



# Systematic Heritability and Heritability Enrichment Analysis for Diabetes Complications in UK Biobank and ACCORD Studies

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**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 single nucleotide polymorphism heritability for diabetes microvascular (diabetic kidney disease and diabetic retinopathy) and macrovascular (cardiovascular events) complications. Heritability for diabetic kidney disease was estimated at 29%. The heritability estimate 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.**

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 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. Siblings with diabetes of probands with DKD had approximately two to four times the risk of developing DKD than siblings with diabetes of probands free of DKD (10–12). A heritability analysis of renal complications in

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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 type 2 diabetes (14).

Early family and twin studies suggested high concordance of diabetic retinopathy (DR) between family members (15,16). Of note, genetic components for the risk of DR 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 DR due to common genetic variants is estimated at 7% (21).

Little is known about the genetic contributions to cardiovascular disease (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 ~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 tailored disease prevention/treatment. In the current 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 (ACCORD) trial—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 AND METHODS

### Study Design and Participants

The UKB study recruited during the years 2006–2010 ~500,000 individuals aged 40–69 from the general population across the U.K. 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: 1) baseline information (2006–2010) and subsequent assessments (2012–2013) at UKB assessment centers, including questionnaires, physical examination measurements, and biological samples, and 2) 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 cases were ascertained according to the following criteria: 1) the first occurrence of any of the following: International Classification of Disease, Ninth (ICD-9) and ICD-10 codes for type 1, type 2, and unspecified diabetes; self-report of diabetes 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; 2) 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, 26,387 non-Hispanic White (NHW) patients with diabetes 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 (Supplementary Fig. 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 participants with type 2 diabetes with HbA<sub>1c</sub> concentrations of ≥7.5% (58.5 mmol/mol) and who were aged 40–79 years with a history of CVD or 55–79 years with evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two risk factors for CVD (dyslipidemia, hypertension, smoking, or obesity). As with the UKB analysis, we excluded individuals with non-European ancestry from the ACCORD cohort 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 5 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, diabetes complications, and their date of the first occurrence are presented in the Supplemental Material.

In the ACCORD trial, all outcomes were prespecified and adjudicated by the outcome committee. The prespecified 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, 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 comp-

lications (e.g., Neph3 and Retin1) to less advanced conditions. A detailed description of the prespecification 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. Approximately 850,000 variants were directly genotyped, and >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 minor allele frequency (MAF) <0.0001, yielding a total of 33,932,888 autosomal SNPs.

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

**Table 1—Outcome definitions for UKB and ACCORD**

Outcome		Definition
UKB	DR	Composite for diabetic eye disease in self-reported, primary care, or hospital admission records
	DKD	Chronic/DKD 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. MI, ischemic stroke, unstable angina, or percutaneous coronary intervention
	MI	MI from self-report, primary care, hospital admissions, or death records. Control subjects were required to have no evidence of certain CVDs
	Stroke any	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. UACR ≥33.9 mg/mmol
	Neph3	ESRD (i.e., initiation of dialysis or a rise of serum creatinine to 3.3 mg/dL [292 μmol/L])
	Neph4	Development of Neph1, Neph2, or Neph3
	Neph5	Development of microalbuminuria. UACR ≥3.4 mg/mmol
	Primary	Composite for CVD. Nonfatal MI, nonfatal/total stroke, death from cardiovascular causes, new/worsening congestive heart failure, or major CHD
	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

UACR, urinary albumin-to-creatinine ratio.

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 individuals (2,335 women and 3,956 men) with 546,800 SNPs in the merged data set. Based on self-reported ethnicity, there were 4,369 NHW, 935 African Americans, 381 Hispanics, and 606 others. After preimputation quality control steps, imputation was performed on the genotype data using a two-step approach: prephasing genotype calls (35) and imputation (36). After imputed SNPs with  $R^2 < 0.3$  and MAF < 0.0003 were discarded, the total number of SNPs was 25,667,109. Additional details are provided in the Supplementary Material.

## Statistical Analysis

### Overview of Methods

We use three different methods to compute heritability: single-component genomic restricted maximum likelihood estimation (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 with 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 the 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 10 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 data sets, 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 case subjects is often overrepresented. In fact, our sample proportion of cases agrees 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 DKD among U.S. 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).

## Data and Resource Availability

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

**Table 2—Characteristics of the non-Hispanic White participants used in the UKB analyses**

Characteristics	N = 26,387
Age in 2010, years	60.9 ± 7.0
Age at first diabetes diagnosis, years	56.4 ± 12.4
BMI, kg/m <sup>2</sup>	31.5 ± 5.7
Lipids at baseline, mmol/L	
HDL	1.2 ± 0.3
LDL	3.0 ± 0.9
Triglycerides	2.3 ± 1.3
Blood pressure at baseline, mmHg	
Systolic	143.5 ± 18.8
Diastolic	83.3 ± 10.9
HbA <sub>1c</sub> at initial visit, mmol/mol	48.8 ± 13.3
HbA <sub>1c</sub> 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
Diabetes type	
Type 1	2.9
Type 2	69.0
Unspecified	28.1

The initial visit occurred between 2006 and 2010, depending on the individual. Data are presented as mean ± SD or percentage of patients.

## RESULTS

Characteristics of the NHW samples used in the UKB and ACCORD analyses are presented in Tables 2 and 3, respectively. Supplementary Figs. 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 Fig. 1A. 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 Fig. 2A. 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 DKD among subjects with type 2 diabetes) (14). We also

ran an additional GREML-SC analysis that includes interaction with the intensive glycemic treatment arm (Supplementary Fig. 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 data sets and the GREML-LDMS-I method are provided as green bars in Figs. 1A and 2A for the UKB and ACCORD, respectively (also see Tables 4 and 5). In UKB, the heritability of DKD 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 DR 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 DR (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.

**Table 3—Characteristics of the NHW participants used in the ACCORD analyses**

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	
HDL	40.2 ± 10.6
LDL	102.8 ± 33.1
Triglycerides	208.7 ± 158.4
Blood pressure at baseline, mmHg	
Systolic	135.2 ± 17.3
Diastolic	74.2 ± 10.8
HbA <sub>1c</sub> 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
No answer	11.7
CVD history at baseline	
Yes	36.1
No	63.9
Glycemic treatment arm	
Intensive	49.8
Standard	50.2

Data are presented as mean ± SD or as percentage of patients.

**Table 4—GREML-SC and GREML-LDMS estimates for individuals with diabetes using the UKB genotype data**

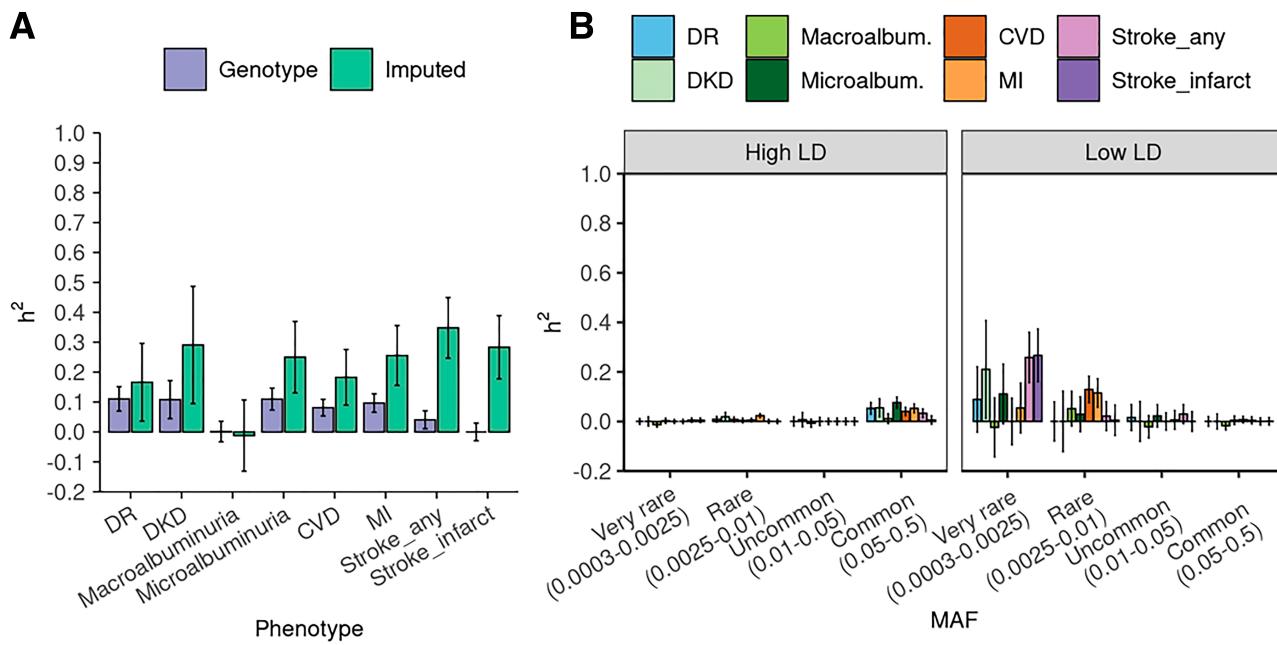
Phenotype	Diabetes (N = 26,387)			Diabetes: type 2 only (N = 18,198)			No diabetes (N = 26,387)		Diabetes and no diabetes (N = 52,774)		
	Proportion of cases	n	V(G)/V(p) (SE)	GREML-SC	GREML-LDMS	Proportion of cases	n	V(G)/V(p) (SE)	GREML-LDMS	V(G)/V(p) (SE)	GREML-LDMS
DR	0.541	11,739	0.110 (0.041)	0.166 (0.130)	0.514	7,516	0.029 (0.199)	NA	NA	NA	NA
DKD	0.256	7,707	0.108 (0.064)	0.291 (0.196)	0.259	4,969	0.237 (0.300)	0.453 (0.15)	0.217 (0.089)	0.026 (0.085)	0.226 (0.079)
Macroalbuminuria	0.029	13,246	0.001 (0.034)	0.000 (0.119)	0.026	9,332	NA	NA	NA	NA	NA
Microalbuminuria	0.238	13,246	0.110 (0.037)	0.250 (0.119)	0.230	9,332	0.214 (0.163)	0.155 (0.201)	0.085 (0.041)	0.141 (0.043)	0.199 (0.044)
CVD	0.159	17,540	0.081 (0.028)	0.183 (0.093)	0.170	11,506	0.208 (0.139)	0.176 (0.069)	0.278 (0.072)	0.141 (0.043)	0.167 (0.045)
MI	0.094	16,310	0.097 (0.031)	0.256 (0.100)	0.099	10,610	0.192 (0.149)	0.278 (0.072)	0.141 (0.043)	0.141 (0.043)	0.199 (0.044)
Stroke any	0.087	16,002	0.041 (0.030)	0.348 (0.101)	0.095	10,434	0.590 (0.151)	NA	NA	NA	NA
Stroke infarct	0.042	15,429	0.000 (0.029)	0.283 (0.106)	0.047	10,030	0.330 (0.158)	0.141 (0.073)	0.167 (0.045)	0.167 (0.045)	0.167 (0.045)

GREML-LDMS estimates were for individuals with 1) diabetes (both type 1 and type 2), 2) type 2 diabetes only, 3) without diabetes, and 4) groups with diabetes and no diabetes combined using the UKB imputed data. Individuals with no diabetes (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 groups with diabetes and no diabetes (N = 52,774). N, number of total samples in the group; n, number of samples without missing phenotype; NA, under GREML-LDMS, the GREML analysis failed to run due to the small sample size; V(G)/V(p), proportion of phenotypic variance explained by genotypes (i.e., heritability, as observed in the study population).

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 ~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. Estimates for either Neph1 or Neph3 are unavailable despite larger sample sizes (4,318 for both Neph1 and Neph3 and 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 DR and the presence/absence of diabetic nephropathy (15,17). Although we cannot confirm the trend of DR in the UKB data (due to the absence of more granular outcome definitions for DR), when restricting the analysis to participants with type 2 diabetes in UKB only, we found the heritability of DR reduces to 0.029 (SE 0.199) from 0.166 (SE 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 DR 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 DR among individuals with type 2 diabetes 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 Figs. 1B and 2B. Notably, the UKB results (Fig. 1B) 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 disease and CVD 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 group with diabetes and ease the computational burden. We also computed estimates after combining groups with and without diabetes 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 group without diabetes (i.e., 0.291 [SE 0.196] in diabetes vs.



**Figure 1**—Heritability estimates and SEs of diabetes complication outcomes using the UKB data. *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 10 genetic principal components. *B*: GREML-LDMS estimates with eight bins (two LD bins for each of the four MAF bins). For each phenotype, the sum of estimates from the eight bins of MAF shown in panel *B* is equal to the estimate represented as the green bar on panel *A*.

0.453 [SE 0.15] without diabetes), while the heritability estimate for microalbuminuria is higher than that in the group without diabetes (i.e., 0.250 [SE 0.119] in diabetes vs. 0.155 [SE 0.201] without 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 type 2 diabetes and progression of CVD was reported previously (49). For DR in the UKB-NHW-Diabetes cohort, 22 variants on 6p21 reached genome-wide significance ( $P < 5 \times 10^{-8}$ ) with rs9273367 ( $P = 1.23 \times 10^{-9}$ , odds ratio 1.18) being the most significant SNP. These variants were in or near HLA regions, whose previous associations with type 1 diabetes have been well documented (50). For DKD, 17 variants had  $P < 5 \times 10^{-8}$ , and 11 of these SNPs were on chromosome 3q26.31, and 6 were in UMOD and PDILT genes (lead SNP rs77924615 with  $P = 7.82 \times 10^{-9}$ , odds ratio 0.75) on chromosome 16p12.3. UMOD was previously reported to be associated with estimated glomerular filtration rate in the meta-analysis combining patients with type 1 and type 2 diabetes 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.

Supplementary Data 1 reports all genome-wide significant GWAS loci for diabetes complications. Supplementary Figs. 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 Fig. 3 (also see Supplementary Figs. 8 and 9). Renal failure or end-stage renal disease (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 Epstein-Barr virus-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., monocytes and T lymphocytes) (52). Despite the larger sample size, no tissues were enriched for the heritability of diabetic complications from the UKB (Supplementary Figs. 10 and 11).

Results from the S-LDSC analysis partitioning heritability into 53 (overlapping) categories used in Finucane et al. (44) are illustrated in Supplementary Fig. 12. In the UKB data, only the coding region shows Bonferroni-corrected ( $0.05/53 = 9.43 \times 10^{-4}$ ) significant enrichment in DKD ( $P = 6.55 \times 10^{-4}$ ). Although only nominally significant,

**Table 5—GREML-SC and GREML-LDMS estimates using the ACCORD genotype and imputed data, respectively**

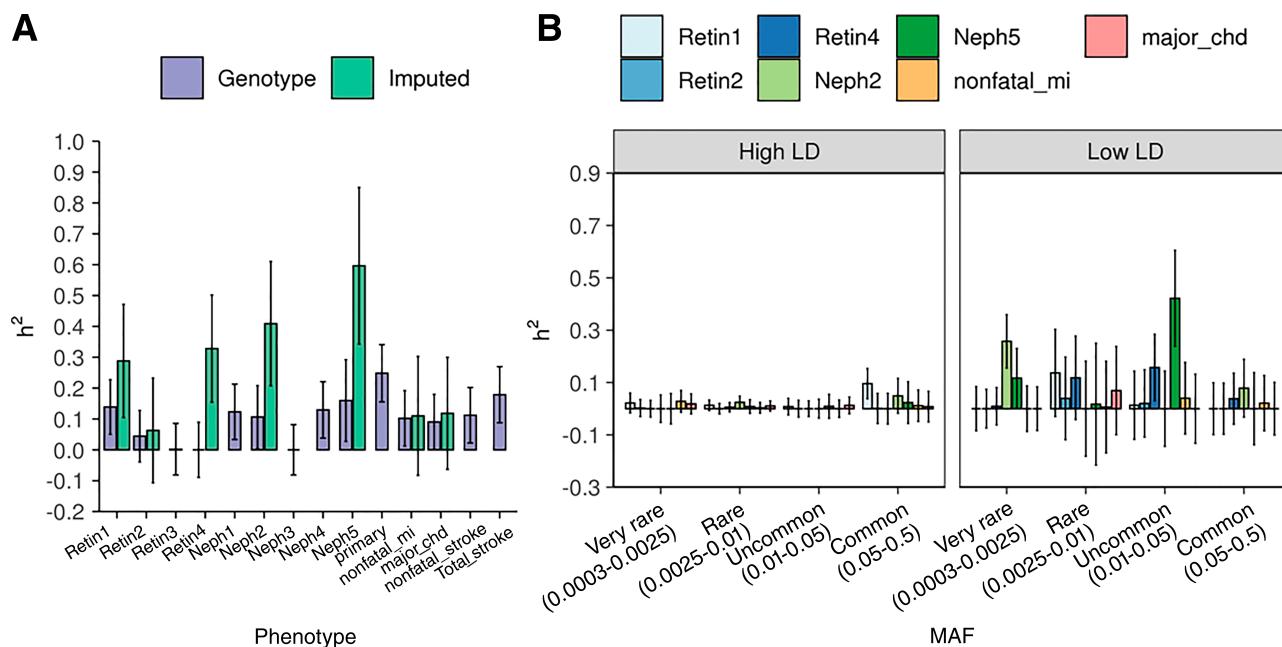
V(G)/V(p) (SE)

Phenotype	Proportion of cases in the sample	n	GREML-SC	GREML-LDMS
Retin1	0.084	4,318	0.139 (0.088)	0.288 (0.183)
Retin2	0.158	4,318	0.044 (0.083)	0.063 (0.169)
Retin3	0.360	4,318	0.002 (0.084)	NA
Retin4	0.068	4,318	0.000 (0.089)	0.328 (0.174)
Neph1	0.591	4,318	0.123 (0.090)	NA
Neph2	0.070	3,866	0.106 (0.101)	0.409 (0.201)
Neph3	0.028	4,318	0.000 (0.082)	NA
Neph4	0.616	4,318	0.129 (0.091)	NA
Neph5	0.241	2,912	0.160 (0.132)	0.596 (0.254)
Primary	0.106	4,318	0.248 (0.093)	NA
Nonfatal MI	0.071	4,318	0.102 (0.090)	0.110 (0.192)
Major CHD	0.129	4,318	0.090 (0.089)	0.118 (0.181)
Total mortality	0.066	4,318	0.013 (0.088)	NA
CVD mortality	0.028	4,318	0.094 (0.089)	NA
Nonfatal stroke	0.015	4,318	0.112 (0.090)	NA
Total stroke	0.018	4,318	0.179 (0.091)	NA

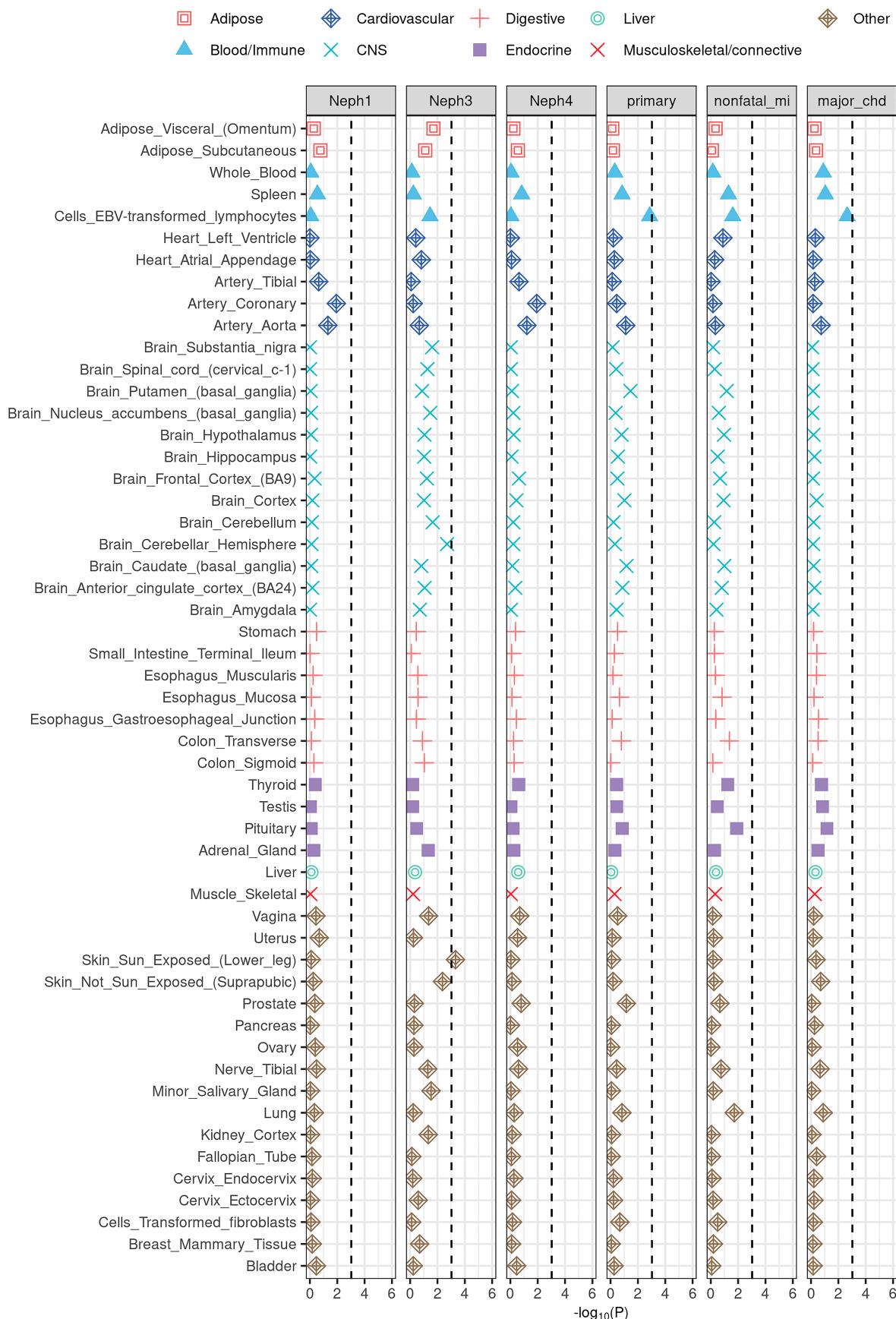
NA under GREML-LDMS, the GREML analysis failed to run due to the small sample size; n, number of samples without missing phenotype; V(G)/V(p), proportion of phenotypic variance explained by genotypes (i.e., heritability, as observed in the study population).

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, and H3k4me1. In the ACCORD data, none of the categories for any phenotype



**Figure 2—**Heritability estimates and SEs of diabetes complications using the ACCORD data. 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. B: GREML-LDMS estimates with eight bins (two LD bins for each of the four MAF bins). For each phenotype, the sum of estimates from the eight 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 ( $P < 0.05/53$ ). CNS, central nervous system; EBV, Epstein-Barr virus.

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 report, 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 data sets 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 a 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 group without diabetes than in the group with diabetes, while heritability for macrovascular complications stays similar between the two groups. Several reasons may explain the differences: 1) outcome misclassifications due to electronic health record-based phenotyping, 2) unaccounted confounders, such as medications, and 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 groups with and without diabetes. It may be because GWAS hits for CVD among the population with diabetes 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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