

Time-to-Event Genome-Wide Association Study for Incident Cardiovascular Disease in People with Type 2 Diabetes Mellitus

SUPPLEMENTARY METHODS

Definition of Type 2 Diabetes and Age at Diagnosis

T2D was defined in each cohort based on meeting one or more of the American Diabetes Association criteria, and the age at diagnosis was determined through self-report or incident diagnosis during follow-up according to each cohort (1). The details on how age at diagnosis was captured is described in **Table S2**. For many cohorts, self-reported or hospital-recorded age was utilized for prevalent diabetes cases at enrollment. For incident cases, the age was determined at the time of the follow-up visit when diabetes was first reported.

Definition of Cardiovascular Disease

CVD was defined as a composite of 1) coronary artery disease (CAD), 2) cerebrovascular disease, and 3) death from a cardiovascular cause. CAD included myocardial infarction, stable or unstable angina, percutaneous coronary intervention, coronary artery bypass grafting, and other cohort-defined events (**Table S3**). Cerebrovascular disease included ischemic stroke, hemorrhagic stroke, transient ischemic attack, carotid stenting, endarterectomy, and other cohort-defined events. Death from cardiovascular causes included death from myocardial infarction, stroke, unexpected death presumed to be from ischemic CVD, and other cohort-defined events. An incident CVD event was defined as the first CVD event occurring at least one year after T2D diagnosis. Participants with any CVD event prior to diagnosis of T2D or within one year after diagnosis of T2D were excluded from incident CVD analysis. If a participant had multiple CVD events, only the first event was considered.

Cox Proportional Hazards Assumption

Before running the Cox proportional hazards model, the model which did not include genotype information was evaluated to determine whether it met the proportional hazard assumption using the `cox.zph()` function in the 'Survival' R package (2). If a variable violated the assumption, this was resolved either by including an interaction term or by stratifying the variables into 3 to 5 subgroups.

Meta-Analysis

Summary statistics of the cohort level results underwent standard quality control procedures using EasyQC software (3). First, the genetic coordinates of GRCh38 were converted to GRCh37/hg19 using LiftOver (4) software. Then variants with unreliably large effect size ($\beta \geq 10$) or large standard error (≥ 10) were excluded in each cohort. Variants with minor allele count ≤ 6 , or variants with a frequency difference > 0.20 compared to the corresponding ancestry in the 1,000 Genomes phase 3 data were also removed. Meta-analysis of cohort-level summary statistics was conducted using an inverse-variance-weighted fixed-effect method as implemented in METAL (5). Genomic control was applied at the cohort level to control for possible inflation in the type I error due to residual population stratification. Both overall meta-analysis and ancestry-level meta-analysis were performed. A genome-wide significance threshold was set as $P < 5.0 \times 10^{-8}$ (6; 7).

Approximate Conditional Analysis

Approximate conditional analysis using summary statistics was carried out using GCTA-Cojo (8) (version 1.93.2). Variants within a 120 kilobase (Kb) region (± 60 Kb) of the lead signal from the meta-analysis were selected. Conditional analyses were approximated using ancestry-specific summary statistics, excluding lead variants that only occurred in one ancestry. Linkage disequilibrium was estimated using GCTA by providing the 1000-Genomes reference panel using super populations 'AFR' to represent our African ancestry, 'EUR' to represent our European ancestry, 'EAS' to represent our East Asian ancestry, and the union of 'AMR', 'CEU' and 'YRI' populations to represent our Hispanic ancestry individuals. We applied a multiple testing

threshold at each locus when considering variants for distinct secondary signals by dividing 0.05 by the number of variants in the 120 Kb region.

Fine-Mapping of Distinct Association Signals to Identify 95% Credible Sets

To fine-map distinct association signals, we computed credible sets with 95% confidence. For each variant within +/- 90 Kb of a lead variant with a minor allele count greater than 40, i.e., the most associated variants in a region, we computed ancestry-specific Bayes factors in favor of association using estimated allelic effect sizes and standard errors from each available ancestry-specific meta-analysis. To find the Bayes factor (Λ_j) for the j th variant in a particular ancestry, we considered

$$\Lambda_j = \sqrt{\frac{V_j}{V_j + \omega}} \exp \left[\frac{\omega \beta_j^2}{2V_j(V_j + \omega)} \right]$$

where β_j and V_j represent the effect estimate and variance, respectively, from the ancestry-specific meta-analysis (9; 10). The constant ω describes the prior variance in allelic effects, which we set to 0.0462.

We then calculated the posterior probability that the j th variant drives the association signal in a particular ancestry (π_j) using

$$\pi_j = \frac{\Lambda_j}{\sum_{k=1}^n \Lambda_k}$$

where n denotes the total number of variants within +/- 90 kilobases of the lead variant (9). This was repeated for all variants in each region.

Functional Annotations

A genome-wide map of 18 distinct human umbilical vein endothelial cell (HUVEC) chromatin state annotations was retrieved from the Common Metabolic Diseases Genome Atlas (CMDGA, <https://cmdga.org/>). These chromatin states were characterized from ENCODE (11) ChIP-seq data using ChromHMM (12) v1.18. Each variant in each ancestry-specific credible set was matched to its corresponding chromatin state annotation.

Colocalization of GWAS and eQTL

To estimate the posterior probability of our genome-wide significant variants and eQTL sharing the identical causal variants, we performed a Bayesian colocalization method as implemented in R package 'coloc' (13) (cran.r-project.org/web/packages/coloc). eQTL data were obtained from the eQTLGen Consortium (14) (31,684 whole blood samples), and GWAS variants were extracted from the summary statistics for variants located within one megabase (Mb) of the lead GWAS variants. We defined the variants as colocalized when the posterior probability of a colocalized signal (PP4) was >0.8 as generally recommended.

Phenome-Wide Association Analysis

The Common Metabolic Disease Knowledge Portal was used to investigate phenome-wide association (<https://hugeamp.org/>). As there were 388 phenotypic traits (some of which are interrelated) included in the portal, the significance threshold was conservatively set as $P < 1.2 \times 10^{-4}$ ($0.05/388$).

SUPPLEMENTARY RESULTS

Downstream Analysis of the Three Loci

An approximate conditional analysis of the three index variants at each of the three regions of interest showed no evidence of secondary signals (**Figure S2**). We performed fine-mapping analysis for each of the three regions to narrow the number of potentially causal variants using credible set analysis in each ancestry (15). We constructed a total of nine ancestry-specific credible sets: four for chromosome 1, one for chromosome 4, and four for chromosome 6 locus. Each credible set accounted for $\geq 95\%$ of the posterior probability of association with T2D in CVD in its corresponding ancestry-specific analysis. The median credible set size (i.e., number of variants included) for the chromosome 1 locus was 468, with a minimum size of 28 (AFR), and a maximum size of 816 (HIS). Likewise, the median size for the chromosome 6 locus was 637, with a minimum size of 42 (EUR), and a maximum size of 867 (AFR). However, the chromosome 4 credible set only contained 4 variants: rs77142250, rs114281229, rs7677123, and rs77129258. Small credible sets like this are favorable for prioritizing variants for functional follow-up.

Functional interrogation for the three loci included chromatin state annotations from HUVEC cell lines, a system relevant to endothelial function, atherosclerosis, and CVD (**Figure S3**). The chromosome 4 locus contained narrow bands of transcription and enhancer annotations near *HS3ST1* and wider bands dispersed upstream. One of the four variants in the credible set, rs114281229, falls within a region containing an active enhancer annotation. Additionally, rs77129258 resides in a region of weak transcription. Given their proximity, rs114281229 and rs77129258 may affect expression of *HS3ST1*, but further investigation is required to substantiate this. The chromosome 1 and 6 locus did not provide meaningful functional prioritizations.

We used colocalization with expression QTL data from the eQTLGen Consortium to further characterize the three new loci(13). We found chromosome 6 rs335407 to be a significant eQTL for *TIAM2* in peripheral leukocytes $P = 7.71 \times 10^{-238}$. *TIAM2* is essential for endothelial barrier and

cell-cell contact maintenance (16). However, posterior probabilities from colocalization analysis did not support rs335407 as causal for both incident CVD and expression of *TIAM2*. Using a phenome-wide association analysis, we surveyed other phenotypes associated with the three novel loci by interrogating the Common Metabolic Disease Knowledge Portal. Metabolic phenotypes nominally ($P < 0.05$) associated included, for chromosome 1 rs147138607, small artery occlusion and stroke; for chromosome 4 rs7714225, sleep with oxyhemoglobin saturation under 90% and BMI; and for chromosome 6 rs335407, BMI and snoring (**Table S9**).

Table S1. Basic Cohort Information

Study Name	Short Study Name	Study Location	Ethnicity	Study Periods	Study Design	Brief Participant Description	Study Reference (PMID)
Atherosclerosis Risk in Communities Study	ARIC	NC, MS, MN, MD, USA	European, African American	1987 - 2014	Population based prospective cohort	Population based cohort to determine the trends in hospitalized heart attack and coronary heart disease death	2646917
BioMe BioBank	BIOME	NY, USA	African American, European, Hispanic	2007 - Current	Hospital based cohort	Participants from Mountain Sinai Health System	33861964
Cardiovascular Health Study	CHS	CA, MD, NC, PA, USA	African American, European	1989 - Current	Population based prospective cohort	Population based cohort of older adults	1669507
Framingham Heart Study	FHS	Framingham, MA, USA	European	1971 - 2014	Population based prospective cohort	Original cohort participants from the town of Framingham, MA	14819398, 474565, 17372189
Jackson Heart Study	JHS	Jackson, MS, USA	African American	2000 - Current	Population based prospective cohort	Population based cohort to investigate CVD risk in African Americans	16320381
Korean Genome and Epidemiology Study	KOGES	Ansung, and Ansan, Republic of Korea	East Asian	2001 - Current	Population based prospective cohort	Population based cohort to investigate genetic and clinical risk factors of common complex	26577716

						disease in Korean population with biannual prospective follow-up	
Multi-Ethnic Study of Atherosclerosis	MESA	USA	African American, East Asian, European, Hispanic	2001 - Current	Population based prospective cohort	MESA researchers study a diverse, population-based sample of 6,814 asymptomatic men and women aged 45-84.	12397006
Mass General Brigham	MGB	Boston, MA, USA	European	2010 - Current	Hospital based cohort	Patients of Partners HealthCare	26784234
Penn Medicine BioBank	PMBB	Philadelphia, PA, USA	African American, European	2013 - Current	Hospital based cohort	Participants from the Univeristy of Pennsylvania Health System	32919613
Prospective Study of Pravastatin in the Elderly at Risk	PROSPER	Scotland, Ireland and the Netherlands	European	1997 - 2002	Randomized controlled trial	Particpants at cardiovascular risk	12457784
Reasons for Geographic and Racial Differences in Stroke Study	REGARDS	USA	African American; European	2003 - Current	Population based prospective cohort	REGARDS was designed to investigate factors associated with the excess stroke mortality of residents of the stroke belt region and that of blacks compared with whites	15990444

Rotterdam Study	ROTTERDAM	Rotterdam, the Netherlands	European	1996 - 2012	Population based prospective cohort	The Rotterdam Study is an ongoing prospective cohort study that started in 1990 in the city of Rotterdam, The Netherlands. The study aims to unravel etiology, preclinical course, natural history and potential targets for intervention for chronic diseases in mid-life and late-life.	32367290
Sanford Health	SANFORD	Upper Midwest, USA	European	1950 - Current	Hospital based cohort (Biobank)	Patients of Sanford Health System	
UK Biobank	UKBB	UK	European only	2006 - Current	Population based prospective cohort	UK Biobank is a major health resource with the aim of improving the prevention, diagnosis and treatment of a wide range of serious and life-threatening illnesses – including cancer, heart diseases, stroke, diabetes, and etc.	30305743

Women's Genome Health Study	WGHS	N. America (almost entirely US)	European only	1992 - Current (endpoint data 2017)	Population based prospective cohort	Female healthcare professionals > 45 at baseline with no known CVD or cancer	18070814, 15753114
Women's Health Initiative	WHI	Seattle, WA	African American, East Asian, European, Hispanic	1992 - Current	Population based cohort and clinical trials	Post-menopausal women (age 50-79 at baseline)	9492970

Table S2. Definition of Type 2 Diabetes			
Short Study Name	Diagnosis of Type 2 Diabetes	Exclusion Criteria	Ascertainment of Age at Diagnosis of Diabetes
ARIC	Self-reported diagnosis of diabetes by a physician or self-reported use of anti-diabetic medication	Prior coronary heart disease or stroke diagnosis; age at diagnosis of diabetes < 40 years; race/ethnicity not reported as black or white; follow-up time < 1 year; CVD diagnosed < 1 year after diabetes ascertainment	For prevalent diabetes cases at enrollment, age at baseline was used. For incident cases, age was taken at the time of the interview when a diabetes diagnosis was first reported.
BIOME	Self-reported diagnosis of diabetes by a physician or self-reported use of anti-diabetic medication	Age at DM diagnosis below 40 years, CVD diagnosed at < 1 year after the DM diagnosis	For prevalent diabetes cases at enrollment, age at baseline was used. For incident cases, age was taken at the time of the interview when a diabetes diagnosis was first reported.
CHS	Fasting glucose \geq 126 mg/dL or non-fasting glucose \geq 200 mg/dL or use of insulin or an oral hypoglycemic agent.	All participants were age 65 or older at baseline and no information was available regarding age at diagnosis of diabetes. Thus, no participants with diabetes were excluded.	For prevalent type 2 diabetes cases, population mean was used from PMID:15671192 . For incident cases, age at follow-up visit that was closest to the date of diagnosis was used.
FHS	Fasting glucose \geq 126 mg/dL or use of insulin or an oral hypoglycemic agent or 2hour glucose \geq 200 mg/dL or Hba1c \geq 6.5%	Age at DM diagnosis below 40 years, CVD diagnosed at < 1 year after the DM diagnosis	For prevalent type 2 diabetes cases, self reported age at diagnosis was used. For incident cases, age at follow-up visit that was closest to the date of diagnosis was used.
JHS	Fasting glucose \geq 126 mg/dL or use of insulin or an oral hypoglycemic agent or 2hour glucose \geq 200 mg/dL or Hba1c \geq 6.5%	Type 1 diabetes, age at diagnosis of diabetes below 40 years, CVD diagnosed at < 1 year after the DM diagnosis	For prevalent type 2 diabetes cases, self reported age at diagnosis was used. For incident cases, age at follow-up visit that was closest to the date of diagnosis was used.
KOGES	Fasting glucose \geq 126 mg/dL, or 75g OGTT 2-h glucose \geq 200 mg/dL, or confirmed by health care provider, or on anti-diabetic medication	Type 1 diabetes, gestational diabetes, age at diagnosis of diabetes below 40 years	For prevalent type 2 diabetes cases, self reported age at diagnosis was used. For incident cases, age at follow-up visit that was closest to the date of diagnosis was used.

MESA	Fasting glucose \geq 126 mg/dL or confirmed by health care provider or on anti-diabetic medication	Type 1 diabetes, age at diagnosis of diabetes below 40 years, CVD diagnosed at < 1 year after the DM diagnosis	For prevalent type 2 diabetes cases, self reported age at diagnosis was used. For incident cases, age at follow-up visit that was closest to the date of diagnosis was used.
MGB	Fasting glucose \geq 126 mg/dL, or 75g OGTT 2-h glucose \geq 200 mg/dL, or confirmed by health care provider, or on anti-diabetic medication	Type 1 diabetes, gestational diabetes, age at diagnosis of diabetes below 40 years	For prevalent type 2 diabetes cases, self reported age at diagnosis was used. For incident cases, age at follow-up visit that was closest to the date of diagnosis was used.
PMBB	(2 or more T2DM Dx codes AND T2DM RX) OR (2 or more T2DM DX codes AND (Random glucose > 200 OR Fasting Glucose > 125 OR any A1c \geq 6.5)) OR (T2DM RX AND (Random glucose > 200 OR Fasting Glucose > 125 OR any A1c \geq 6.5)) Internal OR 2 separate: Random glucose > 200 OR Fasting Glucose > 125 OR A1C \geq 6.5	Age at DM diagnosis below 40 years, CVD diagnosed at < 1 year after the DM diagnosis	Age at first diabetes diagnosis
PROSPER	Known diabetes mellitus or fasting blood glucose \geq 7 mmol/L	Recent stroke, transient ischemic attack, myocardial infarction, arterial surgery, or amputation for vascular disease #6months before study entry; glucose concentration>15 mmol/L	Age at start of the study is used as age at diagnosis of diabetes
REGARDS	Fasting glucose \geq 126 mg/dL or non-fasting glucose \geq 200 mg/dL or self-reported use of insulin or an oral hypoglycemic agent	All participants were age 45 or older at baseline and no information was available regarding age at diagnosis of diabetes. We did not exclude any participants with diabetes.	Age at the start of study (age at computer-assisted telephone interview)
ROTTERDAM	Fasting blood glucose concentration of 7.0 mmol/l or higher, or the use of blood glucose-lowering medications	At baseline, RS has no data on age at diabetes diagnosis, therefore our cases are T2D over the follow-up, are older than 45 years. CVD diagnosed at < 1 year after the DM diagnosis	Age at diagnosis is available for all incident cases.
SANFORD	Diagnosis of type 2 diabetes based on hospital record	Type 1 diabetes, diagnosis of T2D at age < 40	Age at diagnosis is available for all incident cases.

UKBB	Fasting glucose \geq 126 mg/dL, or Hba1c \geq 6.5%, or confirmed by health care provider, or on anti-diabetic medication	Type 1 diabetes, gestational diabetes, age at diagnosis of diabetes below 40 years	Self reported age at diagnosis of diabetes was used.
WGHS	At least one of the following: symptom of hyperglycemia, 2 or more measures of elevated plasma glucose, or use of insulin or an oral hypoglycemic agent by self-report with follow-up in medical records as needed.	Diabetes < 30 years	Self reported age at diagnosis of diabetes was used.
WHI	Self-reported diagnosis of diabetes by a physician or self-reported use of anti-diabetic medication	All subjects were older than 40 years old at baseline, CVD diagnosed at < 1 year after the DM diagnosis	Self reported age at diagnosis of diabetes was used.

Table S3. Definition of CVD Event

Short Study Name	Definition of CVD event			Source of CVD Event Information
	Coronary Artery Disease	Cerebrovascular Disease	Death from Cardiovascular Cause	
ARIC	Hospitalized myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft	Definite, probable, or possible hospitalized stroke	Fatal coronary heart disease or stroke	Adjudicated events data
BIOME	Hospitalized myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft	Definite, probable, or possible hospitalized stroke	Fatal coronary heart disease or stroke	Adjudicated events data
CHS	Fatal or non-fatal myocardial infarction, angina, percutaneous coronary intervention, or coronary artery bypass graft	Fatal or non-fatal stroke (ischemic or hemorrhagic), or transient ischemic attack	Fatal myocardial infarction or fatal stroke	Adjudicated events data
FHS	Fatal or non-fatal myocardial infarction, angina, percutaneous coronary intervention, or coronary artery bypass graft	Fatal or non-fatal stroke (ischemic or hemorrhagic), or transient ischemic attack	Fatal myocardial infarction or fatal stroke	Adjudicated events data
JHS	Fatal or non-fatal MI, Coronary revascularization procedure, or death from CHD.	Stroke or angioplasty of arteries of neck	Fatal coronary heart disease or stroke	Adjudicated events data
KOGES	Myocardial infarction	Stroke	Death from myocardial infarction or stroke. Unexpected death presumed to be from ischemic cardiovascular disease	Self-report and death record registry from Korea National Statistical Office.

MESA	Myocardial infarction, resuscitated cardiac arrest, definite angina, probable angina (if followed by revascularization)	Stroke	Stroke Death CHD Death Other Atherosclerotic Death Other CVD Death	a telephone interviewer contacted each participant to inquire about all interim hospital admissions, cardiovascular outpatient diagnoses and procedures, and deaths. In addition, MESA occasionally identified additional medical encounters through cohort clinic visits, participant call-ins, medical record abstractions or obituaries. In order to verify self-reported diagnoses, we requested copies of all death certificates and medical records for all hospitalizations and selected outpatient cardiovascular diagnoses and procedures. We also obtained next of kin interviews for out of hospital cardiovascular deaths
PBB	Myocardial infarction	Stroke	Death from myocardial infarction or stroke	Hospital based electronic health record
PMBB	Myocardial infarction, chronic ischemic heart disease, Other acute and subacute forms of ischemic heart disease	Stroke	Death from CAD or CVD as assigned by medical records and the National death index.	Hospital based electronic health record and National Death Index data
PROSPER	Incident CHD defined as fatal or non-fatal myocardial infarction, surgical or percutaneous coronary revascularization procedure, or death from CHD.	Stroke	Death from myocardial infarction or stroke	Adjudicated events data

REGARDS	Total CHD including revascularization: first event of definite/probable myocardial infarction OR revascularization OR definite/probable acute CHD death on/before 12/31/2016	Incident stroke (ischemic or hemorrhagic) on or before 09/30/2019	CVD death from definite, probable, or possible MI, heart failure, other cardiac death, or not cardiac but other CVD death on/before 12/31/2016, or probable stroke death identified using National Death Index registry	Adjudicated events data
ROTTERDAM	Incident CHD defined as fatal or non-fatal myocardial infarction, surgical or percutaneous coronary revascularization procedure, or death from CHD.	Stroke	Death from any CVD (CHD, heart failure, stroke)	Outpatient clinic reports, hospital discharge letters, electrocardiograms, and imaging data
SANFORD	Hospitalized myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft	Stroke	Fatal coronary heart disease or stroke	Adjudicated events data
UKBB	Myocardial infarction	Stroke	N/A	Self-report
WGHS	Incident myocardial infarction	Incident stroke	Death from any CVD (CHD, heart failure, stroke) from autopsy reports, death certificates, medical records, and information obtained from family members	Self-report followed by physician review of medical records using WHO standard
WHI	Incident CHD defined as fatal or non-fatal MI, Coronary revascularization procedure, or death from CHD.	Stroke	Death from definite or probable CHD or stroke	Adjudicated events data

Table S4. Time-to-Event GWAS Analysis Software Used

Short Study Name	Analysis Software Used
ARIC	michiganCoxSurv in gwasurvivr version 3.10
BIOME	impute2CoxSurv in gwasurvivr
CHS	GWASTools_1.28.0
FHS	assoCoxPH in GWASTools version 1.33.0
JHS	assoCoxPH in GWASTools version 1.33.0
KOGES	michiganCoxSurv in gwasurvivr version 3.10
MESA	michiganCoxSurv in gwassurvivr version 3.10
PBB	michiganCoxSurv in gwasurvivr version 3.10
PMBB	plinkCoxSurv in gwassurvivr version 3.10
PROSPER	michiganCoxSurv in gwassurvivr version 3.10
REGARDS	plinkCoxSurv in gwassurvivr version 3.10
ROTTERDAM	michiganCoxSurv in gwassurvivr version 3.10
SANFORD	michiganCoxSurv in gwasurvivr version 3.10
UKBB	assoCoxPH in GWASTools version 1.33.0
WGHS	ProbABEL Cox model
WHI	michiganCoxSurv in gwasurvivr version 3.10

Table S5. Genotyping Platform and Imputation

Short Study Name	Array (Platform and Version)	Pre-imputation Variant QC (e.g. Call Rate, HWE, Heterozygosity, MAF)	Imputation Method	Imputation Reference Panel	Measure of Imputation Accuracy	Genome Build
ARIC	Affymetrix Genome-Wide Human SNP Array 6	Call Rate > 0.95, HWE $P > 1.0 \times 10^{-6}$, MAF > 0.01	Michigan Imputation Server	1000G	INFO	GRCh37
BIOME	Affymetrix Genome-Wide Human SNP Array 6	Call Rate > 0.95, HWE $P > 1.0 \times 10^{-6}$, MAF > 0.01	Michigan Imputation Server	1000G	INFO	GRCh37
CHS	Illumina 370CNV (EA), Illumina Omni1M (AA)	Call rate < 97%, HWE $P < 10^{-5}$, > 2 duplicate errors or Mendelian inconsistencies	Michigan Imputation Server	TOPMed F5	R2	GRCh38
FHS	Affymetrix 500K and MIPS 50K	Call Rate > 0.95, HWE $P > 1.0 \times 10^{-6}$, MAF > 0.01	Michigan Imputation Server	1000G	R2	GRCh37
JHS	Affymetrix Genome-Wide Human SNP Array 6	Call Rate > 0.95, HWE $P > 1.0 \times 10^{-6}$	Michigan Imputation Server	1000G	R2	GRCh37
KOGES	Affymetrix Genome-Wide Human SNP Array 5	Call Rate > 0.95, HWE $P > 1.0 \times 10^{-6}$, MAF > 0.01	Michigan Imputation Server	1779 Northeast Asian + 1000 Genomes Project phase 3 (PMID: 31640730)	R2	GRCh37

MESA	Affymetrix Genome-Wide Human SNP Array 6	Call Rate > 0.95, HWE $P > 1.0 \times 10^{-6}$	Michigan Imputation Server	TOPMed F5	R2	GRCh38
PBB	Illumina Multiethnic Beadchip Array	Call Rate > 0.95, HWE $P > 1.0 \times 10^{-6}$, MAF > 0.01	Michigan Imputation Server	HRC	R2	GRCh37
PMBB	Illumina InfiniumOmniExpress-24v1-2_A1; Global Screening Array V1; Global Screening Array V2	Sample call rate <98%; HWE < 1×10^{-6} ; MAF < 0.01	Michigan Imputation Server	TopMed F8	R2	GrCh38
PROSPER	Illumina Beadchip 660K	Call Rate > 0.97, HWE $P > 1.0 \times 10^{-6}$, duplicate errors, sex errors	Michigan Imputation Server	HRC	R2	GRCh37
REGARDS	Illumina Infinium Multi-Ethnic Genotype Array (MEGA Chip)	Call Rate > 0.90, HWE $P > 1.0 \times 10^{-5}$ for EU, HWE $P > 1.0 \times 10^{-12}$ for AA, MAF > 0.05	BioData Catalyst TOPMed Imputation Server	TOPMed F8	R2	GRCh38
ROTTERDAM	Illumina 550 K and 610 K	Sample call rate <98%; HWE < 1×10^{-6} ; MAF < 0.01	MaCH/minimac	HRC	INFO	GRCh38
SANFORD	GSA Version 1	Call Rate > 0.95, HWE $P > 1.0 \times 10^{-6}$	Michigan Imputation Server	TOPMed F8	R2	GRCh37
UKBB	Affymetrix Axiom UK Biobank Genotyping Array	Call Rate > 0.98, HWE $P > 1.0 \times 10^{-6}$, MAF > 0.01, Het < mean ± 3 xs.d.	IMPUTE2	HRC + UK10K	INFO	GRCh37
WGHS	Illumina HumanHap300 Duo "+"	Call rate > 0.90, HWE $P > 1.0 \times 10^{-6}$	Michigan Imputation Server	1000G	R2	GRCh37

WHI-HIPFX	Illumina 550 K and 610 K; Affymatrix 6.0; Illumina humanOmni1-Quad v1-0 B; Illumina HumanOmniEspressExome- 8v1_B; CytoSNP 370k; Affymetrix Gene Titan, Axiom Genome-Wide Human CEU I Array Plate; Multi-Ethnic Genotyping Array; OncoArray	Call rate > 0.98, HWE P > 1.0×10^{-4} , MAF > 0.01	BioData Catalyst TOPMed Imputation Server	TOPMed F8	R2	GRCh38
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Table S6. Sample Size and Event Rate According to Ancestry and Cohort

Ancestry	Cohort	Total (N)	Event (N)	Event Rate (%)
European/European American	ARIC	2,184	543	24.9
	BIOME	851	160	18.8
	CHS	379	225	59.4
	FHS	547	185	33.8
	MESA	392	64	16.3
	MGB	1,161	389	33.5
	PMBB	603	244	40.5
	PROSPER	452	39	8.6
	REGARDS	303	195	64.4
	ROTTERDAM	611	98	16
	SANFORD	2,062	174	8.4
	UKBB	15,643	1,499	9.6
	WGHS	2,043	105	5.1
	WHI	3,887	998	25.7
Subtotal		31,118 (63.2%)	4,918 (54.9%)	15.8
African American	ARIC	1,142	310	27.1
	BIOME	1,764	467	26.5
	CHS	130	76	58.5
	JHS	726	92	12.7
	MESA	508	85	16.7
	PMBB	1,242	388	31.2
	REGARDS	2,483	733	29.5
	WHI	3,129	693	22.1
Subtotal		11,124 (22.6%)	2,844 (31.8%)	25.6
Hispanic/Latino	BIOME	2,681	668	24.9
	MESA	482	89	18.5
	WHI	1,162	177	15.2
Subtotal		4,325 (8.8%)	934 (10.4%)	21.6
East Asian	KOGES	2,317	185	8.0
	MESA	194	42	21.6
	WHI	152	33	21.7
Subtotal		2,663 (5.4%)	260 (2.9%)	9.8
Total		49,230	8,956	18.2

A total of 49,230 participants with T2D from 16 cohorts and of multiple ancestries were included in this study: 31,118 (63.2%) of European, 11,124 (22.6%) of African American, 4,325 (8.8%) of Hispanic/Latino, and 2,663 (5.4%) of East Asian ancestry. The total incident CVD event rate was 18.2% with those of African ancestry having the highest event rate of 25.6%. ARIC, Atherosclerosis Risk in Communities Study; BIOME, BioMe BioBank; CHS, Cardiovascular

Health Study; FHS, Framingham Heart Study; JHS, Jackson Heart Study; KOGES, Korean Genome and Epidemiology Study; MESA, Multi-Ethnic Study of Atherosclerosis; MGB, Mass General Brigham Biobank ; PMBB, Penn Medicine BioBank; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; REGARDS, Reasons for Geographic and Racial Differences in Stroke Study; ROTTERDAM, Rotterdam Study; SANFORD, Sanford Health; UKBB, UK Biobank; WGHS, Women's Genome Health Study; and WHI, Women's Health Initiative.

Table S7. Clinical Characteristics of Each Cohort

Short Study Name		N (F/M)	Mean Age at Diabetes Diagnosis (years)	Mean Observation Time (years)	Mean BMI (kg/m ²)	Treatment for High Blood Pressure, N (%)	Current Smoking, N (%)	Mean Systolic Blood Pressure (mmHg)	Mean Total Cholesterol (mg/dl)	Mean HDL Cholesterol (mg/dl)
ARIC	Total	3326 (1980/1346)	65.2	12.3	31.3	821 (57.6)	262 (18.4)	129.0	208	46
	with CVD event	853 (450/403)	62.5	9.5	31.5	307 (57.1)	115 (21.4)	131.9	217	44
	without CVD event	2473 (1530/943)	66.1	13.2	31.2	514 (57.9)	147 (16.6)	127.3	203	47
BioMe	Total	5983 (3382/2601)	59.9	8.4	31.9	5086 (85.0)	649 (11.1)	135.0	180	48
	with CVD event	1414 (882/532)	59.1	6.0	32.5	1354 (95.8)	136 (9.6)	134.1	185	48
	without CVD event	4569 (2500/2069)	60.2	9.2	31.7	3732 (81.7)	513 (11.6)	135.2	179	48
CHS EU T2D	Total	379 (191/188)	53.2	28.3	28.3	182 (48.0)	42 (11.1)	140.7	206	47
	with CVD event	225 (105/120)	53.2	26.6	28.2	116 (51.6)	26 (11.5)	142.5	208	47
	without CVD event	154 (86/68)	53.2	30.9	28.4	66 (42.9)	16 (10.4)	138.0	203	49
CHS AA T2D	Total	130 (81/49)	48.5	33.7	30.4	74 (56.9)	17 (13.1)	144.8	211	52
	with CVD event	76 (50/26)	48.5	31.6	30.0	42 (55.2)	6 (7.9)	148.8	215	52
	without CVD event	54 (31/23)	48.5	36.6	30.9	32 (59.3)	11 (20.4)	139.2	206	52

FHS	Total	762 (314/ 375)	57.0	13.6	31.0	270 (35.4)	159 (20.9)	134.6	208	44
	with CVD event	283 (107/145)	56.2	12.5	31.1	102 (36.0)	68 (24.0)	138.4	216	41
	without CVD event	479 (207/230)	57.5	14.3	31.0	168 (35.1)	91 (19.0)	132.4	203	46
JHS	Total	726	61.1	10.0	34.5	586 (80.7)	75 (10.3)	130.3	198	50
	with CVD event	92	62.5	6.7	33.5	74 (80.4)	15 (16.3)	135.8	207	49
	without CVD event	634	61.0	10.5	34.7	512 (80.8)	60 (9.5)	129.5	197	50
KOGES	Total	2153 (1046/1107)	55.5	10.0	25.4	416 (19.3)	554 (25.7)	122.4	202	44
	with CVD event	185 (82/103)	55.0	10.7	25.7	56 (30.2)	46 (24.9)	126.9	203	44
	without CVD event	1968 (964/1004)	55.6	10.0	25.4	360 (18.3)	508 (25.8)	122.0	202	44
MESA	Total	1576(798/778)	63.1	12.3	30.5	951 (60.4)	205 (13.0)	130.5	186	48
	with CVD event	280(99/181)	63.2	11.6	29.9	195 (69.6)	31 (11.1)	136.3	186	46
	without CVD event	1296(699/597)	63.1	12.5	30.6	756 (58.4)	174 (13.5)	129.2	186	48
PBB	Total	1161 (524/637)	56.7	8.6	32.4	773 (79.2)	174 (16.1)	129.4	188	46
	with CVD event	389 (130/259)	58.8	6.4	32.2	270 (85.4)	63 (17.6)	131.1	188	44

	without CVD event	772 (394/378)	55.7	9.7	32.5	503 (76.2)	111 (15.3)	128.8	188	48
PMBB	Total	1845 (971/874)	57.4	7.6	33.8	110 (6.0)	NA	132.3	177	46
	with CVD event	632 (304/328)	58.3	6.3	33.3	15 (2.4)	NA	134.2	176	45
	without CVD event	1213 (667/546)	57.0	8.2	34.0	95 (7.8)	NA	131.3	178	46
PROSPER	Total	452 (207/245)	75.2	3.2	28.0	280 (62)	58 (13)	158.4	193	1
	with CVD event	39 (17/22)	74.7	2.5	28.8	25 (64)	4 (10)	156.2	193	1
	without CVD event	413 (190/223)	75.2	3.2	27.9	255 (62)	54 (13)	158.6	193	1
REGARDS AA	Total	2483 (1017/1466)	64.6	8.1	32.9	1955 (78.7)	373 (15.0)	134.2	183	49
	with CVD event	733 (346/387)	66.3	5.0	32.4	601 (85)	120 (16.4)	137.7	187	48
	without CVD event	1750 (671/1079)	64.0	9.4	33.1	1354 (80)	253 (14.5)	132.7	181	49
REGARDS EU	Total	303 (183/120)	67.7	5.2	31.3	197 (65.0)	50 (16.5)	129.7	179	43
	with CVD event	195 (131/64)	68.8	3.0	31.1	137 (71.7)	37 (19)	129.7	178	42
	without CVD event	108 (52/56)	65.7	9.2	31.7	60 (57.7)	13 (12)	129.7	180	45
ROTTERDAM	Total	611 (356/255)	73.0	6.5	29.0	333 (54.5)	137 (22.4)	149.1	232	1

	with CVD event	98 (52/46)	75.2	5.1	28.5	54 (55.1)	31 (31.6)	153.7	232	1
	without CVD event	513 (304/209)	72.6	6.7	29.1	279 (54.4)	106 (20.7)	148.3	193	1
SANFORD	Total	61410 (28170/33240)	63.9	5.4	37.5	30078 (48.98%)	6537 (12.0)	129.6	153	39
	with CVD event	4577 (1838/2739)	67.0	5.6	37.9	2220 (48.5%)	409 (9.8)	131.3	159	39
	without CVD event	56833 (26332/30501)	63.7	5.4	37.5	27858 (49.02%)	6128 (12.1)	129.5	153	39
UKBB	Total	15643 (5725/9918)	54.5	7.2	31.8	10213 (65.3)	1634 (10.5)	142.3	173	46
	with CVD event	1499 (366/1133)	53.1	9.5	32.2	1173 (78.3)	228 (15.2)	142.6	168	43
	without CVD event	14144 (5359/8785)	54.7	7.0	31.8	9040 (63.9)	1406 (9.9)	142.3	173	46
WGHS	Total	2470 (2470/0)	63.2	12.0	30.4	284 (11.5)	284 (11.5)	131.1	218	45
	with CVD event	105 (105/0)	65.3	7.7	30.8	33 (31.4)	15 (14.3)	134.6	222	43
	without CVD event	2365 (2365/0)	63.1	12.3	30.4	640 (27.1)	269 (11.4)	131.0	217	45
WHI-GARNET	Total	1226 (1226/0)	69.3	10.6	32.1	58 (5)	113 (9)	128.3	231	48
	with CVD event	381 (381/0)	69.3	7.8	31.6	10 (3)	32 (8)	132.1	233	46
	without CVD event	845 (845/0)	69.4	11.9	32.3	48 (6)	81 (10)	126.6	230	48

WHI-GECCO	Total	176 (176/0)	70.1	7.7	32.3	11 (7)	9 (5)	129.3	236	47
	with CVD event	40 (40/0)	69.8	7.1	32.5	0 (0)	3 (8)	132.8	234	37
	without CVD event	136 (136/0)	70.1	7.8	32.2	11 (8)	6 (4)	128.3	238	53
WHI-HIPFX	Total	385 (385/0)	73.5	7.3	29.5	13 (3)	35 (9)	131.7	220	49
	with CVD event	108 (108/0)	73.8	7.5	29.2	3 (3)	8 (7)	137.3	224	47
	without CVD event	277 (277/0)	73.3	7.3	29.6	10 (3)	27 (10)	129.5	217	50
WHI-LLS	Total	137 (137/0)	80.1	9.8	28.7	17 (12)	5 (4)	126.5	225	54
	with CVD event	32 (32/0)	76.8	8.8	29.0	2 (6)	1 (3)	125.0	243	53
	without CVD event	105 (105/0)	81.1	10.1	28.6	15 (17)	4 (4)	126.9	219	54
WHI-MOPMAP	Total	281 (281/0)	69.2	8.4	32.4	14 (5)	19 (7)	127.6	224	43
	with CVD event	54 (54/0)	68.1	6.7	32.4	0 (0)	3 (6)	128.4	213	40
	without CVD event	227 (227/0)	69.5	8.8	32.4	14 (5)	16 (7)	127.4	228	45
WHI-ONCO	Total	869 (869/0)	70.4	7.3	31.0	35 (4)	49 (6)	129.5	225	50
	with CVD event	168 (168/0)	70.9	7.6	30.6	5 (3)	12 (7)	132.3	223	46

	without CVD event	701 (701/0)	70.3	7.2	31.1	20 (4)	37 (5)	128.9	226	52
WHI-WHIMS+	Total	803 (803/0)	75.5	9.0	30.7	67 (8)	43 (5)	131.6	220	51
	with CVD event	215 (215/0)	73.8	8.8	31.3	13 (6)	12 (6)	134.2	218	48
	without CVD event	588 (588/0)	76.1	9.1	30.5	54 (9)	31 (5)	130.7	220	52
WHI-SHARe	Total	951 (951/0)	70.0	11.2	33.5	30 (3)	105 (11)	134.2	221	54
	with CVD event	241 (241/0)	66.5	9.3	33.8	5 (2)	38 (16)	137.7	229	50
	without CVD event	710 (710/0)	71.2	11.9	33.4	25 (4)	67 (9)	133.0	219	55
WHI-MEGA AA	Total	2178 (2178/0)	65.8	10.4	32.9	75 (3)	269 (12)	132.8	220	53
	with CVD event	452 (452/0)	65.5	9.0	32.8	16 (4)	63 (14)	138.0	226	51
	without CVD event	1726 (1726/0)	65.8	10.8	32.9	59 (3)	206 (12)	131.5	219	54
WHI-MEGA HA	Total	1162 (1162/0)	66.3	9.6	31.4	67 (6)	101 (9)	127.6	217	48
	with CVD event	177 (177/0)	65.9	9.3	31.9	6 (3)	10 (6)	131.7	220	47
	without CVD event	985 (985/0)	66.4	9.6	31.3	61 (6)	91 (9)	126.9	217	49
WHI-MEGA Asian/PI	Total	152 (152/0)	65.1	8.2	33.2	1 (1)	17 (11)	131.8	215	47

	with CVD event	33 (33/0)	65.1	9.2	34.1	0 (0)	2 (6)	133.1	228	45
	without CVD event	119 (119/0)	65.1	7.9	33.0	1 (1)	15 (13)	131.5	212	47

Table S8. Association of Known 204 CAD Variants in People with T2D

rsID	CHR	Pos (GRCh37)	Nearby Gene	Effect Allele	Reported Beta in General Population	Reported <i>P</i> in General Population	Reported Beta in T2D	Reported <i>P</i> in T2D	Consistent Direction of Association
rs36096196	1	2252205	<i>MORN1</i>	T	0.047	1.3×10^{-8}	0.001	0.9619	Yes
rs2493298	1	3325912	<i>PRDM16</i>	A	0.057	2.0×10^{-9}	0.069	0.0040	Yes
rs61776719	1	38461319	<i>FHL3</i>	A	0.041	1.2×10^{-9}	0.007	0.6772	Yes
rs11206510	1	55496039	<i>PCSK9</i>	T	0.058	3.7×10^{-8}	0.004	0.8556	Yes
rs11591147	1	55505647	<i>PCSK9</i>	G	0.298	7.6×10^{-22}	0.048	0.6048	Yes
rs17114046	1	56966350	<i>PLPP3(PPAP2B)</i>	A	0.115	1.8×10^{-24}	0.015	0.5366	Yes
rs147055617	1	56986303	<i>PLPP3(PPAP2B)</i>	G	0.088	7.8×10^{-14}	0.07	0.0368	Yes
rs112470402	1	57016950	<i>PLPP3(PPAP2B)</i>	TGG	0.051	8.6×10^{-8}	0.009	0.8772	Yes
rs602633	1	109821511	<i>PSRC1(SORT1)</i>	G	0.112	2.0×10^{-59}	0.047	0.0133	Yes
rs11806316	1	115753482	<i>NGF</i>	G	0.037	5.0×10^{-10}	0.002	0.9105	Yes
rs11810571	1	151762308	<i>TDRKH</i>	G	0.055	1.8×10^{-11}	-0.023	0.2438	No
rs4845625	1	154422067	<i>IL6R</i>	T	0.038	2.7×10^{-9}	-0.004	0.7971	No
rs1892094	1	169094459	<i>ATP1B1</i>	C	0.041	4.5×10^{-13}	0.039	0.0241	Yes
rs6700559	1	200646073	<i>DDX59,CAMSAP2</i>	C	0.028	1.8×10^{-8}	0.007	0.6707	Yes
rs2820315	1	201872264	<i>LMOD1</i>	T	0.036	1.1×10^{-10}	-0.042	0.0417	No
rs60154123	1	210468999	<i>HHAT</i>	T	0.044	2.6×10^{-8}	0.011	0.6806	Yes
rs17465637	1	222823529	<i>MIA3</i>	C	0.082	8.5×10^{-31}	0.052	0.0035	Yes
rs699	1	230845794	<i>AGT</i>	G	0.036	2.1×10^{-8}	0.021	0.2396	Yes
rs16986953	2	19942473	<i>OSR1(AK097927)</i>	A	0.097	1.4×10^{-14}	0.02	0.4377	Yes
rs668948	2	21291529	<i>APOB</i>	A	0.063	1.9×10^{-17}	-0.005	0.7979	No
rs6544713	2	44073881	<i>ABCG8,ABCG5</i>	T	0.055	6.5×10^{-19}	-0.017	0.3667	No
rs4076834	2	44081627	<i>ABCG8,ABCG5</i>	T	0.113	1.2×10^{-10}	0.002	0.9411	Yes
rs582384	2	45896437	<i>PRKCE</i>	A	0.033	7.6×10^{-9}	-0.001	0.9762	No
rs1561198	2	85809989	<i>VAMP8,VAMP5</i>	T	0.059	1.5×10^{-20}	0.005	0.7808	Yes
rs6740731	2	145270592	<i>ZEB2,TEX41</i>	A	0.051	3.9×10^{-9}	0.007	0.7282	Yes
rs17678683	2	145286559	<i>ZEB2,TEX41</i>	G	0.056	3.4×10^{-7}	0.01	0.7563	Yes

rs2252641	2	145801461	<i>ZEB2,TEX41</i>	C	0.040	7.3×10^{-13}	-0.017	0.3423	No
rs12999907	2	164957251	<i>FIGN</i>	A	0.056	2.4×10^{-11}	-0.001	0.9553	No
rs840616	2	188196469	<i>CALCRL</i>	C	0.040	3.0×10^{-9}	-0.024	0.1617	No
rs115654617	2	203893999	<i>WDR12,NBEAL1</i>	A	0.118	2.1×10^{-32}	0.065	0.0220	Yes
rs17517928	2	216291359	<i>FN1</i>	C	0.048	1.8×10^{-10}	0.043	0.0380	Yes
rs1250229	2	216304384	<i>FN1</i>	T	0.064	2.5×10^{-19}	0.045	0.0210	Yes
rs61741262	2	218669225	<i>TNS1</i>	T	0.062	2.3×10^{-8}	0.048	0.1527	Yes
rs2571445	2	218683154	<i>TNS1</i>	A	0.037	1.6×10^{-12}	0.029	0.1182	Yes
rs2972146	2	227100698	<i>LOC646736</i>	T	0.049	1.2×10^{-7}	0.007	0.7023	Yes
rs1801251	2	233633460	<i>KCNJ13,GIGYF2</i>	A	0.039	5.2×10^{-6}	0.001	0.9781	Yes
rs11677932	2	238223955	<i>COL6A3</i>	G	0.034	2.6×10^{-8}	0.022	0.2675	Yes
rs13079221	3	14901525	<i>FGD5</i>	C	0.041	1.6×10^{-10}	0.011	0.5114	Yes
rs7633770	3	46688562	<i>SNORD77,ALS2CL</i>	A	0.030	1.1×10^{-8}	0.045	0.0106	Yes
rs7617773	3	48193515	<i>CDC25A</i>	T	0.039	2.4×10^{-11}	-0.008	0.6407	No
rs7623687	3	49448566	<i>RHOA</i>	A	0.053	1.1×10^{-8}	-0.003	0.8859	No
rs4678145	3	124450081	<i>UMPS,ITGB5</i>	C	0.068	1.5×10^{-13}	0.056	0.0378	Yes
rs10512861	3	132257961	<i>DNAJC13</i>	G	0.045	1.5×10^{-8}	-0.044	0.0388	No
rs667920	3	136069472	<i>STAG1</i>	T	0.049	6.1×10^{-15}	0.009	0.6388	Yes
rs185244	3	138092889	<i>MRAS</i>	T	0.074	3.3×10^{-18}	0.02	0.3269	Yes
rs12493885	3	153839866	<i>ARHGEF26</i>	C	0.074	1.1×10^{-14}	0.061	0.0430	Yes
rs4266144	3	156852592	<i>CCNL1</i>	G	0.035	1.4×10^{-8}	0.002	0.9310	Yes
rs12897	3	172115902	<i>FNDC3B</i>	G	0.042	1.9×10^{-10}	0.011	0.5670	Yes
rs16844401	4	3449652	<i>HGFAC,RGS12</i>	A	0.068	4.0×10^{-8}	-0.015	0.6688	No
rs17087335	4	57838583	<i>REST,NOA1</i>	T	0.049	8.4×10^{-8}	-0.007	0.7128	No
rs12500824	4	77416627	<i>SHROOM3</i>	A	0.036	4.1×10^{-10}	0.023	0.1606	Yes
rs10857147	4	81181072	<i>FGF5</i>	T	0.055	1.1×10^{-14}	0.015	0.4497	Yes
rs11099493	4	82587050	<i>HNRNPD</i>	A	0.043	5.1×10^{-10}	0.006	0.7472	Yes
rs3775058	4	96117371	<i>UNC5C</i>	A	0.039	7.6×10^{-9}	0.046	0.0164	Yes
rs7678555	4	120909501	<i>MAD2L1</i>	C	0.056	3.1×10^{-15}	0.016	0.4375	Yes
rs35879803	4	146782837	<i>ZNF827</i>	C	0.033	1.2×10^{-6}	-0.004	0.8179	No
rs4593108	4	148281001	<i>EDNRA</i>	C	0.063	8.1×10^{-15}	0.026	0.1790	Yes
rs6842241	4	148400819	<i>EDNRA</i>	A	0.081	1.3×10^{-23}	0.067	7.5×10^{-4}	Yes

rs13118820	4	156436517	<i>GUCY1A3,MAP9</i>	A	0.042	1.4×10^{-10}	0.034	0.0452	Yes
rs7692387	4	156635309	<i>GUCY1A3,MAP9</i>	G	0.069	4.1×10^{-22}	0.018	0.4454	Yes
rs7696431	4	169687725	<i>PALLD</i>	T	0.035	2.7×10^{-8}	0.004	0.8328	Yes
rs1508798	5	9556694	<i>SEMA5A</i>	T	0.052	4.8×10^{-13}	-0.02	0.3000	No
rs3936511	5	55860781	<i>LOC101928448</i>	G	0.037	3.7×10^{-8}	0.025	0.2302	Yes
rs1800449	5	121413208	<i>LOX</i>	T	0.044	2.0×10^{-7}	-0.032	0.1508	No
rs273909	5	131667353	<i>SLC22A4-SLC22A5</i>	G	0.049	9.9×10^{-4}	0.05	0.0982	Yes
rs246600	5	142516897	<i>ARHGAP26</i>	T	0.048	2.1×10^{-17}	0.03	0.0731	Yes
rs9501744	6	1617143	<i>FOXC1</i>	C	0.055	2.3×10^{-8}	-0.028	0.2151	No
rs1412748	6	12756658	<i>PHACTR1</i>	T	0.052	1.3×10^{-8}	0.014	0.4616	Yes
rs9349379	6	12903957	<i>PHACTR1</i>	G	0.115	4.8×10^{-71}	0.074	3.2×10^{-5}	Yes
rs7766436	6	22598259	<i>HDGFL1</i>	T	0.048	2.5×10^{-12}	0.03	0.0749	Yes
rs2072633	6	31919578	<i>C2</i>	G	0.041	6.3×10^{-13}	0.021	0.2010	Yes
rs2814993	6	34618893	<i>ANKS1A,C6orf16</i>	A	0.061	9.7×10^{-12}	0.03	0.1704	Yes
rs17609940	6	35034800	<i>ANKS1A,C6orf16</i>	G	0.030	7.1×10^{-3}	-0.029	0.2178	No
rs1321309	6	36638636	<i>CDKN1A,PANDAR</i>	A	0.028	3.5×10^{-8}	0.017	0.2977	Yes
rs10947789	6	39174922	<i>KCNK5</i>	T	0.039	1.9×10^{-4}	0.043	0.0414	Yes
rs6905288	6	43758873	<i>VEGFA</i>	A	0.045	1.9×10^{-12}	0.025	0.1137	Yes
rs9367716	6	57160572	<i>PRIM2</i>	G	0.038	9.6×10^{-10}	0.026	0.1214	Yes
rs4613862	6	82612271	<i>RP11-379B8.1</i>	A	0.032	6.6×10^{-10}	0.015	0.3717	Yes
rs1591805	6	126717064	<i>CENPW</i>	A	0.041	2.1×10^{-10}	0.034	0.0405	Yes
rs2327429	6	134209837	<i>TCF21</i>	T	0.071	8.3×10^{-24}	0.02	0.2949	Yes
rs2327433	6	134214227	<i>TCF21</i>	G	0.076	1.0×10^{-8}	0.027	0.3324	Yes
rs17080091	6	150997401	<i>PLEKHG1</i>	C	0.054	6.1×10^{-9}	0.02	0.4371	Yes
rs688359	6	160465291	<i>IGF2R</i>	G	0.053	5.4×10^{-15}	0.026	0.1944	Yes
rs624249	6	160679400	<i>LPA,PLG,LPAL2,SLC22A3</i>	C	0.058	9.1×10^{-11}	-0.012	0.5011	No
rs2048327	6	160863532	<i>LPA,PLG,LPAL2,SLC22A3</i>	C	0.058	7.4×10^{-12}	0.022	0.2382	Yes
rs147555597	6	160911596	<i>LPA,PLG,LPAL2,SLC22A3</i>	A	0.398	2.7×10^{-31}	0.099	0.6113	Yes
rs55730499	6	161005610	<i>LPA,PLG,LPAL2,SLC22A3</i>	T	0.337	3.0×10^{-154}	0.123	6.0×10^{-4}	Yes
rs9365196	6	161056112	<i>LPA,PLG,LPAL2,SLC22A3</i>	C	0.058	8.0×10^{-11}	-0.028	0.3104	No
rs9457995	6	161102643	<i>LPA,PLG,LPAL2,SLC22A3</i>	G	0.071	4.1×10^{-15}	0.042	0.0379	Yes
rs186696265	6	161111700	<i>LPA,PLG,LPAL2,SLC22A3</i>	T	0.547	4.6×10^{-92}	0.18	0.0816	Yes

rs4252120	6	161143608	<i>LPA,PLG,LPAL2,SLC22A3</i>	T	0.039	8.2×10^{-5}	0.02	0.2921	Yes
rs10267593	7	1937261	<i>MAD1L1</i>	G	0.036	1.9×10^{-8}	0.017	0.3871	Yes
rs10951983	7	6446027	<i>DAGLB</i>	A	0.038	1.1×10^{-7}	0.01	0.6586	Yes
rs11509880	7	12261911	<i>TMEM106B</i>	A	0.037	2.9×10^{-8}	-0.026	0.1074	No
rs2107595	7	19049388	<i>HDAC9</i>	A	0.082	3.8×10^{-24}	0.055	0.0047	Yes
rs2107732	7	45077978	<i>CCM2</i>	G	0.057	3.6×10^{-8}	0.084	0.0166	Yes
rs10953541	7	107244545	<i>7q22(BCAP29)</i>	C	0.030	5.8×10^{-3}	0.04	0.0712	Yes
rs975722	7	117332914	<i>CFTR,CCTNBP2</i>	G	0.028	4.2×10^{-8}	0.001	0.9426	Yes
rs11556924	7	129663496	<i>ZC3HC1</i>	C	0.058	1.9×10^{-18}	-0.001	0.9727	No
rs10237377	7	139757136	<i>PARP12</i>	G	0.034	6.5×10^{-9}	-0.016	0.3437	No
rs3918226	7	150690176	<i>NOS3</i>	T	0.122	3.3×10^{-21}	0.031	0.3835	Yes
rs6997340	8	18286997	<i>NAT2</i>	T	0.036	5.0×10^{-9}	-0.011	0.5533	No
rs6997330	8	19800529	<i>LPL</i>	C	0.129	7.7×10^{-11}	0	0.9908	No
rs15285	8	19824667	<i>LPL</i>	C	0.052	8.4×10^{-14}	0.005	0.7907	Yes
rs6984210	8	22033615	<i>BMP1</i>	G	0.085	2.2×10^{-11}	0.03	0.2955	Yes
rs10093110	8	106565414	<i>ZFPM2</i>	G	0.032	1.9×10^{-8}	0.013	0.4529	Yes
rs2954029	8	126490972	<i>TRIB1</i>	A	0.055	5.8×10^{-23}	-0.001	0.9354	No
rs896655	9	21706571	<i>CDKN2B,CDKN2A</i>	A	0.040	1.6×10^{-12}	0.047	0.0054	Yes
rs3731249	9	21970916	<i>CDKN2B,CDKN2A</i>	T	0.171	5.4×10^{-11}	-0.044	0.4951	No
rs4977754	9	22062012	<i>CDKN2B,CDKN2A</i>	A	0.108	5.9×10^{-8}	0.008	0.8478	Yes
rs1855185	9	22073996	<i>CDKN2B,CDKN2A</i>	G	0.128	8.5×10^{-11}	-0.012	0.7387	No
rs2891168	9	22098619	<i>CDKN2B,CDKN2A</i>	G	0.189	5.2×10^{-204}	0.063	1.3×10^{-4}	Yes
rs13301964	9	22113324	<i>CDKN2B,CDKN2A</i>	G	0.212	9.6×10^{-10}	0.169	0.0216	Yes
rs944172	9	110517794	<i>KLF4</i>	C	0.042	1.1×10^{-11}	0.025	0.1603	Yes
rs111245230	9	113169775	<i>SVEP1</i>	C	0.098	8.0×10^{-9}	0.181	2.3×10^{-4}	Yes
rs885150	9	124420173	<i>DAB2IP</i>	C	0.036	7.9×10^{-10}	-0.004	0.8496	No
rs507666	9	136149399	<i>ABO</i>	A	0.073	4.7×10^{-20}	0.01	0.6524	Yes
rs61848342	10	12303813	<i>CDC123</i>	C	0.036	6.4×10^{-10}	-0.005	0.7550	No
rs9337951	10	30317073	<i>KIAA1462</i>	A	0.062	1.1×10^{-17}	0.032	0.1660	Yes
rs1870634	10	44480811	<i>CXCL12</i>	G	0.060	3.5×10^{-24}	0.019	0.2410	Yes
rs1657346	10	44777560	<i>CXCL12</i>	G	0.092	1.6×10^{-24}	0.03	0.2069	Yes
rs17680741	10	82251514	<i>TSPAN14</i>	T	0.047	2.3×10^{-11}	-0.008	0.6738	No

rs2246942	10	91004886	LIPA	G	0.071	2.2×10^{-24}	0.019	0.2648	Yes
rs3740390	10	104638480	AS3MT,CYP17A1,CNNM2	C	0.072	4.4×10^{-15}	0.008	0.7783	Yes
rs4918072	10	105693644	STN1	A	0.042	2.6×10^{-9}	0.011	0.5477	Yes
rs4752700	10	124237612	HTRA1	G	0.033	8.0×10^{-11}	0.024	0.1488	Yes
rs11601507	11	5701074	TRIM5,TRIM22	A	0.084	2.1×10^{-12}	0.005	0.8808	Yes
rs10840293	11	9751196	SWAP70	A	0.046	9.0×10^{-13}	0.014	0.3747	Yes
rs11042937	11	10745394	MRVI1,CTR9	T	0.010	2.0×10^{-1}	-0.001	0.9321	No
rs1351525	11	13301548	ARNTL	T	0.048	4.1×10^{-8}	-0.026	0.1092	No
rs7116641	11	43696917	HSD17B12	G	0.031	1.0×10^{-8}	-0.008	0.6300	No
rs12801636	11	65391317	PCNX3	G	0.040	2.3×10^{-11}	0.002	0.8969	Yes
rs590121	11	75274150	SERPINH1	T	0.039	2.4×10^{-10}	0.018	0.2757	Yes
rs659418	11	75284334	SERPINH1	T	0.053	3.9×10^{-9}	0.006	0.7557	Yes
rs7947761	11	100624599	ARHGAP42	G	0.042	3.0×10^{-9}	-0.012	0.4990	No
rs974819	11	103660567	PDGFD,DYNC2H1	T	0.073	1.2×10^{-25}	0.004	0.8418	Yes
rs964184	11	116648917	APOA1-A5-A4-C3,ZNF259	G	0.071	8.0×10^{-15}	0.003	0.8913	Yes
rs11838267	12	7175872	C1S	T	0.051	6.2×10^{-10}	0.002	0.9474	Yes
rs10841443	12	20220033	LOC156393	G	0.051	7.9×10^{-14}	0	0.9869	Yes
rs11170820	12	54513915	HOXC4	G	0.097	1.1×10^{-13}	0.044	0.0782	Yes
rs11172113	12	57527283	LRP1	C	0.039	2.4×10^{-5}	0.025	0.1074	Yes
rs2681492	12	90013089	ATP2B1	C	0.063	2.6×10^{-15}	0.016	0.4504	Yes
rs7306455	12	95355541	NDUFA12	G	0.055	1.0×10^{-8}	-0.005	0.8370	No
rs3184504	12	111884608	SH2B3,ATXN2,HNF1A	T	0.074	5.1×10^{-30}	0.007	0.7100	Yes
rs11830157	12	118265441	KSR2	G	0.030	1.7×10^{-3}	-0.034	0.0546	No
rs2244608	12	121416988	HNF1A	G	0.052	7.3×10^{-19}	0.03	0.0925	Yes
rs11057401	12	124427306	SCARB1,CCDC92	T	0.038	2.2×10^{-8}	0.011	0.5417	Yes
rs11057830	12	125307053	SCARB1,CCDC92	A	0.082	2.7×10^{-20}	0.085	7.8×10^{-5}	Yes
rs9319428	13	28973621	FLT1	A	0.039	1.0×10^{-6}	0.021	0.2153	Yes
rs9591012	13	33058333	N4BP2L2	G	0.044	7.0×10^{-11}	-0.005	0.7997	No
rs11617955	13	110818102	COL4A1/A2	T	0.081	3.6×10^{-17}	-0.002	0.9505	No
rs3809346	13	110960943	COL4A1/A2	A	0.050	8.9×10^{-18}	-0.007	0.6887	No
rs11838776	13	111040681	COL4A1/A2	A	0.055	3.6×10^{-9}	0.078	1.7×10^{-5}	Yes
rs9515203	13	111049623	COL4A1/A2	T	0.068	5.8×10^{-24}	0.03	0.1037	Yes

rs1317507	13	113631780	MCF2L	A	0.043	8.5×10^{-12}	0.038	0.0468	Yes
rs2145598	14	58794001	ARID4A	G	0.028	4.3×10^{-8}	0.004	0.7857	Yes
rs3832966	14	75614504	TMED10	ACC CG	0.053	5.8×10^{-10}	-0.03	0.2477	No
rs112635299	14	94838142	SERPINA1,SERPINA2	G	0.136	8.4×10^{-10}	-0.044	0.6096	No
rs2895811	14	100133942	HHIPL1,CYP46A1	C	0.039	9.1×10^{-7}	0.034	0.0469	Yes
rs8003602	14	100148961	HHIPL1,CYP46A1	C	0.061	4.9×10^{-16}	0.053	0.0028	Yes
rs6494488	15	65024204	OAZ2,RBPMS2	A	0.038	3.9×10^{-8}	0.025	0.2126	Yes
rs17228058	15	67450305	SMAD3	A	0.066	3.7×10^{-17}	-0.004	0.8331	No
rs8039034	15	79017861	ADAMTS7	C	0.073	4.9×10^{-14}	-0.001	0.9716	No
rs11637783	15	79139000	ADAMTS7	T	0.074	1.2×10^{-30}	0.016	0.3533	Yes
rs8042271	15	89574218	MFGE8-ABHD2	G	0.086	6.1×10^{-7}	0.014	0.5480	Yes
rs17514846	15	91416550	FURIN	A	0.061	7.8×10^{-27}	-0.012	0.5012	No
rs17581137	15	96146414	LINC00924 (15q26.2)	A	0.037	1.2×10^{-8}	0.034	0.0743	Yes
rs1800775	16	56995236	CETP	C	0.039	2.5×10^{-6}	0.013	0.3903	Yes
rs1050362	16	72130815	DHX38,TXNL4B	A	0.039	2.7×10^{-11}	0.011	0.5159	Yes
rs12930452	16	75462055	CFDP1	G	0.052	1.2×10^{-15}	0.011	0.5676	Yes
rs7199941	16	81906423	PLCG2	A	0.040	9.2×10^{-13}	0.012	0.4924	Yes
rs7500448	16	83045790	CDH13	A	0.063	1.6×10^{-16}	-0.01	0.6623	No
rs216172	17	2126504	SMG6,SRR	C	0.039	2.3×10^{-5}	0.004	0.8156	Yes
rs170041	17	2170216	SMG6,SRR	C	0.051	9.3×10^{-17}	-0.01	0.5928	No
rs12936587	17	17543722	RASD1, SMCR3, PEMT	G	0.030	1.8×10^{-3}	0.009	0.5821	Yes
rs13723	17	27941886	CORO6,ANKRD13B	G	0.040	5.6×10^{-10}	-0.011	0.5259	No
rs76954792	17	30033514	(17q11.2)	T	0.039	1.2×10^{-8}	0.018	0.4069	Yes
rs2074158	17	40257163	DHX58,KAT2A	C	0.054	2.3×10^{-10}	0.047	0.0123	Yes
rs17608766	17	45013271	GOSR2	C	0.047	8.2×10^{-10}	-0.032	0.2493	No
rs3895874	17	47047868	UBE2Z,GIP	A	0.041	1.5×10^{-9}	0.024	0.1543	Yes
rs16948048	17	47440466	UBE2Z,ZNF652	G	0.053	2.7×10^{-16}	0.025	0.1110	Yes
rs7212798	17	59013488	BCAS3	C	0.068	2.2×10^{-8}	0.037	0.0951	Yes
rs1867624	17	62387091	PECAM1	T	0.037	8.1×10^{-11}	0.003	0.8606	Yes
rs9964304	18	47229717	ACAA2	C	0.038	1.1×10^{-9}	0.036	0.0284	Yes
rs663129	18	57838401	PMAIP1,MC4R	A	0.039	1.8×10^{-5}	0.016	0.3634	Yes

rs116843064	19	8429323	<i>ANGPTL4</i>	G	0.161	1.3×10^{-11}	0.02	0.7975	Yes
rs6511720	19	11202306	<i>LDLR</i>	G	0.136	4.9×10^{-41}	0.037	0.1253	Yes
rs4804573	19	11277232	<i>LDLR</i>	G	0.049	1.9×10^{-8}	-0.011	0.5313	No
rs73015714	19	17855763	<i>MAP1S,FCHO1</i>	G	0.059	8.4×10^{-14}	-0.006	0.7225	No
rs12976411	19	32882020	<i>ZNF507,LOC400684</i>	A	0.039	2.9×10^{-2}	-0.083	0.0145	No
rs60315715	19	41790086	<i>TGFB1,CCDC97</i>	G	0.070	9.4×10^{-9}	-0.009	0.7506	No
rs12980942	19	41832231	<i>TGFB1,CCDC97</i>	G	0.061	7.4×10^{-15}	0.002	0.9372	Yes
rs4803455	19	41851509	<i>TGFB1,CCDC97</i>	C	0.054	3.8×10^{-17}	0.016	0.3134	Yes
rs7412	19	45412079	<i>APOE,APOC1,TOMM4</i>	C	0.160	3.0×10^{-39}	0.08	0.0062	Yes
rs4420638	19	45422946	<i>APOE,APOC1,TOMM4</i>	G	0.090	2.7×10^{-14}	0.004	0.8577	Yes
rs1964272	19	46190268	<i>SNRPD2</i>	G	0.046	7.5×10^{-8}	0.017	0.2833	Yes
rs6088590	20	33313566	<i>NCOA6</i>	C	0.034	2.3×10^{-9}	0.011	0.4885	Yes
rs867186	20	33764554	<i>PROCR</i>	A	0.057	6.8×10^{-12}	-0.008	0.7686	No
rs6102343	20	39924279	<i>ZHX3</i>	A	0.037	1.1×10^{-8}	0.016	0.3394	Yes
rs3827066	20	44586023	<i>PCIF1,ZNF335</i>	T	0.042	4.4×10^{-9}	0.067	0.0057	Yes
rs260020	20	57714025	<i>ZNF831</i>	T	0.052	8.0×10^{-10}	-0.014	0.4950	No
rs2832227	21	30533076	<i>MAP3K7CL</i>	G	0.044	1.7×10^{-9}	0.055	0.0030	Yes
rs28451064	21	35593827	<i>MRPS6</i>	A	0.119	7.1×10^{-33}	0.037	0.2016	Yes
rs180803	22	24658858	<i>POM121L9P,ADORA2A</i>	G	0.168	3.3×10^{-10}	-0.055	0.4329	No

CHR, chromosome; POS, position in GRCh37; rsID, reference SNP id. Bold indicate $P < 0.05$ and those in red indicate $P < 0.00024$ (0.05/204)

Table S9. Phenome-wide associatino of three significant variant in Common Metabolic Disease Knowledge Portal

Variant	CHR	POS	Phenotype	P	Beta	Std Err	N	Data Set
rs147138607	1	181855562	TOAST small artery occlusion	0.000663	1.432	0.421	42,161	GWAS_MEGASTROKE_eu
			Any stroke	0.001524	1.169	0.369	117,779	GWAS_MEGASTROKE_eu
			All ischemic stroke	0.001702	1.176	0.375	114,513	GWAS_MEGASTROKE_eu
			Iron deficiency	0.00318	0.318	0.108	9,335	GWAS_GERA_eu
			Ulcerative colitis	0.01242	-0.237	0.095	58,715	GWAS_IBDGenetics_eu
			Waist-hip ratio adj BMI	0.01832	0.202	0.086	1,200	
			HbA1c	0.02227	0.038	0.017	42,790	GWAS_BBJ_ea
			Triglycerides	0.02344	0.01	0.004	1,391,500	GWAS_BBJ_ea
			All diabetic kidney disease	0.03642	-0.235	0.096	18,449	GWAS_DNCRI
			All diabetic kidney disease vs. controls	0.03879	-0.224	0.108	26,180	Sandholm_2021_GENIE_EU
			Type 2 diabetes adj BMI	0.044	0.14	0.071	59,918	GWAS_DIAGRAMimputed_eu
			Peripheral vascular disease	0.04567	-0.197	0.099	15,897	GWAS_GERA_eu
rs77142250	4	11444867	Percentage of sleep with oxyhemoglobin saturation under 90%	0.000149	4.475	1.18	2,300	Cade2021_SleepApnea_Mixed_Female_Male
			Percentage of sleep with oxyhemoglobin saturation under 90%	0.00022	5.213	1.411	1,374	Cade2021_SleepApnea_Mixed_Female_Male

			Average oxyhemoglobin saturation during sleep	0.02535	- 0.782	0.35	1,340	Cade2021_SleepApnea_Mixed_Female
			Minimum oxyhemoglobin saturation during sleep	0.02813	- 1.907	0.869	2,264	Cade2021_SleepApnea_Mixed_Female_Male
			BMI	0.03446	0.053	0.036	498,806	GWAS_UKBiobankGIANT_eu
			Serum albumin	0.04183	0.091	0.042	14,126	Gurdasani2019_UGR_metabolic_traits_af
rs335407	6	155665441	BMI	0.003705	0.014	0.005	878,357	GWAS_GiantUKBB_eu
			Snoring adj BMI	0.0046	- 0.009	0.003	380,804	GWAS_UKBiobankSnoringAdjBMI_eu
			Snoring	0.013	- 0.008	0.003	381,973	GWAS_UKBiobankSnoring_eu
			Fasting glucose adj BMI	0.02331	- 0.008	0.004	221,149	GWAS_FUSION_eu
			CAD or stroke or peripheral vascular disease in type 2 diabetes	0.02376	0.255	0.113	300	GWAS_CUHK_ea
			Disposition index	0.02424	0.11	0.047	5,130	GWAS_MAGIC-InsulinSecretionOGTT_eu
			Diabetic nephropathy	0.02611	0.2	0.09	3,854	GWAS_FinnGen_eu
			Controls vs thin	0.02867	0.273	0.125	4,792	GWAS_SCOOPaSTILTS_eu
			Sleep midpoint timing	0.033	- 0.031	0.015	85,502	
			Mean arterial pressure	0.0357	0.037	0.018	136,482	GWAS_BBJ_ea
			Any stroke	0.04133	1.061	0.52	404,096	GWAS_MEGASTROKE_eu
			TOAST cardio- aortic embolism	0.04259	1.133	0.559	259,206	GWAS_MEGASTROKE_eu

Corrected insulin response adj Matsuda ISI	0.04625	0.099	0.049	4,789	GWAS_MAGIC-InsulinSecretionOGTT_eu
Insulin sensitivity	0.04756	0.161	0.082	2,765	GWAS_GENESIS_eu
Proliferative diabetic retinopathy vs no DR	0.04887	- 0.342	0.158	1,487	GWAS_DiabeticRetino_aa
Proliferative diabetic retinopathy vs no DR acct DoD-GC	0.04899	-0.29	0.146	1,487	GWAS_DiabeticRetino_aa

REFERENCES

1. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, Collins BS, Hilliard ME, Isaacs D, Johnson EL, Kahan S, Khunti K, Leon J, Lyons SK, Perry ML, Prahalad P, Pratley RE, Seley JJ, Stanton RC, Gabbay RA, on behalf of the American Diabetes A. 2. Classification and Diagnosis of Diabetes: Standards of Care in Diabetes-2023. *Diabetes Care* 2023;46:S19-S40
2. Therneau TM. A Package for Survival Analysis in R. 2022;
3. Winkler TW, Day FR, Croteau-Chonka DC, Wood AR, Locke AE, Magi R, Ferreira T, Fall T, Graff M, Justice AE, Luan J, Gustafsson S, Randall JC, Vedantam S, Workalemahu T, Kilpelainen TO, Scherag A, Esko T, Kutalik Z, Heid IM, Loos RJ, Genetic Investigation of Anthropometric Traits C. Quality control and conduct of genome-wide association meta-analyses. *Nat Protoc* 2014;9:1192-1212
4. Hinrichs AS, Karolchik D, Baertsch R, Barber GP, Bejerano G, Clawson H, Diekhans M, Furey TS, Harte RA, Hsu F, Hillman-Jackson J, Kuhn RM, Pedersen JS, Pohl A, Raney BJ, Rosenbloom KR, Siepel A, Smith KE, Sugnet CW, Sultan-Qurraie A, Thomas DJ, Trumbower H, Weber RJ, Weirauch M, Zweig AS, Haussler D, Kent WJ. The UCSC Genome Browser Database: update 2006. *Nucleic Acids Res* 2006;34:D590-598
5. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics* 2010;26:2190-2191
6. Pe'er I, Yelensky R, Altshuler D, Daly MJ. Estimation of the multiple testing burden for genomewide association studies of nearly all common variants. *Genet Epidemiol* 2008;32:381-385
7. Suzuki K, Hatzikotoulas K, Southam L, Taylor HJ, Yin X, Lorenz KM, Mandla R, Huerta-Chagoya A, Melloni GEM, Kanoni S, Rayner NW, Bocher O, Arruda AL, Sonehara K, Namba S, Lee SSK, Preuss MH, Petty LE, Schroeder P, Vanderwerff B, Kals M, Bragg F, Lin K, Guo X, Zhang W, Yao J, Kim YJ, Graff M, Takeuchi F, Nano J, Lamri A, Nakatochi M, Moon S, Scott RA, Cook JP, Lee JJ, Pan I, Taliun D, Parra EJ, Chai JF, Bielak LF, Tabara Y, Hai Y, Thorleifsson G, Grarup N, Sofer T, Wuttke M, Sarnowski C, Gieger C, Nounsou D, Trompet S, Kwak SH, Long J, Sun M, Tong L, Chen WM, Nongmaithem SS, Noordam R, Lim VJY, Tam CHT, Joo YY, Chen CH, Raffield LM, Prins BP, Nicolas A, Yanek LR, Chen G, Brody JA, Kabagambe E, An P, Xiang AH, Choi HS, Cade BE, Tan J, Broadaway KA, Williamson A, Kamali Z, Cui J, Thangam M, Adair LS, Adeyemo A, Aguilar-Salinas CA, Ahluwalia TS, Anand SS, Bertoni A, Bork-Jensen J, Brandslund I, Buchanan TA, Burant CF, Butterworth AS, Canouil M, Chan JCN, Chang LC, Chee ML, Chen J, Chen SH, Chen YT, Chen Z, Chuang LM, Cushman M, Danesh J, Das SK, de Silva HJ, Dedoussis G, Dimitrov L, Doumatey AP, Du S, Duan Q, Eckardt KU, Emery LS, Evans DS, Evans MK, Fischer K, Floyd JS, Ford I, Franco OH, Frayling TM, Freedman BI, Genter P, Gerstein HC, Giedraitis V, Gonzalez-Villalpando C, Gonzalez-Villalpando ME, Gordon-Larsen P, Gross M, Guare LA, Hackinger S, Hakaste L, Han S, Hattersley AT, Herder C, Horikoshi M, Howard AG, Hsueh W, Huang M, Huang W, Hung YJ, Hwang MY, Hwu CM, Ichihara S, Ikram MA, Ingelsson M, Islam MT, Isono M, Jang HM, Jasmine F, Jiang G, Jonas JB, Jorgensen T, Kamanu FK, Kandeel FR, Kasturiratne A, Katsuya T, Kaur V, Kawaguchi T, Keaton JM, Kho AN, Khor CC, Kibriya MG, Kim DH, Kronenberg F, Kuusisto J, Lall K, Lange LA, Lee KM, Lee MS, Lee NR, Leong A, Li L, Li Y, Li-Gao R, Ligthart S, Lindgren CM, Linneberg A, Liu CT, Liu J, Locke AE, Louie T, Luan J, Luk AO, Luo X, Lv J, Lynch JA, Lyssenko V, Maeda S, Mamakou V, Mansuri SR, Matsuda K, Meitinger T, Melander O, Metspalu A, Mo H, Morris AD, Moura FA, Nadler JL, Nalls MA, Nayak U, Ntalla I, Okada Y, Orozco L, Patel SR, Patil S, Pei P, Pereira MA, Peters A, Pirie FJ, Polikowsky HG, Porneala B, Prasad G, Rasmussen-Torvik LJ, Reiner AP, Roden M, Rohde R, Roll K, Sabanayagam C, Sandow K, Sankareswaran A, Sattar N, Schonherr S, Shahriar M, Shen B, Shi J, Shin DM, Shojima N, Smith JA, So WY, Stancakova A, Steinthorsdottir V, Stilp AM, Strauch K, Taylor KD, Thorand B, Thorsteinsdottir U, Tomlinson B, Tran TC, Tsai FJ, Tuomilehto

J, Tusie-Luna T, Udler MS, Valladares-Salgado A, van Dam RM, van Klinken JB, Varma R, Wachter-Rodarte N, Wheeler E, Wickremasinghe AR, van Dijk KW, Witte DR, Yajnik CS, Yamamoto K, Yamamoto K, Yoon K, Yu C, Yuan JM, Yusuf S, Zawistowski M, Zhang L, Zheng W, Program VAMV, Raffel LJ, Igase M, Ipp E, Redline S, Cho YS, Lind L, Province MA, Fornage M, Hanis CL, Ingelsson E, Zonderman AB, Psaty BM, Wang YX, Rotimi CN, Becker DM, Matsuda F, Liu Y, Yokota M, Kardia SLR, Peyser PA, Pankow JS, Engert JC, Bonnefond A, Froguel P, Wilson JG, Sheu WHH, Wu JY, Hayes MG, Ma RCW, Wong TY, Mook-Kanamori DO, Tuomi T, Chandak GR, Collins FS, Bharadwaj D, Pare G, Sale MM, Ahsan H, Motala AA, Shu XO, Park KS, Jukema JW, Cruz M, Chen YI, Rich SS, McKean-Cowdin R, Grallert H, Cheng CY, Ghanbari M, Tai ES, Dupuis J, Kato N, Laakso M, Kottgen A, Koh WP, Bowden DW, Palmer CNA, Kooner JS, Kooperberg C, Liu S, North KE, Saleheen D, Hansen T, Pedersen O, Wareham NJ, Lee J, Kim BJ, Millwood IY, Walters RG, Stefansson K, Ahlqvist E, Goodarzi MO, Mohlke KL, Langenberg C, Haiman CA, Loos RJF, Florez JC, Rader DJ, Ritchie MD, Zollner S, Magi R, Marston NA, Ruff CT, van Heel DA, Finer S, Denny JC, Yamauchi T, Kadowaki T, Chambers JC, Ng MCY, Sim X, Below JE, Tsao PS, Chang KM, McCarthy MI, Meigs JB, Mahajan A, Spracklen CN, Mercader JM, Boehnke M, Rotter JI, Vujkovic M, Voight BF, Morris AP, Zeggini E. Genetic drivers of heterogeneity in type 2 diabetes pathophysiology. *Nature* 2024;

8. Yang J, Ferreira T, Morris AP, Medland SE, Genetic Investigation of ATC, Replication DIG, Meta-analysis C, Madden PA, Heath AC, Martin NG, Montgomery GW, Weedon MN, Loos RJ, Frayling TM, McCarthy MI, Hirschhorn JN, Goddard ME, Visscher PM. Conditional and joint multiple-SNP analysis of GWAS summary statistics identifies additional variants influencing complex traits. *Nat Genet* 2012;44:369-375, S361-363

9. Mahajan A, Wessel J, Willems SM, Zhao W, Robertson NR, Chu AY, Gan W, Kitajima H, Taliun D, Rayner NW, Guo X, Lu Y, Li M, Jensen RA, Hu Y, Huo S, Lohman KK, Zhang W, Cook JP, Prins BP, Flannick J, Grarup N, Trubetskoy VV, Kravic J, Kim YJ, Rybin DV, Yaghootkar H, Muller-Nurasyid M, Meidtner K, Li-Gao R, Varga TV, Marten J, Li J, Smith AV, An P, Ligthart S, Gustafsson S, Malerba G, Demirkan A, Tajes JF, Steinthorsdottir V, Wuttke M, Lecoeur C, Preuss M, Bielak LF, Graff M, Highland HM, Justice AE, Liu DJ, Marouli E, Peloso GM, Warren HR, Exome BPC, Consortium M, Consortium G, Afaq S, Afzal S, Ahlqvist E, Almgren P, Amin N, Bang LB, Bertoni AG, Bombieri C, Bork-Jensen J, Brandslund I, Brody JA, Burtt NP, Canouil M, Chen YI, Cho YS, Christensen C, Eastwood SV, Eckardt KU, Fischer K, Gambaro G, Giedraitis V, Grove ML, de Haan HG, Hackinger S, Hai Y, Han S, Tybjaerg-Hansen A, Hivert MF, Isomaa B, Jager S, Jorgensen ME, Jorgensen T, Karajamaki A, Kim BJ, Kim SS, Koistinen HA, Kovacs P, Kriebel J, Kronenberg F, Lall K, Lange LA, Lee JJ, Lehne B, Li H, Lin KH, Linneberg A, Liu CT, Liu J, Loh M, Magi R, Mamakou V, McKean-Cowdin R, Nadkarni G, Neville M, Nielsen SF, Ntalla I, Peyser PA, Rathmann W, Rice K, Rich SS, Rode L, Rolandsson O, Schonherr S, Selvin E, Small KS, Stancakova A, Surendran P, Taylor KD, Teslovich TM, Thorand B, Thorleifsson G, Tin A, Tonjes A, Varbo A, Witte DR, Wood AR, Yajnik P, Yao J, Yengo L, Young R, Amouyel P, Boeing H, Boerwinkle E, Bottinger EP, Chowdhury R, Collins FS, Dedoussis G, Dehghan A, Deloukas P, Ferrario MM, Ferrieres J, Florez JC, Frossard P, Gudnason V, Harris TB, Heckbert SR, Howson JMM, Ingelsson M, Kathiresan S, Kee F, Kuusisto J, Langenberg C, Launer LJ, Lindgren CM, Mannisto S, Meitinger T, Melander O, Mohlke KL, Moitry M, Morris AD, Murray AD, de Mutsert R, Orho-Melander M, Owen KR, Perola M, Peters A, Province MA, Rasheed A, Ridker PM, Rivadineira F, Rosendaal FR, Rosengren AH, Salomaa V, Sheu WH, Sladek R, Smith BH, Strauch K, Uitterlinden AG, Varma R, Willer CJ, Bluher M, Butterworth AS, Chambers JC, Chasman DI, Danesh J, van Duijn C, Dupuis J, Franco OH, Franks PW, Froguel P, Grallert H, Groop L, Han BG, Hansen T, Hattersley AT, Hayward C, Ingelsson E, Kardia SLR, Karpe F, Kooner JS, Kottgen A, Kuulasmaa K, Laakso M, Lin X, Lind L, Liu Y, Loos RJF, Marchini J, Metspalu A, Mook-Kanamori D, Nordestgaard BG, Palmer CNA, Pankow JS, Pedersen O, Psaty BM, Rauramaa R, Sattar N, Schulze MB, Soranzo N, Spector TD, Stefansson K, Stumvoll M, Thorsteinsdottir U, Tuomi T, Tuomilehto J, Wareham NJ, Wilson JG, Zeggini E, Scott RA, Barroso

- I, Frayling TM, Goodarzi MO, Meigs JB, Boehnke M, Saleheen D, Morris AP, Rotter JI, McCarthy MI. Refining the accuracy of validated target identification through coding variant fine-mapping in type 2 diabetes. *Nat Genet* 2018;50:559-571
10. Wakefield J. A Bayesian measure of the probability of false discovery in genetic epidemiology studies. *Am J Hum Genet* 2007;81:208-227
11. Consortium EP. An integrated encyclopedia of DNA elements in the human genome. *Nature* 2012;489:57-74
12. Ernst J, Kellis M. ChromHMM: automating chromatin-state discovery and characterization. *Nat Methods* 2012;9:215-216
13. Wallace C. Eliciting priors and relaxing the single causal variant assumption in colocalisation analyses. *PLoS Genet* 2020;16:e1008720
14. Vosa U, Claringbould A, Westra HJ, Bonder MJ, Deelen P, Zeng B, Kirsten H, Saha A, Kreuzhuber R, Yazar S, Brugge H, Oelen R, de Vries DH, van der Wijst MGP, Kasela S, Pervjakova N, Alves I, Fave MJ, Agbessi M, Christiansen MW, Jansen R, Seppala I, Tong L, Teumer A, Schramm K, Hemani G, Verlouw J, Yaghootkar H, Sonmez Flitman R, Brown A, Kukushkina V, Kalnapekns A, Rueger S, Porcu E, Kronberg J, Kettunen J, Lee B, Zhang F, Qi T, Hernandez JA, Arindrarto W, Beutner F, Consortium B, i QTLC, Dmitrieva J, Elansary M, Fairfax BP, Georges M, Heijmans BT, Hewitt AW, Kahonen M, Kim Y, Knight JC, Kovacs P, Krohn K, Li S, Loeffler M, Marigorta UM, Mei H, Momozawa Y, Muller-Nurasyid M, Nauck M, Nivard MG, Penninx B, Pritchard JK, Raitakari OT, Rotzschke O, Slagboom EP, Stehouwer CDA, Stumvoll M, Sullivan P, t Hoen PAC, Thiery J, Tonjes A, van Dongen J, van Iterson M, Veldink JH, Volker U, Warmerdam R, Wijmenga C, Swertz M, Andiappan A, Montgomery GW, Ripatti S, Perola M, Kutalik Z, Dermitzakis E, Bergmann S, Frayling T, van Meurs J, Prokisch H, Ahsan H, Pierce BL, Lehtimäki T, Boomsma DI, Psaty BM, Gharib SA, Awadalla P, Milani L, Ouwehand WH, Downes K, Stegle O, Battle A, Visscher PM, Yang J, Scholz M, Powell J, Gibson G, Esko T, Franke L. Large-scale cis- and trans-eQTL analyses identify thousands of genetic loci and polygenic scores that regulate blood gene expression. *Nat Genet* 2021;53:1300-1310
15. Mahajan A, Taliun D, Thurner M, Robertson NR, Torres JM, Rayner NW, Payne AJ, Steinthorsdottir V, Scott RA, Grarup N, Cook JP, Schmidt EM, Wuttke M, Sarnowski C, Magi R, Nano J, Gieger C, Trompet S, Lecoeur C, Preuss MH, Prins BP, Guo X, Bielak LF, Below JE, Bowden DW, Chambers JC, Kim YJ, Ng MCY, Petty LE, Sim X, Zhang W, Bennett AJ, Bork-Jensen J, Brummett CM, Canouil M, Ec Kardt KU, Fischer K, Kardina SLR, Kronenberg F, Lall K, Liu CT, Locke AE, Luan J, Ntalla I, Nylander V, Schönherr S, Schurmann C, Yengo L, Bottinger EP, Brandslund I, Christensen C, Dedoussis G, Florez JC, Ford I, Franco OH, Frayling TM, Giedraitis V, Hackinger S, Hattersley AT, Herder C, Ikram MA, Ingelsson M, Jorgensen ME, Jorgensen T, Kriebel J, Kuusisto J, Ligthart S, Lindgren CM, Linneberg A, Lyssenko V, Mamakou V, Meitinger T, Mohlke KL, Morris AD, Nadkarni G, Pankow JS, Peters A, Sattar N, Stancakova A, Strauch K, Taylor KD, Thorand B, Thorleifsson G, Thorsteinsdottir U, Tuomilehto J, Witte DR, Dupuis J, Peyser PA, Zeggini E, Loos RJF, Froguel P, Ingelsson E, Lind L, Groop L, Laakso M, Collins FS, Jukema JW, Palmer CNA, Grallert H, Metspalu A, Dehghan A, Kottgen A, Abecasis GR, Meigs JB, Rotter JI, Marchini J, Pedersen O, Hansen T, Langenberg C, Wareham NJ, Stefansson K, Gloyn AL, Morris AP, Boehnke M, McCarthy MI. Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. *Nat Genet* 2018;50:1505-1513
16. Amado-Azevedo J, Reinhard NR, van Bezu J, de Menezes RX, van Beusechem VW, van Nieuw Amerongen GP, van Hinsbergh VWM, Hordijk PL. A CDC42-centered signaling unit is a dominant positive regulator of endothelial integrity. *Sci Rep* 2017;7:10132

