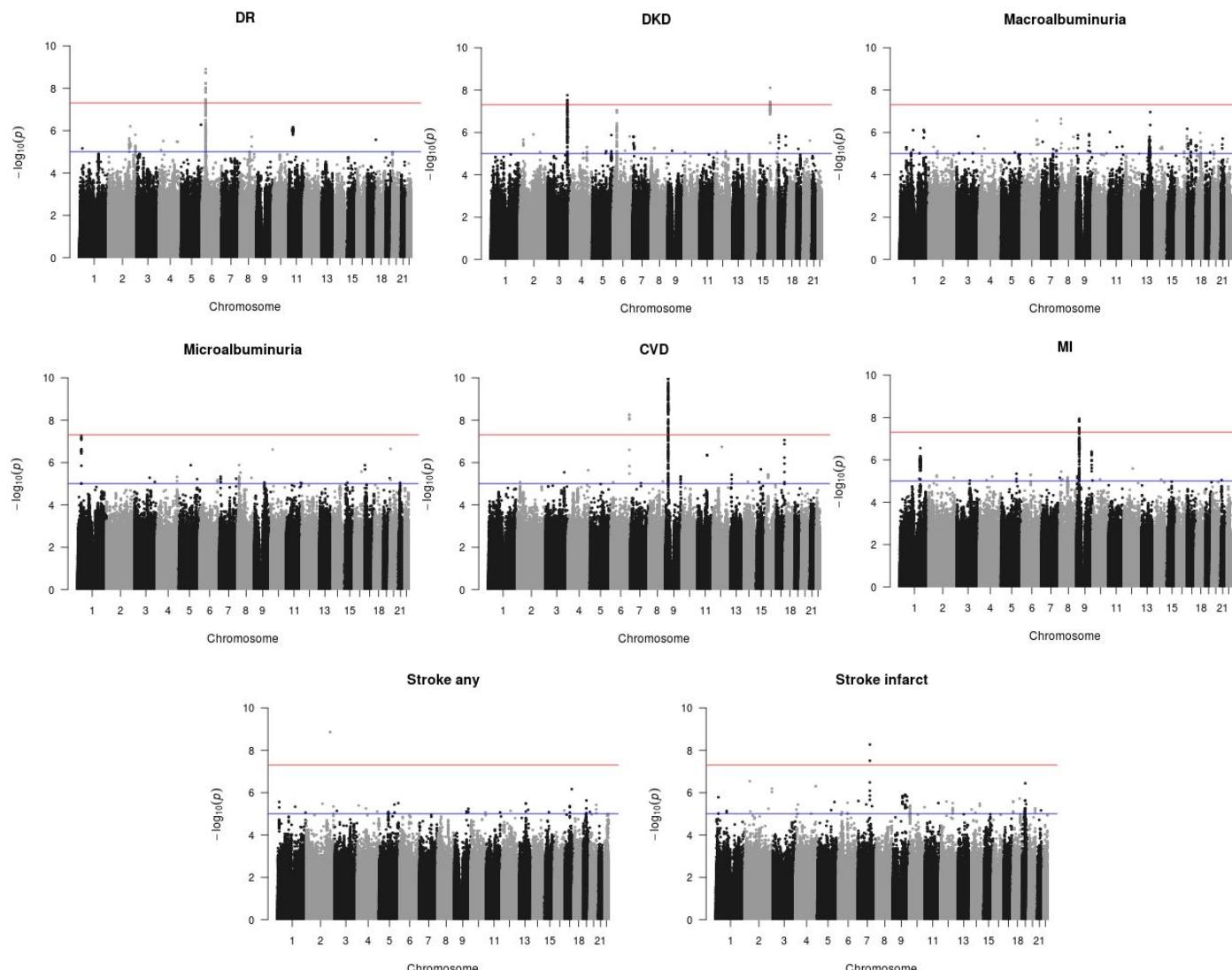


Supplemental Figure 2. Diagram depicting a flow of participants used in the ACCORD analyses. DM, diabetes mellitus. NHW, non-Hispanic white.

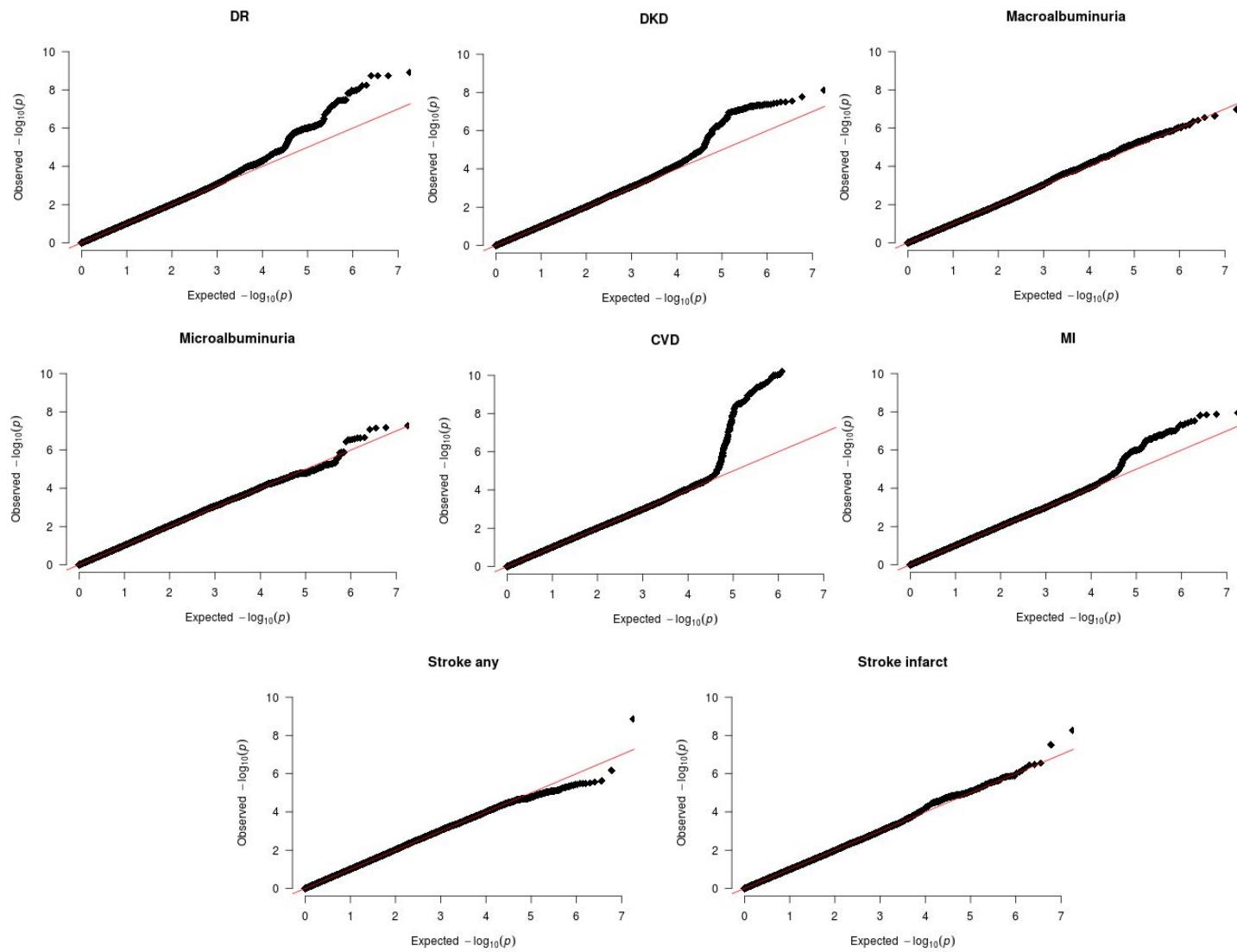


Supplemental Figure 3. Heritability estimates and standard errors of diabetes complication outcomes using the ACCORD genotype data and incorporating interaction with intensive glycemic treatment.

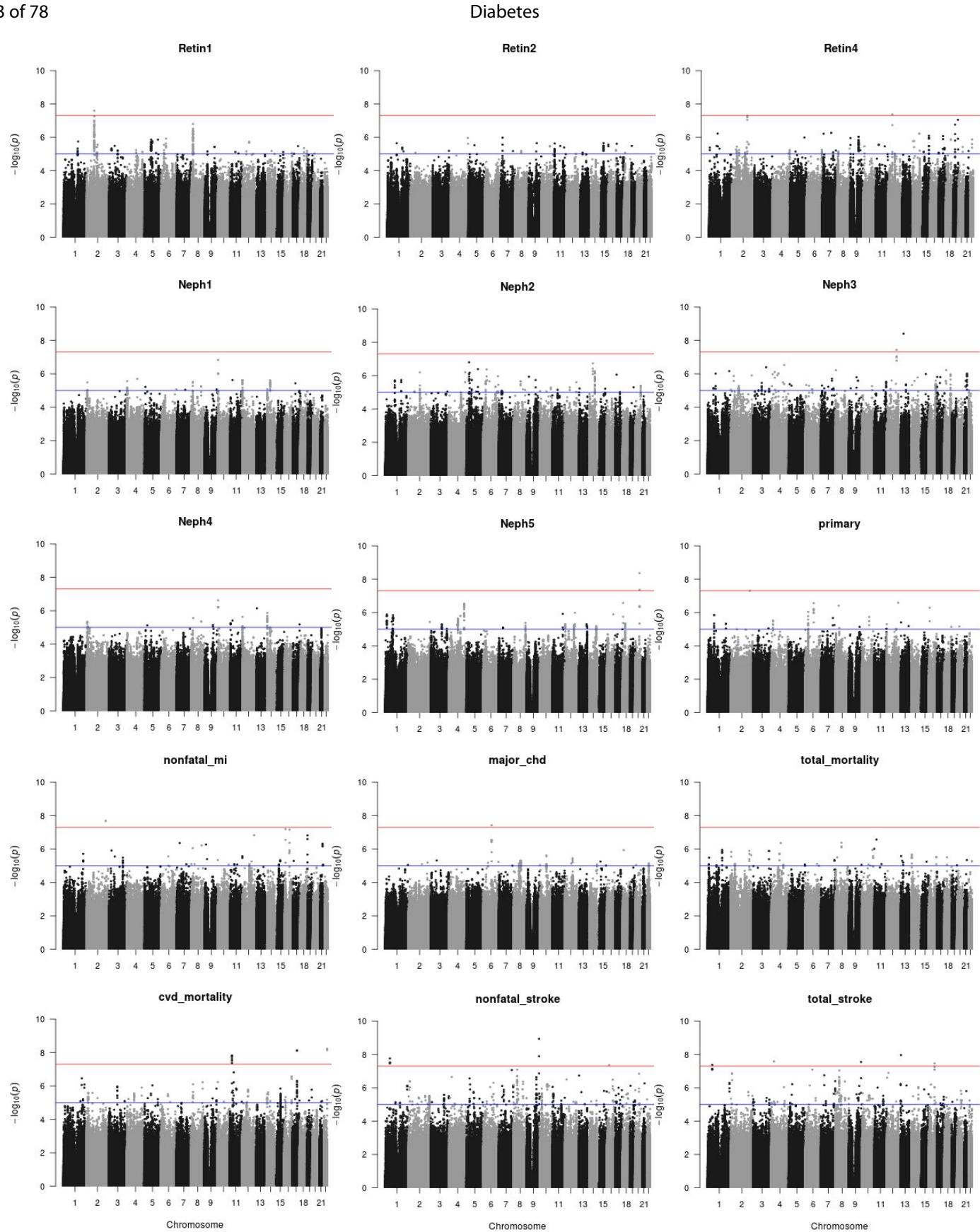
The grey bar represents the genetic plus interaction components, while the white bar signifies the interaction component.  $V(G)$ , genetic variance.  $V(GxT)$ , variance for interaction between genetics and intensive treatment.  $Vp$ , phenotypic variance.



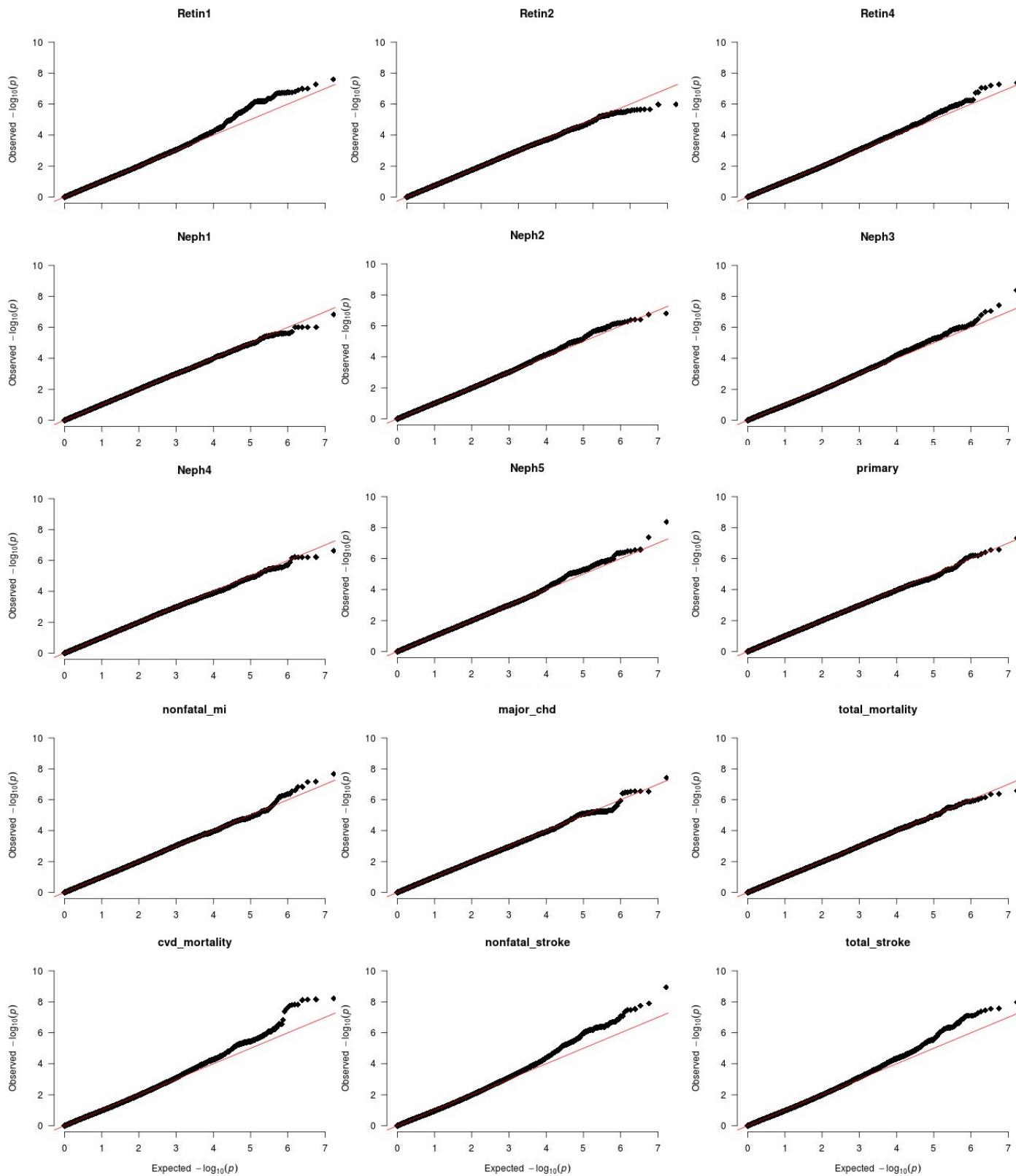
**Supplemental Figure 4.** Manhattan plots of GWAS  $p$ -values for the UKB phenotypes. The red line signifies a genome-wide significance level ( $p = 5 \times 10^{-8}$ ), while the blue line is a suggestive line ( $p = 1 \times 10^{-5}$ ).

Supplemental Figure 5. QQ plots of GWAS  $p$ -values for the UKB phenotypes.

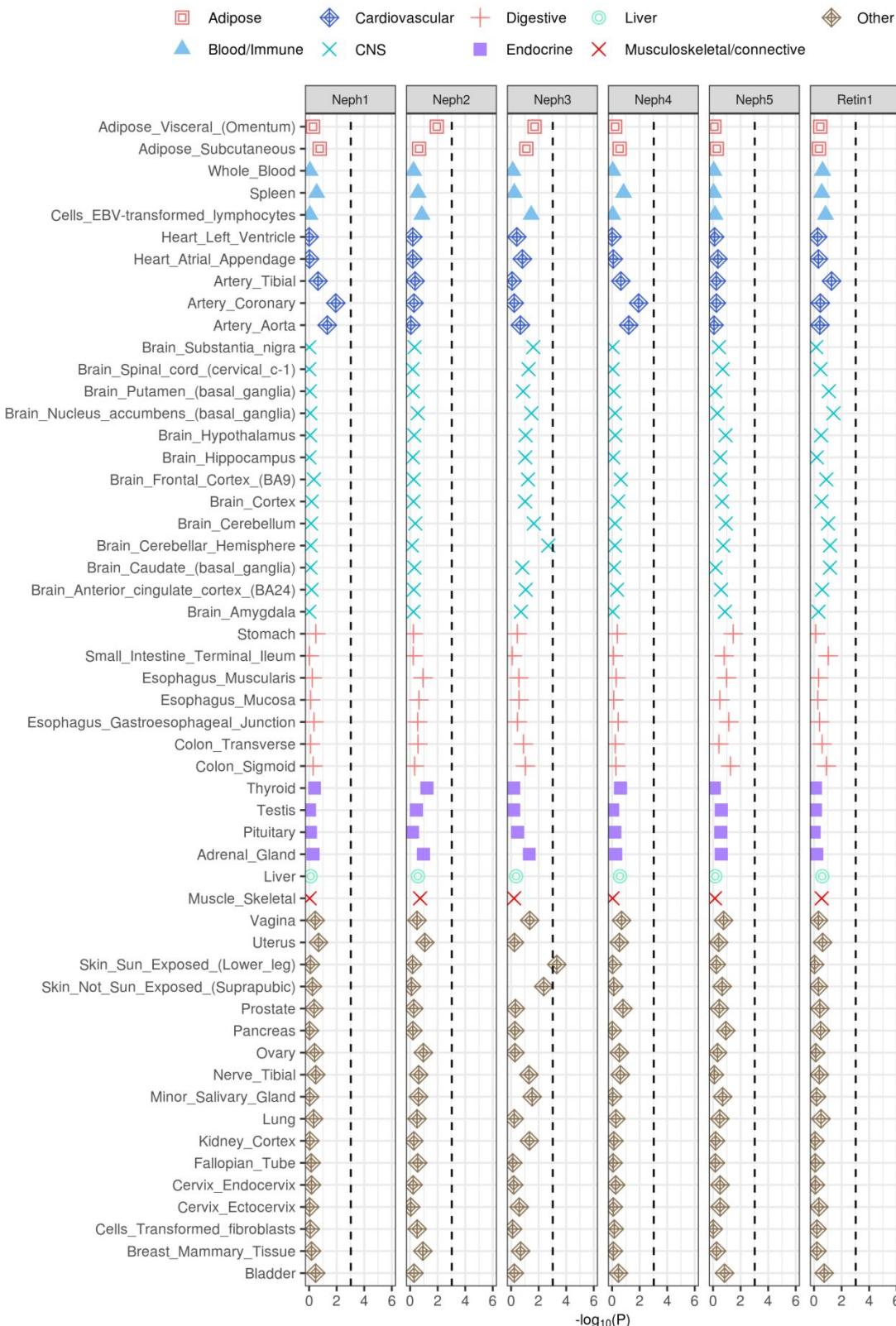




**Supplemental Figure 6. Manhattan plots of GWAS  $p$ -values for the ACCORD phenotypes.**  
The red line signifies a genome-wide significance level ( $p = 5 \times 10^{-8}$ ), while the blue line is a suggestive line ( $p = 1 \times 10^{-5}$ ).

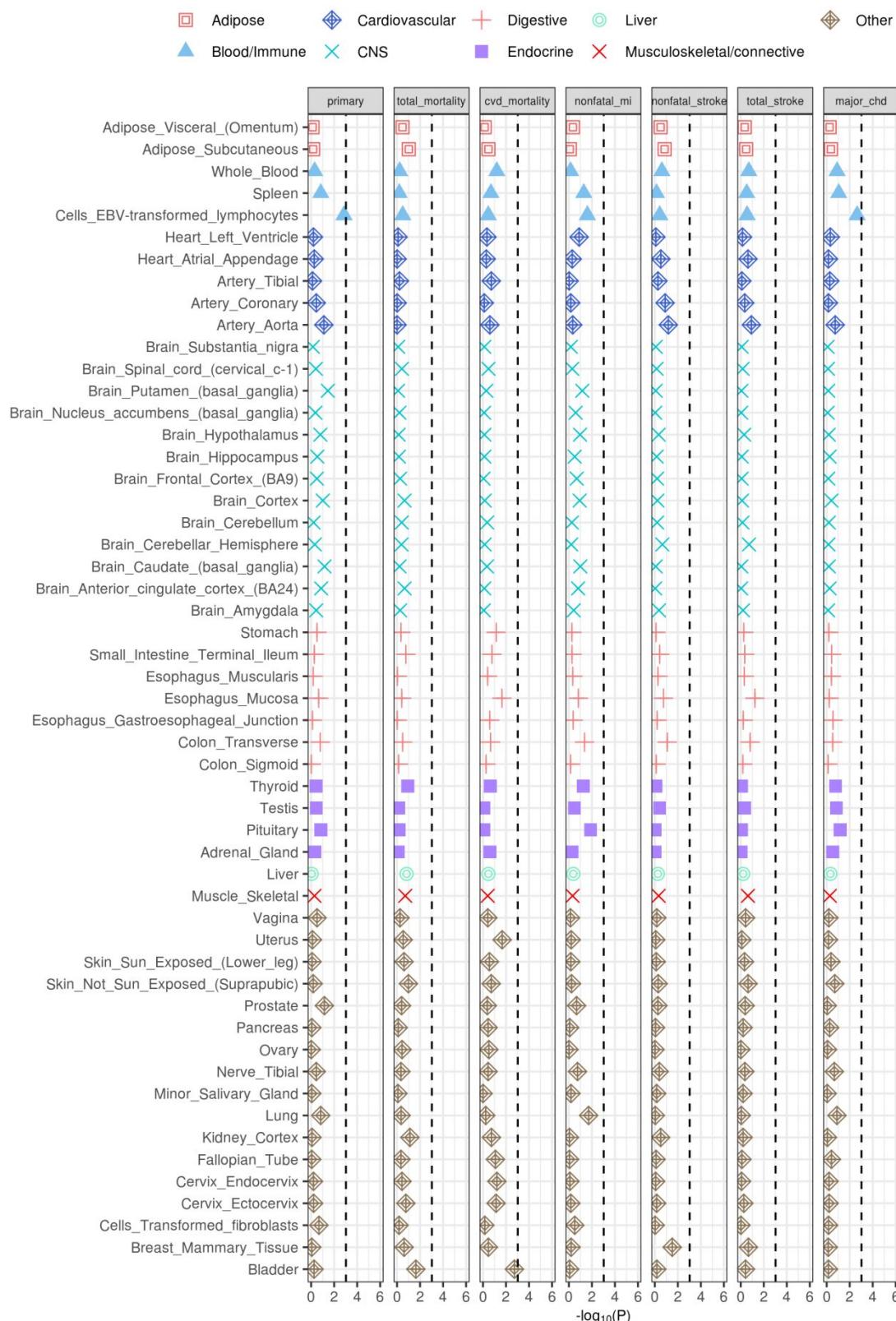


Supplemental Figure 7. QQ plots of GWAS  $p$ -values for the ACCORD phenotypes.



Supplemental Figure 8. Enrichment of the ACCORD microvascular complication phenotypes in tissue-specific gene expression annotations used in Finucane et al. (17).

The black dashed lines indicate the Bonferroni significance threshold ( $p < 0.05/53$ ).



Supplemental Figure 9. Enrichment of the ACCORD macrovascular complication phenotypes in tissue-specific gene expression annotations used in Finucane et al. (1).

The black dashed lines indicate the Bonferroni significance threshold ( $p < 0.05/53$ ).

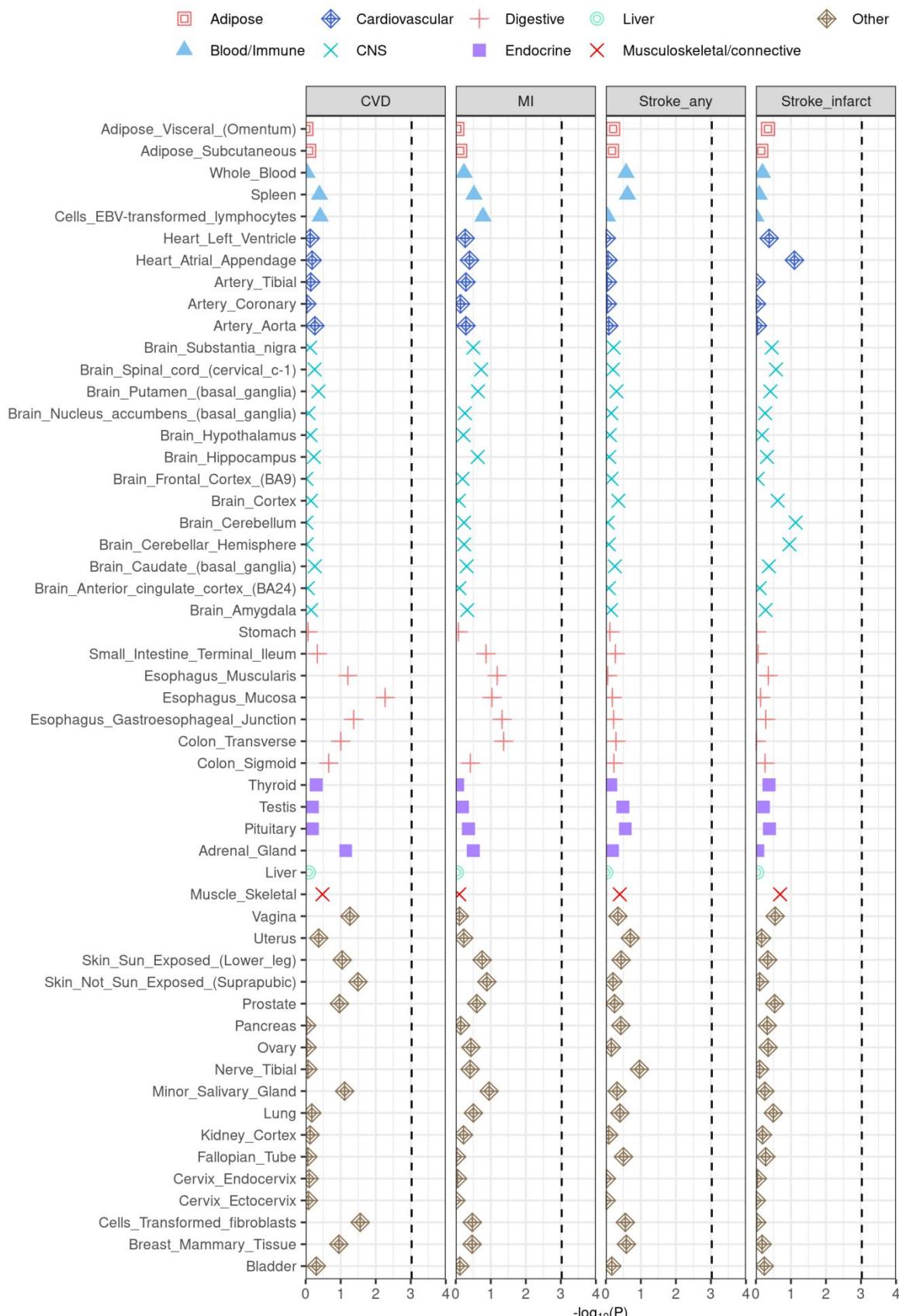
## Diabetes



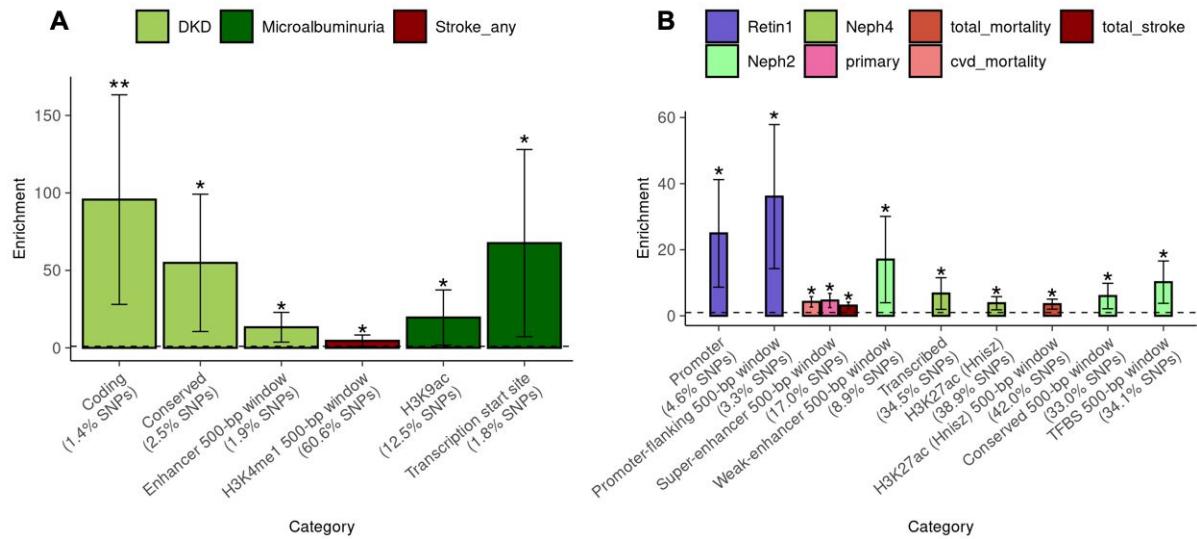
Supplemental Figure 10. Enrichment of the UKB microvascular complication phenotypes in tissue-specific gene expression annotations used in Finucane et al. (1).  
The black dashed lines indicate the Bonferroni significance threshold ( $p < 0.05/53$ ).

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## Diabetes



Supplemental Figure 11. Enrichment of the UKB macrovascular complication phenotypes in tissue-specific gene expression annotations used in Finucane et al. (1).  
The black dashed lines indicate the Bonferroni significance threshold ( $p < 0.05/53$ ).



Supplemental Figure 12. Enrichment estimates for selected annotations and traits using the (A) UKB and (B) ACCORD imputed data.

The dashed line represents no enrichment (enrichment=1). One asterisk indicates nominal significance at  $p < 0.05$ . Enrichment =  $\text{Pr}(h^2)/\text{Pr}(\text{SNPs})$ . TFBS, Transcription factor binding site. DHS, DNase I hypersensitivity sites.

	Neph1	Neph2	Neph4	Neph5	Retin1
primary	-0.54 (0.41)	0.12 (0.43)	-0.53 (0.40)	0.14 (0.42)	-0.52 (0.39)
Neph1		0.47 (0.62)	0.96 (0.05)	0.25 (0.57)	0.19 (0.50)
Neph2			0.49 (0.57)	0.11 (0.62)	0.70 (0.67)
Neph4				0.33 (0.56)	0.32 (0.51)
Neph5					0.52 (0.59)

Supplemental Table 1. Genetic correlation estimates and the standard errors between selected phenotypes using the ACCORD genotype data.

Adjusted for sex, CVD history at baseline, age at baseline, and the top five genetic principal components.

	DKD	Microalbuminuria	DR
CVD	0.25 (0.28)	-0.11 (0.24)	0.26 (0.25)
DKD		0.36 (0.27)	0.35 (0.35)
Microalbuminuria			0.07 (0.25)

Supplemental Table 2. Genetic correlation estimates and the standard errors between selected phenotypes using the UKB genotype data.

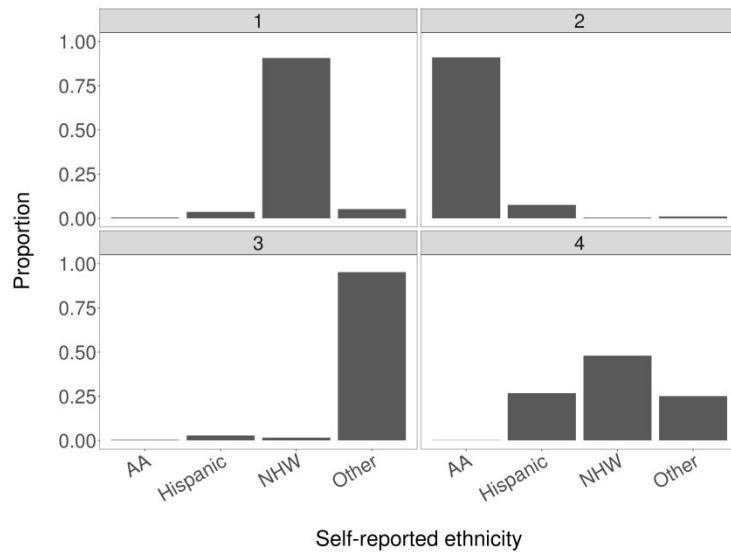
Adjusted for sex, age in 2010, and the top ten genetic principal components.

## Methods

### Genotyping in UKB and ACCORD

**UKB.** Genome-wide genotyping was performed on all UK Biobank participants using the UK Biobank Axiom Array.

**ACCORD.** After downloading the data from dbGap (Study Accession: phs001411.v1.p1), we used genetic variants genotyped on Affymetrix Axiom Biobank 1 chips from the University of North Carolina (UNC) and merged data under two different institutional review board (IRB) protocols—HMB-IRB (73941) and DS-CDKD-IRB (73944). There were 6,291 (2,335 females and 3,956 males) with 546,800 SNPs in the merged dataset. Based on self-reported ethnicity, there were 4,369 non-Hispanic whites (NHW), 935 African-Americans (AA), 381 Hispanics, and 606 others. We checked the validity of self-reported ethnicity by running the ADMIXTURE software (2) with K=4, categorizing each individual into a group with the highest probability, and comparing the categories against self-reported ethnicity (see Supplemental Figure 13). We can infer that the ADMIXTURE ancestry groups 1, 2, 3, and 4 represent NHW, AA, Other, and Hispanic, respectively. Considering that Hispanics are a highly genetically heterogeneous admixed group, the distribution in ADMIXTURE ancestry group 4 (Supplemental Figure 13) appears reasonable.



Supplemental Figure 13. Bar graph indicating the percentage of self-reported ethnicity groups categorized into each ADMIXTURE bin.

Each individual is binned based on the largest proportion from ADMIXTURE.

## Heritability estimation using genotype data

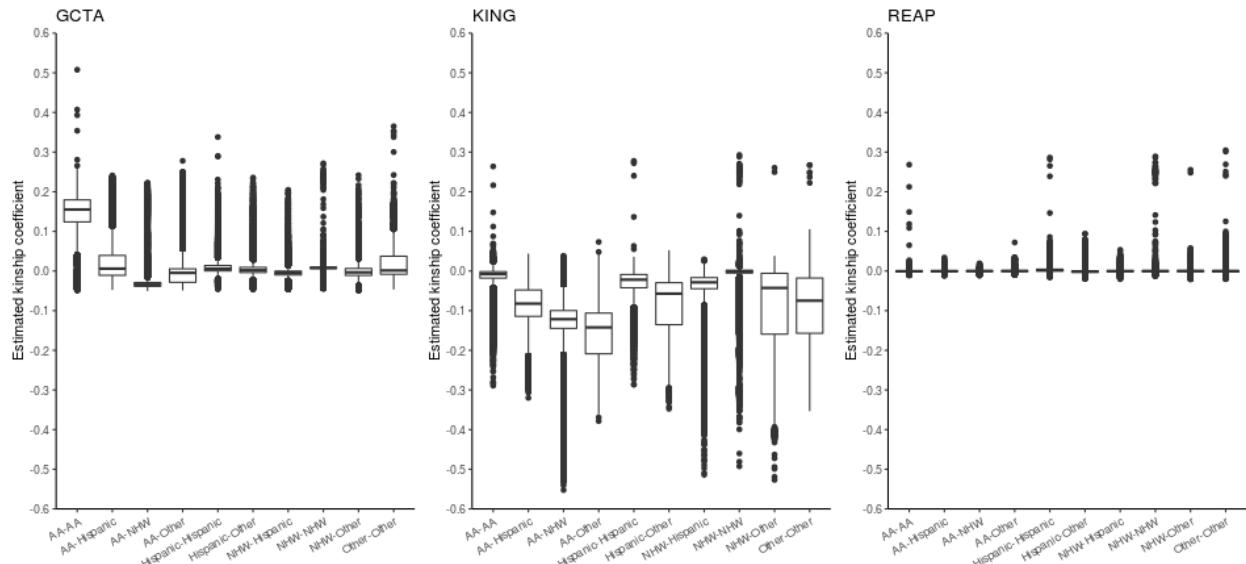
**UKB.** We extracted the NHW diabetes cohort (n=26,387) and computed the GRM via the REAP approach, for which necessary proportions were obtained from the ADMIXTURE software with K=3. No individuals were pruned out under the relatedness threshold (0.1768). We estimated heritability using the GREML-SC approach while adjusting for sex, age in 2010, and the top ten genetic principal components. Also calculated using the UKB genotype data were genetic correlations between phenotypes (see Supplemental Table 2).

**ACCORD.** We calculated a Genetic Relationship Matrix (GRM) using SNPs from all autosomes. The GRM uses SNP data to measure the relatedness between each pair of individuals in our sample. This GRM replaces the known information about relatedness found in pedigrees. While the ACCORD trial did not deliberately recruit related individuals, we took a step to avoid inflation caused by cryptic (i.e., unknown) relatedness. We selectively excluded one of any pair of individuals with an estimated kinship greater than the separation between full and half-siblings (estimated kinship  $> (1/2)^{5/2} = 0.1768$ ) in a way to maximize the remaining sample size (3; 4). Initially, we used the software package Genome-wide Complex Trait Analysis (GCTA) (5) to construct the GRM. However, the degree of relatedness calculated by GCTA appeared inflated (See Supplemental Figure 14). The inflation may be mainly due to population heterogeneity in the data. Next, we tried Kinship-based INference for Genome-wide association studies (KING) (3). As seen in Supplemental Figure 14, estimated kinship-coefficient values from KING were systematically negative, which ultimately led the GRM to be not positive semi-definite. Finally, we used Relatedness Estimation in Admixed Populations (REAP) (6), which produced more robust results. The REAP approach requires individual ancestry proportions and allele frequencies for each ancestral population. Both proportions were obtained using the

ADMIIXTURE software (2) with the number of ancestral populations specified as four (K=4).

The number four was chosen because there were four different self-reported ethnic groups (NHW, AA, Hispanic and other).

We only extracted NHW samples after pruning related individuals, leaving us with 4,329 samples. With the GRM constructed from REAP, heritability was estimated via GCTA (4). We adjusted for sex, CVD history at baseline, age at baseline, and the top five genetic principal components. An additional analysis that incorporated interaction with glycemic intensive treatment arm (intensive=1, standard=0) is shown in Supplementary Figure 3. We also estimated the genetic correlation between binary traits via the GCTA software (4; 8), including sex, CVD history at baseline, age at baseline, and the top five genetic principal components as covariates.



Supplemental Figure 14. Estimated kinship coefficients from software packages GCTA, KING, and REAP.

Estimates from GCTA have been divided by 2 for comparability with other packages.

## Imputation

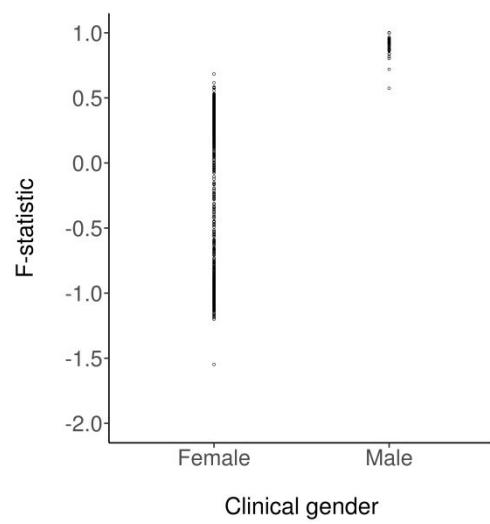
**UKB.** We used the imputed datasets released by UK Biobank. After extracting autosomal variants with imputation info score  $> 0.3$  and removing multiallelic variants from the imputed datasets, we excluded variants with missing genotype rate  $> 0.05$ , HWE test  $p < 1 \times 10^{-6}$ , and MAF  $< 0.0001$ . After the filtering steps, we had a total of 33,932,888 variants.

**ACCORD.** Prior to imputation, we performed quality control steps on the data. First, we checked if there are mismatches between genetic gender and clinical gender. We ran plinkv1.9 --check-sex option along with --split-x and made an F-statistic against sex-label plot (see Supplemental Figure 15). As expected, we saw a big tight clump near 1 for males while a more widely dispersed set of values centered near 0 (7). Even though some individuals did not pass the default threshold set in plink, we decided not to remove any individuals since the data exhibit an expected pattern.

Next, following the procedure in (4), we computed Hardy-Weinberg equilibrium (HWE)  $\chi^2$  values for each of the self-reported ethnicity groups: NHW, AA, Hispanic, and other. Any SNPs deviating from  $p$  value  $1 \times 10^{-5}$  in at least two of the four groups were excluded. This step reduced the number of variants to 542,847. Additionally, we checked alleles to allow only A, C, G, T and excluded SNPs with a missing rate  $> 3\%$  and monomorphic sites (MAF  $< 0.0000001$ ). We also excluded individuals with a genotype missing rate  $> 0.03$ . After the aforementioned step, we retained 6,279 individuals and 465,011 variants.

Data imputation was done using a two-step approach where the genotype calls were pre-phased using Eagle v2.4.1 (8) and then imputation was done using Minimac4 (9) with default options. Both steps used the 1000 Genomes Project Phase 3 (10) as a reference panel.

After discarding imputed variants with  $R^2 < 0.3$  and MAF < 0.0003, we had a total of 25,667,109 imputed variants for the downstream analyses. Additionally, we extracted the NHW samples filtered from the REAP approach earlier (n=4,329). With 11 out of 4,329 individuals removed during the pre-imputation QC steps, we proceeded with the downstream analyses with 4,318 NHW individuals.



Supplemental Figure 15. Distribution of F (inbreeding) coefficients against clinical gender.

## GREML-LDMS

On the imputed datasets, we employed the GREML-LDMS method. For the GREML-LDMS-I approach, we followed the design laid out in (11). First, we calculated segment-based LD scores using the default settings—200-kb block size with a 100-kb overlap—using the GCTA software and stratify SNPs into high LD and low LD score groups using the median as a threshold. In each LD group, SNPs were further partitioned into four MAF bins: common ( $\text{MAF} \geq 0.05$ ), uncommon ( $0.01 \leq \text{MAF} < 0.05$ ), rare ( $0.0025 \leq \text{MAF} < 0.01$ ), and very rare ( $0.0003 \leq \text{MAF} < 0.0025$ ). Then GRMs were computed using SNPs stratified into eight groups, hence creating eight GRMs. Finally, we ran GREML analyses on each binary phenotype with fixed covariates.

**UKB.** On the UKB imputed datasets, we adjusted for sex, age in 2010, and the top ten genetic principal components.

**ACCORD.** After filtering steps, the ACCORD imputed dataset contained 4,318 NHW individuals and 15,349,988 variants. We included sex, age at baseline, history of CVD at baseline, and the top five genetic principal components as covariates.

## GWAS

**UKB.** GWAS for complications was performed in 26,387 NHW samples. After MAF filtration ( $\text{MAF} \geq 0.01$ ), 8,949,996 variants formed the GWAS panel. We adjusted for sex, age in 2010, and the top ten genetic principal components. Manhattan and QQ plots are provided in Supplemental Figure 4 and Supplemental Figure 5 and respectively.

**ACCORD.** GWAS for complications were performed in 4,318 NHW participants. After filtration for variants with  $\text{MAF} \geq 0.01$ , as done in Bulik-Sullivan et al. (12), 8,480,081 SNPs formed the GWAS panel. The association between each variant and each complication was tested by logistic regression in PLINK2.0 (7), assuming an additive genetic model and adjusting for sex, CVD history at baseline, age at baseline, and the top five genetic principal components. Manhattan and quantile-quantile (QQ) plots are provided in Supplemental Figure 6 and Supplemental Figure 7, respectively.

### Stratified LD score regression (S-LDSC)

We partitioned SNP heritability, applying S-LDSC to GWAS summary statistics for the trait of interest. We conducted S-LDSC analysis using the ‘full baseline model’ generated by Finucane al. (13). The full baseline model is comprised of 53 overlapping functional categories (including coding, promoter, enhancer, and conserved regions) and is not specific to any cell type. We also conducted tissue-type specific analyses where we used the 53 specifically expressed gene annotations curated from the Genotype-Tissue Expression (GTEx) project (14) by Finucane et al. (1). For all S-LDSC analyses, we used 1000 Genomes Project Phase 3 (10) European population SNPs as an LD reference panel. All annotations and reference panel data were obtained from Alkes Price’s group data repository (see URLs).

## URLs

Baseline LDSC annotations, <https://data.broadinstitute.org/alkesgroup/LDSCORE/>; Finucane GTEX annotations, [https://data.broadinstitute.org/alkesgroup/LDSCORE/LDSC\\_SEG\\_ldscores/](https://data.broadinstitute.org/alkesgroup/LDSCORE/LDSC_SEG_ldscores/);  
LDSC, <https://github.com/bulik/ldsc/wiki>.

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CHROM CVD	POS	ID	REF	ALT	A1	FIRTH?
6	160985526	rs118039278	G	A	A	N
6	160997118	rs74617384	A	T	T	N
6	161005610	rs55730499	C	T	T	N
6	161010118	rs10455872	A	G	G	N
9	22040765	rs1333037	C	T	C	N
9	22045317	rs1360589	C	T	C	N
9	22048414	rs7028268	G	A	A	N
9	22050613	rs944799	A	G	G	N
9	22051670	rs944801	G	C	G	N
9	22052734	rs6475604	T	C	T	N
9	22052810	rs10757267	G	C	C	N
9	22053687	rs10965219	A	G	G	N
9	22053709	rs7027048	A	G	G	N
9	22054040	rs7030641	C	T	C	N
9	22054690	rs7874604	T	C	C	N
9	22055048	rs2383204	A	G	G	N
9	22056295	rs7853090	T	C	T	N
9	22056359	rs7866783	A	G	A	N
9	22056499	rs10120688	G	A	A	N
9	22060935	rs2383205	A	G	A	N
9	22061562	rs2184061	C	A	C	N
9	22061614	rs1537378	A	G	A	N
9	22064391	rs8181050	G	A	G	N
9	22065002	rs10811647	C	G	G	N
9	22065657	rs1333039	G	C	G	N
9	22066211	9:22066211_AATT		A	ATT	N
9	22066363	rs4977755	T	A	T	N
9	22067004	rs10965223	G	A	G	N
9	22067276	rs10965224	T	A	T	N
9	22067542	rs10811648	C	T	C	N
9	22067554	rs10811649	C	T	C	N
9	22067593	rs10811650	A	G	G	N
9	22067830	rs10811651	G	A	G	N
9	22068652	rs4977756	G	A	G	N
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9	22071750	rs4451405	C	T	C	N
9	22071751	rs4645630	G	A	G	N
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9	22072719	rs10757270	A	G	G	N
9	22076071	rs1831733	T	C	C	N
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9	22088090 rs10738606	A	T	T	N
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9	22099746 rs5896965	T	TA	TA	N
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9	22124140 rs7857118	A	T	A		N
9	22124450 rs10757277	A	G	G		N
9	22124472 rs10811656	C	T	T		N
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9	22124504 rs1333047	A	T	A		N
9	22124630 rs10757279	A	G	G		N
9	22124744 rs4977575	C	G	C		N
9	22125347 rs1333048	A	C	C		N
9	22125503 rs1333049	G	C	C		N
<b>MI</b>						
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9	22072301 rs9632884	G	C	G		N
9	22076071 rs1831733	T	C	C		N
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9	22077085 rs10811652	A	C	A		N
9	22124450 rs10757277	A	G	G		N
9	22124477 rs10757278	A	G	G		N
9	22124504 rs1333047	A	T	A		N
9	22124630 rs10757279	A	G	G		N
9	22124744 rs4977575	C	G	C		N
<b>PCI</b>						
6	160985526 rs118039278	G	A	A		N
6	160997118 rs74617384	A	T	T		N
6	161005610 rs55730499	C	T	T		N
6	161010118 rs10455872	A	G	G		N
6	161013013 rs140570886	T	C	C		N
9	22031005 rs7865618	G	A	G		N
9	22033366 rs2157719	C	T	C		N
9	22036112 rs1008878	G	T	G		N
9	22036367 rs1556515	C	T	C		N
9	22040765 rs1333037	C	T	C		N
9	22043926 rs1412829	A	G	G		N
9	22045317 rs1360589	C	T	C		N
9	22048414 rs7028268	G	A	A		N
9	22049482 rs34713115	C	CTT	C		N
9	22051670 rs944801	G	C	G		N
9	22052734 rs6475604	T	C	T		N
9	22052810 rs10757267	G	C	C		N
9	22053687 rs10965219	A	G	G		N
9	22053709 rs7027048	A	G	G		N
9	22053956 9:22053956_TTA		T	TA		N

9	22054040 rs7030641	C	T	C	N
9	22054690 rs7874604	T	C	C	N
9	22055048 rs2383204	A	G	G	N
9	22056295 rs7853090	T	C	T	N
9	22056359 rs7866783	A	G	A	N
9	22060935 rs2383205	A	G	A	N
9	22061562 rs2184061	C	A	C	N
9	22061614 rs1537378	A	G	A	N
9	22064391 rs8181050	G	A	G	N
9	22065002 rs10811647	C	G	G	N
9	22065657 rs1333039	G	C	G	N
9	22066211 9:22066211_FATT		A	ATT	N
9	22066363 rs4977755	T	A	T	N
9	22067004 rs10965223	G	A	G	N
9	22067276 rs10965224	T	A	T	N
9	22067542 rs10811648	C	T	C	N
9	22067554 rs10811649	C	T	C	N
9	22067593 rs10811650	A	G	G	N
9	22067830 rs10811651	G	A	G	N
9	22068652 rs4977756	G	A	G	N
9	22069354 rs35572758	A	AT	A	N
9	22071750 rs4451405	C	T	C	N
9	22071751 rs4645630	G	A	G	N
9	22072264 rs10757269	A	G	A	N
9	22072301 rs9632884	G	C	G	N
9	22072638 rs9632885	G	A	A	N
9	22072719 rs10757270	A	G	G	N
9	22076071 rs1831733	T	C	C	N
9	22076795 rs10757271	A	G	A	N
9	22077085 rs10811652	A	C	A	N
9	22081397 rs10116277	G	T	T	N
9	22081850 rs6475606	C	T	T	N
9	22084310 rs1537370	C	T	T	N
9	22085598 rs1970112	T	C	C	N
9	22088090 rs10738606	A	T	T	N
9	22088094 rs10738607	A	G	G	N
9	22088260 rs10757272	C	T	T	N
9	22090521 rs9644859	G	A	G	N
9	22090603 rs9644860	C	T	C	N
9	22090935 rs9644861	C	T	C	N
9	22090936 rs9644862	T	G	T	N
9	22091069 rs10811653	C	T	C	N
9	22091924 rs7866503	G	T	G	N
9	22092257 rs2210538	G	A	G	N
9	22092924 rs10811654	A	G	G	N
9	22093299 rs4007642	A	T	T	N

9	22094330	rs4977757	A	G	A	N
9	22094796	rs10738608	A	C	A	N
9	22096055	rs10757274	A	G	G	N
9	22098574	rs4977574	A	G	G	N
9	22098619	rs2891168	A	G	G	N
9	22099568	rs1537371	C	A	C	N
9	22099746	rs5896965	T	TA	TA	N
9	22100176	rs1556516	G	C	G	N
9	22102165	rs7859727	C	T	T	N
9	22103183	rs1537372	G	T	T	N
9	22103341	rs1537373	T	G	T	N
9	22103813	rs1333042	A	G	A	N
9	22105927	rs7859362	T	C	T	N
9	22106225	rs10757275	G	A	A	N
9	22106271	rs6475609	A	G	A	N
9	22106731	rs1333043	T	A	T	N
9	22110131	rs1412834	T	C	T	N
9	22111584	rs112917455	T	TATTTG	T	N
9	22112241	rs7341786	A	C	A	N
9	22112427	rs7341791	A	G	A	N
9	22112599	rs10511701	T	C	T	N
9	22114469	rs10733376	G	C	G	N
9	22115026	rs2383206	A	G	A	N
9	22115286	rs944797	T	C	T	N
9	22115589	rs1004638	A	T	A	N
9	22115959	rs2383207	A	G	A	N
9	22116046	rs1537374	A	G	A	N
9	22116071	rs1537375	T	C	T	N
9	22116220	rs1537376	T	C	T	N
9	22119195	rs1333045	T	C	T	N
9	22120482	rs67452501	C	CT	C	N
9	22121349	rs10217586	A	T	A	N
9	22121369	rs66653240	T	TA	T	N
9	22123766	rs10738610	A	C	C	N
9	22124123	rs1333046	T	A	A	N
9	22124140	rs7857118	A	T	A	N
9	22124450	rs10757277	A	G	G	N
9	22124472	rs10811656	C	T	T	N
9	22124477	rs10757278	A	G	G	N
9	22124504	rs1333047	A	T	A	N
9	22124630	rs10757279	A	G	G	N
9	22124744	rs4977575	C	G	C	N
9	22125347	rs1333048	A	C	C	N
9	22125503	rs1333049	G	C	C	N
<b>Stroke infarct</b>						
7	102845295	rs188434692	G	A	A	N

7	103003667 rs142060250	T	G	G	N
<b>Stroke any</b>					
2	205486017 2:205486017_TC		T	T	N
<b>DR</b>					
6	32585504 rs3129761	G	C	C	N
6	32585967 rs3104412	A	G	G	N
6	32604152 rs9272324	A	G	G	N
6	32606314 rs9272505	C	T	T	N
6	32606315 rs9272506	A	G	G	N
6	32606819 rs9272539	G	A	A	N
6	32607516 rs9272588	T	C	C	N
6	32626272 rs9273363	C	A	A	N
6	32626302 rs9273364	T	G	G	N
6	32626438 rs9273367	A	T	T	N
6	32626475 rs9273368	G	A	A	N
6	32673894 rs1794269	C	T	T	N
6	32743744 rs9276625	G	A	A	N
6	32747502 rs4947258	A	G	G	N
6	32747790 rs4947349	G	T	T	N
6	32751244 rs9276688	C	T	T	N
6	32752333 rs719655	C	T	T	N
6	32752844 rs9276691	A	G	G	N
6	32755290 rs7762279	T	C	C	N
6	32756653 rs9276700	C	T	T	N
6	32776921 rs1054684	T	C	C	N
6	32780724 rs11244	G	A	A	N
<b>DKD</b>					
3	171313412 rs73038008	T	C	C	N
3	171313506 rs73038011	A	G	G	N
3	171318013 rs6768605	A	G	G	N
3	171331725 rs6798359	A	G	G	N
3	171339992 rs113658125	C	A	A	N
3	171342247 rs113437354	T	G	G	N
3	171342259 rs113613931	T	C	C	N
3	171342999 rs530489985	C	A	A	N
3	171343910 rs112243343	T	C	C	N
3	171345230 rs113186627	G	C	C	N
3	171346987 rs113611537	A	G	G	N
16	20359267 rs28640218	G	T	T	N
16	20365082 rs113878851	C	CT	CT	N
16	20365234 rs4997081	G	C	C	N
16	20366507 rs13329952	T	C	C	N
16	20366949 rs7204775	T	C	C	N
16	20392332 rs77924615	G	A	A	N

TEST	OBS_CT	OR	LOG(OR)_SE	Z_STAT	P
ADD	17540	1.35208	0.0517123	5.83319	5.44E-09
ADD	17540	1.34397	0.0514689	5.74386	9.25E-09
ADD	17540	1.34521	0.0514029	5.76908	7.97E-09
ADD	17540	1.34944	0.0514383	5.82618	5.67E-09
ADD	17540	0.846046	0.0304936	-5.48252	4.19E-08
ADD	17540	0.845016	0.030616	-5.50039	3.79E-08
ADD	17540	1.19225	0.0308631	5.69746	1.22E-08
ADD	17540	1.18685	0.03021	5.67038	1.42E-08
ADD	17540	0.844667	0.0306159	-5.51389	3.51E-08
ADD	17540	0.843213	0.0305985	-5.57334	2.50E-08
ADD	17540	1.18933	0.0301786	5.74544	9.17E-09
ADD	17540	1.1872	0.0301701	5.68764	1.29E-08
ADD	17540	1.18814	0.0301764	5.71279	1.11E-08
ADD	17540	0.843819	0.0305868	-5.55197	2.82E-08
ADD	17540	1.18704	0.0302041	5.6768	1.37E-08
ADD	17540	1.18766	0.0301834	5.6981	1.21E-08
ADD	17540	0.843345	0.0306372	-5.5612	2.68E-08
ADD	17540	0.844099	0.0306428	-5.53101	3.18E-08
ADD	17540	1.18403	0.0301706	5.59905	2.16E-08
ADD	17540	0.831787	0.0310722	-5.92747	3.08E-09
ADD	17540	0.829393	0.0310632	-6.02197	1.72E-09
ADD	17540	0.831297	0.0310723	-5.9464	2.74E-09
ADD	17540	0.83223	0.0310465	-5.9152	3.31E-09
ADD	17540	1.21362	0.0303035	6.38908	1.67E-10
ADD	17540	0.832202	0.0310358	-5.91833	3.25E-09
ADD	17540	0.83235	0.0314391	-5.83677	5.32E-09
ADD	17540	0.831931	0.0310507	-5.92597	3.10E-09
ADD	17540	0.832815	0.0310191	-5.8978	3.68E-09
ADD	17540	0.832481	0.0310185	-5.91081	3.40E-09
ADD	17540	0.833492	0.0310499	-5.86578	4.47E-09
ADD	17540	0.833612	0.0310449	-5.86206	4.57E-09
ADD	17540	1.21136	0.0302838	6.3315	2.43E-10
ADD	17540	0.832641	0.0310203	-5.9043	3.54E-09
ADD	17540	0.832444	0.0310112	-5.91365	3.35E-09
ADD	17540	0.832235	0.0310826	-5.90817	3.46E-09
ADD	17540	0.829826	0.0310731	-6.00323	1.93E-09
ADD	17540	0.832239	0.031141	-5.89691	3.70E-09
ADD	17540	0.812595	0.0301887	-6.87418	6.23E-12
ADD	17540	0.811984	0.0301901	-6.89877	5.25E-12
ADD	17540	1.23431	0.030171	6.97727	3.01E-12
ADD	17540	1.22477	0.0303491	6.68076	2.38E-11
ADD	17540	1.23163	0.0302029	6.8981	5.27E-12
ADD	17540	0.811718	0.0301581	-6.91695	4.61E-12
ADD	17540	0.811175	0.0301584	-6.9391	3.95E-12

ADD	17540	1.19766	0.0300543	6.00158	1.95E-09
ADD	17540	1.19687	0.0300493	5.9806	2.22E-09
ADD	17540	1.20215	0.0300996	6.11669	9.55E-10
ADD	17540	1.20459	0.0301227	6.17938	6.44E-10
ADD	17540	1.20075	0.030007	6.09688	1.08E-09
ADD	17540	1.20101	0.0300077	6.10374	1.04E-09
ADD	17540	1.20254	0.0299826	6.15145	7.68E-10
ADD	17540	0.831874	0.030045	-6.12663	8.98E-10
ADD	17540	0.831855	0.0300449	-6.12738	8.93E-10
ADD	17540	0.827903	0.030072	-6.28025	3.38E-10
ADD	17540	0.827904	0.0300721	-6.28017	3.38E-10
ADD	17540	0.83188	0.0300463	-6.12613	9.00E-10
ADD	17540	0.831856	0.0300492	-6.12648	8.98E-10
ADD	17540	0.832586	0.0300615	-6.09479	1.10E-09
ADD	17540	1.20595	0.0300969	6.22213	4.90E-10
ADD	17540	1.1944	0.030152	5.89163	3.82E-09
ADD	17540	0.830926	0.0300997	-6.15337	7.59E-10
ADD	17540	0.830937	0.0300987	-6.15312	7.60E-10
ADD	17540	1.20757	0.0300493	6.27674	3.46E-10
ADD	17540	1.20601	0.030046	6.23436	4.54E-10
ADD	17540	1.20621	0.0300525	6.23853	4.42E-10
ADD	17540	0.828633	0.0300862	-6.248	4.16E-10
ADD	17540	1.2066	0.0300726	6.24516	4.23E-10
ADD	17540	0.828669	0.0300847	-6.24687	4.19E-10
ADD	17540	1.20929	0.0300794	6.31784	2.65E-10
ADD	17540	1.18681	0.0302877	5.6547	1.56E-08
ADD	17540	0.827278	0.0300822	-6.30321	2.92E-10
ADD	17540	0.827252	0.0300934	-6.30189	2.94E-10
ADD	17540	0.836478	0.0300779	-5.93642	2.91E-09
ADD	17540	1.19481	0.0300558	5.92188	3.18E-09
ADD	17540	0.836443	0.0300787	-5.93765	2.89E-09
ADD	17540	0.836635	0.0300804	-5.92969	3.04E-09
ADD	17540	0.836567	0.0300806	-5.93236	2.99E-09
ADD	17540	0.8347	0.0301274	-5.9973	2.01E-09
ADD	17540	0.835516	0.0301021	-5.9699	2.37E-09
ADD	17540	0.835485	0.0301042	-5.97068	2.36E-09
ADD	17540	0.835398	0.0300822	-5.97853	2.25E-09
ADD	17540	0.836615	0.0300772	-5.93111	3.01E-09
ADD	17540	0.836707	0.0300578	-5.93129	3.01E-09
ADD	17540	0.836747	0.0300579	-5.92966	3.04E-09
ADD	17540	0.836107	0.030073	-5.95214	2.65E-09
ADD	17540	0.835248	0.0300643	-5.98805	2.12E-09
ADD	17540	0.835882	0.0300768	-5.96033	2.52E-09
ADD	17540	0.835695	0.0300678	-5.96957	2.38E-09
ADD	17540	0.836646	0.0300578	-5.93371	2.96E-09
ADD	17540	0.834783	0.0298794	-6.04375	1.51E-09

ADD	17540	0.836122	0.0301521	-5.93592	2.92E-09
ADD	17540	0.837522	0.0300433	-5.90175	3.60E-09
ADD	17540	0.835626	0.0302013	-5.94592	2.75E-09
ADD	17540	1.2134	0.0300144	6.4445	1.16E-10
ADD	17540	1.20974	0.0300165	6.34326	2.25E-10
ADD	17540	0.825703	0.0300585	-6.37157	1.87E-10
ADD	17540	1.21324	0.0299149	6.46139	1.04E-10
ADD	17540	1.20328	0.0299029	6.18829	6.08E-10
ADD	17540	1.21316	0.0299133	6.45955	1.05E-10
ADD	17540	0.822283	0.0299388	-6.53571	6.33E-11
ADD	17540	1.21318	0.0299057	6.46192	1.03E-10
ADD	17540	0.823628	0.02994	-6.48086	9.12E-11
ADD	17540	1.20034	0.0299877	6.0893	1.13E-09
ADD	17540	1.20253	0.0299265	6.16256	7.16E-10
ADD	16310	0.807985	0.0387219	-5.50625	3.67E-08
ADD	16310	0.807297	0.0387257	-5.52769	3.24E-08
ADD	16310	1.23955	0.0387562	5.54109	3.01E-08
ADD	16310	0.803148	0.0386872	-5.66639	1.46E-08
ADD	16310	0.802634	0.0386867	-5.68299	1.32E-08
ADD	16310	1.23387	0.0383856	5.47478	4.38E-08
ADD	16310	1.2329	0.0383866	5.45426	4.92E-08
ADD	16310	0.803025	0.0384239	-5.7092	1.14E-08
ADD	16310	1.23274	0.0383755	5.45247	4.97E-08
ADD	16310	0.804609	0.0384218	-5.65821	1.53E-08
ADD	16252	1.49386	0.0658924	6.09119	1.12E-09
ADD	16252	1.48404	0.065568	6.02078	1.74E-09
ADD	16252	1.48634	0.0654855	6.05194	1.43E-09
ADD	16252	1.49419	0.0654635	6.1345	8.54E-10
ADD	16252	2.07877	0.13149	5.56528	2.62E-08
ADD	16252	0.798021	0.0407025	-5.54316	2.97E-08
ADD	16252	0.795498	0.0406714	-5.62524	1.85E-08
ADD	16252	0.798378	0.0407062	-5.53168	3.17E-08
ADD	16252	0.795062	0.0407334	-5.63015	1.80E-08
ADD	16252	0.787617	0.0408053	-5.85079	4.89E-09
ADD	16252	0.799274	0.0410461	-5.45852	4.80E-08
ADD	16252	0.790348	0.0409594	-5.74428	9.23E-09
ADD	16252	1.25174	0.0408058	5.50244	3.75E-08
ADD	16252	0.791678	0.0409676	-5.70207	1.18E-08
ADD	16252	0.789041	0.0409668	-5.78364	7.31E-09
ADD	16252	0.787409	0.0409438	-5.83745	5.30E-09
ADD	16252	1.25024	0.0401613	5.561	2.68E-08
ADD	16252	1.24561	0.0401441	5.471	4.47E-08
ADD	16252	1.24691	0.0401547	5.49543	3.90E-08
ADD	16252	0.797801	0.0412508	-5.47615	4.35E-08

ADD	16252	0.787987	0.0409231	-5.82246	5.80E-09
ADD	16252	1.24785	0.0401943	5.50876	3.61E-08
ADD	16252	1.24609	0.0401662	5.47743	4.32E-08
ADD	16252	0.788525	0.040984	-5.79718	6.74E-09
ADD	16252	0.787639	0.041002	-5.82204	5.81E-09
ADD	16252	0.784493	0.0415486	-5.84178	5.16E-09
ADD	16252	0.783978	0.0415231	-5.86117	4.60E-09
ADD	16252	0.783247	0.0415516	-5.8796	4.11E-09
ADD	16252	0.787424	0.0415045	-5.75813	8.50E-09
ADD	16252	1.26827	0.0401609	5.91749	3.27E-09
ADD	16252	0.79023	0.0414686	-5.67734	1.37E-08
ADD	16252	0.787305	0.0420262	-5.69024	1.27E-08
ADD	16252	0.789187	0.0414915	-5.70603	1.16E-08
ADD	16252	0.792107	0.0414371	-5.62439	1.86E-08
ADD	16252	0.792368	0.0414338	-5.61688	1.94E-08
ADD	16252	0.793083	0.0414776	-5.5892	2.28E-08
ADD	16252	0.793027	0.0414721	-5.59166	2.25E-08
ADD	16252	1.2649	0.0401375	5.85468	4.78E-09
ADD	16252	0.792592	0.0414374	-5.60958	2.03E-08
ADD	16252	0.792525	0.0414231	-5.61357	1.98E-08
ADD	16252	0.78672	0.0415601	-5.77194	7.84E-09
ADD	16252	0.786921	0.0415294	-5.77008	7.92E-09
ADD	16252	0.79209	0.0415909	-5.60411	2.09E-08
ADD	16252	0.763002	0.0400841	-6.74819	1.50E-11
ADD	16252	0.762227	0.0400878	-6.7729	1.26E-11
ADD	16252	1.31742	0.0400895	6.87659	6.13E-12
ADD	16252	1.28059	0.0402156	6.14988	7.75E-10
ADD	16252	1.30551	0.0401368	6.6422	3.09E-11
ADD	16252	0.763039	0.0400597	-6.75109	1.47E-11
ADD	16252	0.763418	0.0400567	-6.73919	1.59E-11
ADD	16252	1.27525	0.0399271	6.08971	1.13E-09
ADD	16252	1.2741	0.0399205	6.06808	1.29E-09
ADD	16252	1.27431	0.0399749	6.06399	1.33E-09
ADD	16252	1.27536	0.0400155	6.07839	1.21E-09
ADD	16252	1.28842	0.0399257	6.3472	2.19E-10
ADD	16252	1.28885	0.0399273	6.35529	2.08E-10
ADD	16252	1.29238	0.0398902	6.42982	1.28E-10
ADD	16252	0.771175	0.0399781	-6.49957	8.06E-11
ADD	16252	0.771148	0.039978	-6.50045	8.01E-11
ADD	16252	0.768648	0.0400071	-6.57689	4.80E-11
ADD	16252	0.768649	0.0400072	-6.57684	4.81E-11
ADD	16252	0.771117	0.0399801	-6.5011	7.97E-11
ADD	16252	0.770991	0.0399847	-6.50445	7.80E-11
ADD	16252	0.772105	0.0400069	-6.46475	1.01E-10
ADD	16252	1.29349	0.0400565	6.42456	1.32E-10
ADD	16252	1.29423	0.0401579	6.4225	1.34E-10

ADD	16252	0.77365	0.0400465	-6.40845	1.47E-10
ADD	16252	0.773599	0.0400456	-6.41023	1.45E-10
ADD	16252	1.29743	0.0399911	6.51113	7.46E-11
ADD	16252	1.29494	0.0399893	6.46337	1.02E-10
ADD	16252	1.29553	0.0399984	6.4732	9.59E-11
ADD	16252	0.770134	0.0400369	-6.52374	6.86E-11
ADD	16252	1.29575	0.0400268	6.47282	9.62E-11
ADD	16252	0.77014	0.0400344	-6.52397	6.85E-11
ADD	16252	1.29844	0.0400208	6.52572	6.77E-11
ADD	16252	1.24961	0.0401538	5.54951	2.86E-08
ADD	16252	0.768608	0.0400202	-6.57603	4.83E-11
ADD	16252	0.768835	0.0400412	-6.56522	5.20E-11
ADD	16252	0.779837	0.0400353	-6.21127	5.26E-10
ADD	16252	1.2784	0.0400056	6.13935	8.29E-10
ADD	16252	0.77993	0.040036	-6.20821	5.36E-10
ADD	16252	0.78006	0.0400387	-6.20359	5.52E-10
ADD	16252	0.779727	0.0400399	-6.2141	5.16E-10
ADD	16252	0.775445	0.040128	-6.33768	2.33E-10
ADD	16252	0.777808	0.0400825	-6.26896	3.63E-10
ADD	16252	0.777728	0.0400862	-6.27094	3.59E-10
ADD	16252	0.778253	0.0400557	-6.25886	3.88E-10
ADD	16252	0.781206	0.0400274	-6.16868	6.89E-10
ADD	16252	0.782595	0.0400021	-6.12816	8.89E-10
ADD	16252	0.782633	0.0400023	-6.12694	8.96E-10
ADD	16252	0.781308	0.0400221	-6.16623	6.99E-10
ADD	16252	0.780079	0.0400138	-6.20685	5.41E-10
ADD	16252	0.781045	0.0400249	-6.17422	6.65E-10
ADD	16252	0.781951	0.0400113	-6.14733	7.88E-10
ADD	16252	0.782691	0.0400011	-6.12526	9.05E-10
ADD	16252	0.78348	0.0397943	-6.13177	8.69E-10
ADD	16252	0.787071	0.040196	-5.95673	2.57E-09
ADD	16252	0.784171	0.0400678	-6.06793	1.30E-09
ADD	16252	0.784215	0.0402746	-6.03537	1.59E-09
ADD	16252	1.29173	0.039947	6.40811	1.47E-10
ADD	16252	1.29251	0.0399584	6.42134	1.35E-10
ADD	16252	0.770549	0.0400126	-6.51426	7.31E-11
ADD	16252	1.29664	0.0397687	6.53208	6.49E-11
ADD	16252	1.29169	0.0397638	6.43688	1.22E-10
ADD	16252	1.29581	0.0397695	6.51586	7.23E-11
ADD	16252	0.768303	0.0398012	-6.62218	3.54E-11
ADD	16252	1.29561	0.039757	6.5142	7.31E-11
ADD	16252	0.768634	0.0397998	-6.61158	3.80E-11
ADD	16252	1.28929	0.0399441	6.36118	2.00E-10
ADD	16252	1.28791	0.0397992	6.35747	2.05E-10
ADD	15429	2.4981	0.165381	5.53588	3.10E-08

ADD	15429	2.65043	0.167013	5.8362	5.34E-09
ADD	16002	2.83086	0.17173	6.05941	1.37E-09
ADD	11739	1.16265	0.0262315	5.74522	9.18E-09
ADD	11739	1.16127	0.0261163	5.72487	1.04E-08
ADD	11739	1.16457	0.0261902	5.81699	5.99E-09
ADD	11739	1.16126	0.0261805	5.71072	1.12E-08
ADD	11739	1.16126	0.0261805	5.71072	1.12E-08
ADD	11739	1.15947	0.0261365	5.66127	1.50E-08
ADD	11739	1.16036	0.0263006	5.65488	1.56E-08
ADD	11739	1.17853	0.0273416	6.00795	1.88E-09
ADD	11739	1.17874	0.0273405	6.01469	1.80E-09
ADD	11739	1.18064	0.0273307	6.07588	1.23E-09
ADD	11739	1.17853	0.0273437	6.00759	1.88E-09
ADD	11739	1.16583	0.0263369	5.82591	5.68E-09
ADD	11739	1.24389	0.0400127	5.45445	4.91E-08
ADD	11739	1.24658	0.0400044	5.50941	3.60E-08
ADD	11739	1.24673	0.0400053	5.51231	3.54E-08
ADD	11739	1.24657	0.0400044	5.50938	3.60E-08
ADD	11739	1.24653	0.0400046	5.50854	3.62E-08
ADD	11739	1.2468	0.0400003	5.51446	3.50E-08
ADD	11739	1.24644	0.0400008	5.5071	3.65E-08
ADD	11739	1.24701	0.0399947	5.51943	3.40E-08
ADD	11739	1.25074	0.0405235	5.52119	3.37E-08
ADD	11739	1.17568	0.0295603	5.4752	4.37E-08
ADD	7707	2.55243	0.166258	5.63608	1.74E-08
ADD	7707	2.51349	0.168349	5.47476	4.38E-08
ADD	7707	2.50417	0.167382	5.48422	4.15E-08
ADD	7707	2.49498	0.16725	5.46656	4.59E-08
ADD	7707	2.49349	0.167233	5.46354	4.67E-08
ADD	7707	2.49347	0.167244	5.46312	4.68E-08
ADD	7707	2.49321	0.167238	5.4627	4.69E-08
ADD	7707	2.60342	0.172557	5.54498	2.94E-08
ADD	7707	2.54443	0.168872	5.53028	3.20E-08
ADD	7707	2.49313	0.167231	5.46275	4.69E-08
ADD	7707	2.54425	0.168864	5.5301	3.20E-08
ADD	7707	0.755282	0.0511811	-5.48374	4.16E-08
ADD	7707	0.74074	0.0545308	-5.50342	3.73E-08
ADD	7707	0.755945	0.0510184	-5.48403	4.16E-08
ADD	7707	0.754364	0.0511734	-5.50834	3.62E-08
ADD	7707	0.757199	0.0510189	-5.45149	4.99E-08
ADD	7707	0.745124	0.0509682	-5.77233	7.82E-09

CHROM <b>primary</b>	POS	ID	REF	ALT	A1	FIRTH?
	2	209025961	2:209025961:A	G	G	N
<b>CVD mortality</b>						
	11	24854411	11:24854411:G	C	C	N
	11	24874851	11:24874851:A	G	G	N
	11	24877057	11:24877057:G	A	A	N
	11	24877800	11:24877800:C	T	T	N
	11	24882158	11:24882158:C	T	T	N
	11	24884031	11:24884031:A	C	C	N
	11	24890069	11:24890069:T	C	C	N
	17	51616084	17:51616084:A	G	G	N
	17	51620518	17:51620518:C	G	G	N
	22	50473684	22:50473684:C	G	G	N
	22	50479680	22:50479680:A	G	G	N
<b>nonfatal MI</b>						
	2	209025961	2:209025961:A	G	G	N
<b>nonfatal stroke</b>						
	1	48563675	1:48563675:AA	G	G	N
	1	48567686	1:48567686:AA	G	G	N
	1	48568156	1:48568156:TT	C	C	N
	1	48579492	1:48579492:CC	T	T	N
	9	132630589	9:132630589:C	T	T	N
	9	132635527	9:132635527:T	G	G	N
	16	24681417	16:24681417:C	T	T	N
<b>total stroke</b>						
	1	48579492	1:48579492:CC	T	T	N
	4	31080738	4:31080738:GG	A	A	N
	9	132630589	9:132630589:C	T	T	N
	13	22395044	13:22395044:A	C	C	N
	16	63996813	16:63996813:C	G	G	N
<b>major CHD</b>						
	6	92860714	6:92860714:AA	T	A	N
<b>Neph3</b>						
	12	108635932	12:108635932C	T	T	N
	13	50067102	13:50067102:C	A	A	N
<b>Neph5</b>						
	20	46578217	20:46578217:G	T	T	N
	20	46663205	20:46663205:C	T	T	N
<b>Retin1</b>						
	2	84704112	2:84704112:CC	T	T	N
<b>Retin4</b>						
	12	46025200	12:46025200:T	C	C	N

TEST	OBS_CT	OR	LOG(OR)_SE	Z_STAT	P
ADD	4318	7.93059	0.379586	5.45523	4.89E-08
ADD	4318	3.75324	0.238884	5.53666	3.08E-08
ADD	4318	3.43552	0.221073	5.58262	2.37E-08
ADD	4318	3.48023	0.220503	5.65569	1.55E-08
ADD	4318	3.48435	0.220579	5.65912	1.52E-08
ADD	4318	3.33149	0.213736	5.63041	1.80E-08
ADD	4318	3.3009	0.211387	5.64933	1.61E-08
ADD	4318	3.32042	0.219107	5.4772	4.32E-08
ADD	4318	2.29722	0.14387	5.78092	7.43E-09
ADD	4318	2.2958	0.143899	5.77546	7.67E-09
ADD	4318	7.24028	0.342058	5.7875	7.14E-09
ADD	4318	6.84222	0.330482	5.81912	5.92E-09
ADD	4318	9.71953	0.405727	5.60509	2.08E-08
ADD	4318	24.8131	0.579397	5.54261	2.98E-08
ADD	4318	25.5691	0.587	5.52195	3.35E-08
ADD	4318	25.5691	0.587	5.52195	3.35E-08
ADD	4318	27.5977	0.588432	5.63826	1.72E-08
ADD	4318	10.8685	0.391926	6.08756	1.15E-09
ADD	4318	7.99041	0.365244	5.69001	1.27E-08
ADD	4318	8.97061	0.40059	5.4768	4.33E-08
ADD	4318	24.3145	0.58209	5.48209	4.20E-08
ADD	4318	9.81624	0.410296	5.56681	2.59E-08
ADD	4318	8.68293	0.389183	5.55359	2.80E-08
ADD	4318	13.5738	0.456139	5.71786	1.08E-08
ADD	4318	6.65245	0.343414	5.51808	3.43E-08
ADD	4318	1.5754	0.082592	5.50307	3.73E-08
ADD	4318	7.16476	0.357588	5.50682	3.65E-08
ADD	4318	11.3581	0.412889	5.88519	3.98E-09
ADD	2912	3.06186	0.204317	5.47689	4.33E-08
ADD	2912	2.97416	0.185639	5.87139	4.32E-09
ADD	4318	3.86086	0.242507	5.57052	2.54E-08
ADD	4318	3.02128	0.201646	5.48328	4.18E-08