

Genetic predisposition to type 2 diabetes and risk of subclinical atherosclerosis and cardiovascular diseases among 160,000 Chinese adults

Genetic predisposition to type 2 diabetes and CVD risk

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Abstract

In observational studies, type 2 diabetes is associated with 2- to 4-fold higher risks of cardiovascular diseases (CVD). Using data from the China Kadoorie Biobank, we examined associations of genetically-predicted type 2 diabetes with CVD among ~160,000 participants, to assess whether these relationships are causal. A type 2 diabetes genetic risk score (comprising 48 established risk variants) was associated with the presence of carotid plaque (OR 1.17 [95% CI 1.05, 1.29] per 1 unit higher log-odds of type 2 diabetes; n=6,819), and elevated risk of ischaemic stroke (IS) (1.08 [1.02, 1.14]; n=17,097), non-lacunar IS (1.09 [1.03, 1.16]; n=13,924) and major coronary event (1.12 [1.02, 1.23]; n= 5,081). There was no significant association with lacunar IS (1.03 [0.91, 1.16], n=3,173) or intracerebral haemorrhage (ICH) (1.01 [0.94, 1.10], n=6,973), although effect estimates were imprecise. These associations were consistent with observational associations of type 2 diabetes with CVD in CKB (p for heterogeneity>0.3), and with the associations of type 2 diabetes with IS, ICH and coronary heart disease in two-sample Mendelian randomisation analyses based on summary statistics from European population GWAS (p for heterogeneity>0.2). In conclusion, among Chinese adults, genetic predisposition to type 2 diabetes was associated with atherosclerotic CVD, consistent with a causal association.

Cardiovascular diseases (CVD) remain the major cause of death among individuals with diabetes (1). In observational studies, diabetes has been associated with 2- to 4-fold higher risks of CVD, in particular various types of atherosclerotic CVD (ASCVD), such as coronary heart disease (CHD), ischaemic stroke (IS) and peripheral arterial disease (2-4). However, it remains unclear whether this reflects a causal effect, or confounding by shared genetic or other risk factors. Furthermore, the associations of diabetes with subclinical atherosclerosis (5-7) and other CVD types, including haemorrhagic stroke (2-4; 8), are less well-understood. Although randomised controlled trials can assess causality, existing trial evidence for the effects of intensive glycaemic control in diabetes (9), and of interventions to reduce or delay progression of pre-diabetes to diabetes (10; 11), on risk of CVD are inconclusive.

Genome-wide association studies (GWAS) have identified multiple type 2 diabetes-associated genetic variants, which can be used as a genetic instrument for type 2 diabetes in so-called “Mendelian randomisation” (MR) studies to help assess causal associations (12). An effect of type 2 diabetes on CVD, independent of environmental and other factors potentially confounding observational risk estimates, can then be inferred from an association of these variants with CVD, subject to the assumption that the effect of the variants is through type 2 diabetes aetiological pathways. Several studies have examined the association of genetically-predicted type 2 diabetes with CVD (13-18). However, these have mainly involved populations of European ancestry, and focused largely on CHD (13; 14; 16), with limited evidence on stroke (15), particularly haemorrhagic stroke (17), and subclinical atherosclerosis (18; 19). The characteristically high rates of stroke, with a higher proportion of haemorrhagic stroke, in Chinese, compared with Western, populations (20) provides a valuable opportunity to examine the causal relevance of type 2 diabetes for CVD subtypes.

Using data from the prospective China Kadoorie Biobank (CKB) we aim to: (i) examine the association of genetically-predicted type 2 diabetes with different CVD and with subclinical

atherosclerosis; and (ii) compare the associations of genetically-predicted type 2 diabetes with different CVD in Chinese and European populations.

Research design and methods

Study population

Details of the CKB study design and population have been described previously (21). Briefly, 512,713 Chinese adults, aged 30 to 79 years at enrolment, were recruited between 2004 and 2008 from 10 diverse areas (5 urban, 5 rural) across China. All participants provided written consent prior to participation, including permission for follow-up. Ethics approval was obtained from Oxford University, the Chinese Centre for Disease Control and Prevention (CDC), and the ten study areas' local CDCs.

Data collection

Participants were interviewed by trained health workers using laptop-based questionnaires, collecting information on socio-demographic and lifestyle factors (eg, smoking, alcohol intake, educational attainment), medical history and current medication. Physical measurements were recorded (including blood pressure and anthropometry), using calibrated instruments and standard protocols. A 10 ml non-fasting venous blood sample was collected (with time since participants last ate recorded) for long-term storage and on-site testing of random plasma glucose (RPG) levels (SureStep Plus meter, LifeScan, Milpitas, CA, USA). Individuals with a RPG level ≥ 7.8 and < 11.1 mmol/L were invited to return for a fasting plasma glucose test the next day. Plasma concentrations of total-, LDL- and HDL-cholesterol and triglycerides were assayed (AU680 analyser, Beckman-Coulter; Wolfson Laboratory, CTSU, Oxford) among 18,256 participants (including 10,434 incident stroke and 1,287 incident CHD cases) included in a nested case-control study of CVD, of whom 17,948 also had genotyping data. A five-yearly resurvey of a 5% randomly-selected sample of surviving CKB participants was undertaken, collecting the same data as at baseline plus certain

enhancements. In the 2013-14 resurvey (n=24,822), carotid ultrasound measures (Panasonic CardioHealth Station), including carotid intima-media thickness (cIMT) and assessment for the presence of carotid artery plaque, were undertaken (22).

Follow-up for morbidity and mortality

The vital status of study participants was confirmed by active annual follow-up through local residential and administrative records, and by linkage to death registries based at China's Disease Surveillance Points (23). Cause of death information was supplemented by medical record review, and, for the small proportion of deaths (<5%) without recent prior medical attention, was determined through verbal autopsy. Information on disease diagnoses resulting in, and during, hospitalisations was obtained through linkage, via unique national identification number, to established disease registries (for CHD, stroke, diabetes and cancer), and to the national health insurance system (>98% coverage). All events were ICD-10 coded by trained staff blinded to baseline information. Participants were followed-up until 1 January 2017 (mean 9 years).

Diagnostic criteria for diabetes

Prevalent type 2 diabetes was defined as self-reported physician-diagnosed or screen-detected (no prior diabetes diagnosis with a plasma glucose concentration ≥ 7.8 mmol/L and fasting time ≥ 8 h, or a plasma glucose concentration ≥ 11.1 mmol/L and fasting time < 8 h, or a fasting plasma glucose concentration ≥ 7.0 mmol/L) diabetes at baseline (excluding individuals with possible type 1 diabetes, defined as diagnosis at < 30 years of age and using insulin [n=35]) (24). Incident type 2 diabetes included diabetes diagnoses (ICD-10 E11 to E14) recorded during follow-up in the disease surveillance system or health insurance databases or as underlying or contributing to death on death certificates among individuals without prevalent type 2 diabetes.

Diagnostic criteria for CVD

The primary disease endpoints for the present study were IS (ICD-10: I63, I69.3) (further classified into lacunar and non-lacunar), intracerebral haemorrhage (ICH) (ICD-10: I61, I69.1) and major coronary event (MCE) (non-fatal myocardial infarction [MI] [ICD-10 I21-I23] or fatal CHD [ICD-10: I20-I25]). Presence of carotid artery plaque was defined as focal thickening or protrusion from the artery wall into the lumen with cIMT >1.5 mm thickness (22; 25; 26). Additional analyses examined fatal total stroke (TS) (ICD-10: I60, I61, I63, I64) and cardiovascular mortality (ICD-10: I00-I25, I27-I88, I95-I99). By 1 January 2017, 37,289 (7.3%) participants had died and 4,875 (<1%) were lost to follow-up (CKB database version 13.0).

Genotyping and genetic instruments

A 384-single-nucleotide polymorphism (SNP) array was used to genotype 95,680 participants on the Illumina Golden Gate platform (SNP panel). This was custom-designed in October 2012, and included SNPs associated with CVD, their risk factors and related phenotypes. In addition, 96,330 participants were genotyped using a custom-designed 800K-SNP Affymetrix Axiom array and imputed to 1000 Genomes Phase III (GWAS panel). Case and non-case samples were genotyped in the same batches and assays were conducted blind to case status. After applying quality control criteria, 159,528 participants remained for inclusion in the current analyses (**Supplementary Figure 1**), including a subset of 24,519 participants genotyped using both arrays. Concordance for type 2 diabetes-related variants between the two arrays was high ($r \geq 0.9$); where discordant, SNP panel genotypes were used. Info scores for type 2 diabetes-related variants not directly genotyped on the GWAS panel ($n=7$) were high (>0.94) and estimated allele dosages were used for imputed SNPs. The total genotyped population included a population-based genotyped sample ($n=148,512$) randomly selected from the total CKB cohort and included in all genetic analyses, and 11,016 additional stroke or CHD cases included only in CVD outcome analyses.

59 type 2 diabetes risk variants identified in GWAS at the time of SNP panel design were included on both the SNP and GWAS panels, including 5, 15 and 36 originally reported among South

Asians, East Asians and Europeans, respectively. After exclusion of monomorphic variants (n=1), and variants with genotype calling failure (n=3), with parent-of-origin-specific effects (n=1), demonstrating heterogeneity in associations with type 2 diabetes between European and East Asian populations if first reported in Europeans (n=2), located on the X-chromosome (n=1), with low genotyping rate (n=1), or acting primarily through obesity (n=2), 48 independent variants remained for inclusion in the type 2 diabetes genetic risk score (GRS-T2D48) (**Supplementary Tables 1 and 2**). Additional analyses examined GRS comprising type 2 diabetes-associated variants with specific pathophysiological mechanisms: beta cell dysfunction (GRS-BC, 24 SNPs), insulin resistance (GRS-IR, 6 SNPs) or unclassified (GRS-Un, 18 SNPs) (27). Sensitivity analyses included: (i) analyses excluding SNPs associated with plasma lipids, stroke and CHD (**Supplementary Table 2**); (ii) analyses using internal weights calculated through 1000-fold cross validation; (iii) analyses restricted to the population-based genotyped sample; (iv) analyses using an 86 SNP GRS (GRS-T2D86) (comprising 86 of 101 SNPs associated with type 2 diabetes in GWAS studies by December 2016 selected using criteria described for GRS-T2D48) among individuals genotyped with the GWAS panel; (v) summary statistics-based analyses using SNP-type 2 diabetes effect estimates derived from trans-ethnic type 2 diabetes GWAS (28; 29) and SNP-CVD effect estimates derived from CKB; and (vi) analyses using only those SNPs associated with type 2 diabetes at genome-wide significance level.

Statistical analysis

Observational analyses

Prevalence and mean values of baseline characteristics were calculated by type 2 diabetes status, standardised by 5-year age group, sex and study area. Observational analyses excluded individuals with prior CVD (CHD, stroke or transient ischaemic attack; n= 23,129) or missing body mass index (BMI) (n=2). After applying these exclusions, 489,549 participants (200,118 men, 289,431 women) remained. Cox proportional hazards models, with time since entry into the study as the underlying

timescale, were used to estimate hazard ratios (HRs) of CVD for prevalent type 2 diabetes (n=26,381) versus not, stratified by age-at-risk, sex, study area, and adjusted for education, smoking, alcohol consumption, systolic blood pressure (SBP), physical activity and BMI.

Genetic analyses

In genetic analyses, type 2 diabetes was defined as combined prevalent and incident type 2 diabetes. Missing genotypes were imputed by assigning the participant's mean study area genotype. An unweighted GRS-T2D (GRS-T2D48) was developed by summing the number of type 2 diabetes risk-increasing alleles. A weighted GRS-T2D (GRS-T2D48w) was constructed by weighting SNPs by the natural logarithm of the per-allele odds ratio (OR) derived from trans-ethnic type 2 diabetes GWAS (28; 29), which represented the best-performing external weights (27).

An inverse-variance weighted two-stage regression approach, with weighted or unweighted GRS-T2D as the instrumental variable, was used to assess the causal role of genetically-predicted type 2 diabetes in CVD, subclinical atherosclerosis, and cardiometabolic risk factors in CKB (12). The associations between GRS-T2D and type 2 diabetes were examined using logistic regression adjusted for age, sex and study area. The associations of the resulting predicted values with CVD and with binary CVD risk factors were examined using logistic regression, adjusting for the same variables. Linear regression was applied to the second stage when testing associations with continuous traits. Further analyses additionally adjusted for known CVD risk factors (SBP and adiposity). To enable comparison with observational estimates, genetic estimates of the odds of CVD associated with type 2 diabetes were estimated using the formula $OR = 1 + \frac{1 - \exp(\beta)}{(\exp(\beta) - \exp(1)) \times A}$ where β is the regression coefficient of the GRS association with CVD as a function of the GRS association with type 2 diabetes, and A is the prevalence of type 2 diabetes in CKB (16). Heterogeneity between observational and genetic risk estimates was assessed using Cochran's Q test. Two-sample MR was used to estimate the associations of genetically-predicted type 2 diabetes

with risk of CVD in individuals of European ancestry using 1000 Genomes-based GWAS summary statistics for SNPs included in GRS-T2D86 obtained from DIAGRAM (26,676 type 2 diabetes cases and 132,532 controls) (30), CARDIoGRAMplusC4D (60,801 CHD cases and 123,504 controls) (31) and the International Stroke Genetics Consortium (12,389 IS cases and 62,004 controls; 1,545, ICH cases and 1,481 controls) (32-34). Inverse-variance weighted analysis was performed by regression of the SNP-CVD associations on the SNP-type 2 diabetes associations. Two-sample MR analysis was performed using the R TwoSampleMR package (35). Cochran's Q test was used to assess heterogeneity between associations in CKB and European populations. Additional sensitivity analyses, assessing the robustness of the two-sample MR results, included: (i) MR-Egger (36); (ii) weighted median MR (37); and (iii) weighted mode MR (38).

Analyses were conducted using SAS version 9.4 and R version 3.0.2.

Results

Characteristics of genotyped participants

Among the 148,512 participants (60,073 men, 88,439 women) included in the population-based genotyped sample, mean (SD) baseline age was 52.0 (10.7) years and 9.2% (n=13,713) had type 2 diabetes (8,886 prevalent and 4,827 new-onset during follow-up) (**Table 1**). Participants with type 2 diabetes were older, more likely to be residents of urban areas, and had higher levels of adiposity ($p<0.0001$) and blood pressure ($p<0.0001$), and higher plasma total cholesterol ($p=0.001$) and triglyceride ($p<0.0001$) concentrations, than those without type 2 diabetes. Individuals with type 2 diabetes were more likely to have prior CVD and a family history of diabetes or CVD ($p<0.0001$). The characteristics of genotyped participants were similar to those of the whole CKB cohort (**Supplementary Table 4**).

Observational associations of type 2 diabetes with CVD and subclinical atherosclerosis

During follow-up, 36,407 IS (including 4,562 lacunar IS), 8,487 ICH, 6,868 MCE and 11,917 cardiovascular deaths were recorded among 489,549 participants without prior CVD. Type 2 diabetes at baseline was associated with significantly higher risks of incident IS (HR=1.56, 95% CI 1.51, 1.61) and its subtypes, specifically non-lacunar (1.62, 95% CI 1.56, 1.67) and lacunar (1.18, 95% CI 1.07, 1.30) IS, ICH (1.38, 95% CI 1.28, 1.49), MCE (2.06, 95% CI 1.92, 2.20) and cardiovascular mortality (1.94, 95% CI 1.84, 2.05) (**Figure 1**). Type 2 diabetes at baseline was associated with higher risk of carotid artery plaque (OR=1.74, 95% CI 1.50, 2.02) and greater cIMT ($\beta=0.015$, 95% CI 0.009, 0.025 mm).

Genetic associations of individual variants and GRS-T2D with type 2 diabetes

Of the 48 SNPs included in GRS-T2D48, 14 were associated with type 2 diabetes at a genome-wide significance level ($p < 5 \times 10^{-8}$) in CKB, 35 showed statistically significant associations with type 2 diabetes after correction for multiple testing (using a false discovery rate method (39) with a cut-off of 0.05), and 47 showed directionally-consistent associations with type 2 diabetes. There was no evidence of heterogeneity between CKB and European GWAS studies (**Supplementary Table 1**). Both GRS-T2D48 (unweighted GRS-T2D) and GRS-T2D48w (externally-weighted GRS-T2D) were robustly associated with risk of type 2 diabetes ($p=8.48 \times 10^{-217}$ and $p=4.64 \times 10^{-295}$, respectively). Externally-weighted (28; 29) GRS-IR ($p=4.85 \times 10^{-12}$) and GRS-BC ($p=3.04 \times 10^{-235}$) were highly significantly associated with type 2 diabetes risk. GRS-T2D48w explained 1.4% of the type 2 diabetes liability-scale variance (using Nagelkerke's pseudo R^2 (40)) (F-statistic 212), indicating it was a strong instrument.

Genetic associations of GRS-T2D with CVD risk factors

In CKB, GRS-T2D48w was weakly positively associated with SBP ($\beta=0.33$ mmHg, 95% CI 0.02, 0.64 per 1-unit log-odds higher type 2 diabetes, $p=0.04$) (**Table 2**). It was inversely associated with general (BMI $\beta=-0.29$, 95% CI -0.34, -0.24, $p=4.55 \times 10^{-28}$; percentage body fat $\beta=-0.44$, 95% CI -0.54, -0.33, $p=1.72 \times 10^{-16}$) and central (waist circumference $\beta=-0.58$, 95% CI -0.73, -0.43,

$p=6.59\times 10^{-15}$) adiposity, but positively associated with waist circumference adjusted for BMI ($\beta=0.10$, 95% CI 0.03, 0.17, $p=3.98\times 10^{-3}$) and waist-to-hip ratio adjusted for BMI ($\beta=0.24$, 95% CI 0.16, 0.32, $p=1.20\times 10^{-9}$). GRS-T2D48w was not associated with other CVD risk factors.

Genetic associations of individual variants and GRS-T2D with CVD and subclinical atherosclerosis

There was modest genetic correlation between type 2 diabetes and ASCVD in CKB (**Supplementary Table 5**). GRS-T2D48w was associated with greater cIMT ($\beta=0.011$, 95% CI 0.006, 0.016 mm per 1-unit higher log-odds of type 2 diabetes, $p=1.97\times 10^{-5}$) and with the presence of carotid plaque (OR=1.17, 95% CI 1.05, 1.29, $p=3.74\times 10^{-3}$) (**Table 2**). Likewise, GRS-T2D48w was associated with an elevated risk of MCE (1.12, 95% CI 1.02, 1.23; $n=5,081$), IS (1.08, 95% CI 1.02, 1.14; $n=17,097$), non-lacunar (1.09, 95% CI 1.03-1.16; $n=13,924$) but not lacunar (1.03, 95% CI 0.91, 1.16; $n=3,173$) IS, fatal TS (1.01, 95% CI 0.91, 1.11; $n=4,319$) and cardiovascular mortality (1.03, 95% CI 0.96, 1.11; $n=9,006$) (**Supplementary Table 6**). There was no statistically significant association of GRS-T2D48w with risk of ICH (1.01, 95% CI 0.94-1.10; $n=6,973$). Similar effect estimates were observed in genetic analyses adjusting for known CVD risk factors (BMI, waist circumference, body fat percentage and SBP) (**Supplementary Table 6**). There was a strong, highly significant association of genetically-predicted type 2 diabetes with diabetic microvascular diseases (retinopathy, nephropathy, neuropathy) (OR=2.80, 95% CI 2.33-3.36; $n=1,140$), included as a positive control. To enable comparison with observational estimates, genetic estimates of the odds of CVD associated with type 2 diabetes, compared with no type 2 diabetes, were estimated (**Figure 1**); there was no evidence of heterogeneity between observational and genetic effect estimates (p for heterogeneity ≥ 0.3).

Sensitivity analyses using unweighted or internally-weighted GRS-T2D, excluding variants with documented associations with lipids or CVD, or limited to the population-based sample, did not materially alter the associations (**Supplementary Table 7**). Similar results were found using weighted and unweighted GRS-T2D86 (86 SNP GRS-T2D) and a summary statistics-based two-

sample approach (**Supplementary Tables 8 and 10**). Estimates of the associations of insulin resistance-related variants (GRS-IR) were non-significantly stronger than those of beta-cell dysfunction-related variants (GRS-BC) for any and non-lacunar IS, ICH, MCE, presence of carotid plaque and cIMT ($p > 0.08$) (**Supplementary Table 11**).

Comparison of associations of genetically predicted T2D with CVD among Chinese and European populations

In two-sample MR analyses, based on summary statistics from European ancestry population GWAS consortia (30-34), each 1-unit higher log-odds of genetically-predicted type 2 diabetes was associated with 12% (OR=1.12, 95%CI 1.03, 1.22, $p=7.90 \times 10^{-3}$), 24% (1.24, 95% CI 1.07, 1.44, $p=4.53 \times 10^{-3}$) and 9% (1.09, 95% CI 1.04, 1.15, $p=9.32 \times 10^{-4}$) higher odds of IS, large artery stroke and CHD, respectively (**Table 3, Supplementary Table 12**). There was no significant association with small vessel stroke (1.15, 95% CI 0.97, 1.35, $p=0.11$) or ICH (1.14, 95% CI 0.93, 1.40, $p=0.20$), but risk estimates were imprecise. Sensitivity analyses using weighted median, weighted mode and MR-Egger approaches showed similar findings, as did analyses based on GRS-T2D86, and there was no evidence of unbalanced pleiotropy (p for pleiotropy from MR-Egger ≥ 0.31) (**Supplementary Figure 2**). There were no statistically significant differences between Chinese and European population MR effect estimates for IS, CHD or ICH (p for heterogeneity 0.28, 0.90 and 0.21, respectively) (**Table 3**).

Discussion

This large study in a Chinese population provides new evidence for a robust association of genetic predisposition to type 2 diabetes with subclinical and clinical ASCVD, including coronary and cerebral manifestations. This is consistent with a causal role for type 2 diabetes in ASCVD, although shared heritability and unidentified pleiotropic effects of type 2 diabetes-associated variants may also contribute to the identified associations. There was no significant association

between genetic predisposition to type 2 diabetes and risk of ICH, but statistical power to reliably confirm (or refute) any modest association was inadequate (**Supplementary Table 14**).

Large prospective observational studies (3; 4), including CKB (2), have reported 2- to 4-fold higher risks of CHD in diabetes. Two previous MR analyses, using summary level data from the same or related GWAS consortia, have provided evidence supporting a causal role of type 2 diabetes in CHD (13; 16). The present study provides further strong evidence for a causal role of type 2 diabetes in CHD in a Chinese population. Few previous studies have examined the genetic association of type 2 diabetes with stroke (15; 17), and only one has investigated IS (15). Based on European population GWAS summary statistics, and including a similar number of stroke cases as the present study (18,476 and 17,097 events, respectively), there was an elevated risk of IS associated with genetically-predicted type 2 diabetes (OR 1.12, 95% CI 1.07, 1.17 per 1-unit higher log odds of type 2 diabetes) (15). This is broadly consistent with effect estimates reported in observational analyses (3; 4), including in CKB, and with associations of genetically-predicted type 2 diabetes in CKB.

The associations of genetic predisposition to type 2 diabetes with CHD and IS provide evidence in support of a causal role of pathways leading to type 2 diabetes, or type 2 diabetes itself, in ASCVD. In the present study, in general, we found non-significantly stronger associations of genetically-predicted, compared with observed, type 2 diabetes, possibly reflecting the lifelong influence of genetic variants. Previous observational (5-7) and genetic (18; 19) epidemiological studies examining the association of type 2 diabetes with subclinical atherosclerosis, defined in various ways, have reported conflicting findings. A study, including ~12,000 individuals from the US, found no significant effect of a 62-SNP GRS-T2D on various measures of subclinical atherosclerosis (19). In contrast, in a population-based study of ~11,000 Chinese adults, a 34-SNP GRS-T2D was associated with 24% (95% CI 6%, 47%) higher risk of increased arterial stiffness (18). These conflicting findings may reflect differences in subclinical atherosclerosis assessment

methods, inadequate statistical power, or differences between ancestries. CKB included approximately the same number of participants as previous studies combined, and provides the strongest evidence to-date of a causal role of type 2 diabetes for subclinical atherosclerosis.

Previous observational study findings on the association of type 2 diabetes with risk of IS subtypes have been conflicting (41; 42). One European population genetic study reported 15% (95% CI 4%, 25%) higher odds of imaging-confirmed lacunar IS (n=2,191) associated with genetically-predicted type 2 diabetes (17), whilst another, using summary estimates from the same type 2 diabetes and, for a proportion of events, stroke GWAS consortia, found 21% (95% CI 10%, 33%) higher odds of imaging-confirmed small vessel (equivalent to lacunar (43)) IS (15). We found a weaker, non-significant, association of genetically-predicted type 2 diabetes with lacunar IS (1.03). Widespread use of CT and MR imaging in China, often resulting in detection of lacunar infarcts without apparent neurological deficit (44), may partly explain this difference. Moreover, although 18.6% of IS included in the present genetic analyses were lacunar IS, there was still limited statistical power (0.08) to detect a modest association (**Supplementary Table 14**). The estimated association of genetically-predicted type 2 diabetes with non-lacunar IS in CKB (1.09) lies between previous estimates of the association of genetically-predicted type 2 diabetes with large vessel (atherosclerotic) (1.28, 95% CI 1.16, 1.40) and cardioembolic (1.06, 95% CI 0.97, 1.15) IS (15), the two major non-lacunar IS subtypes.

Large prospective observational studies have reported 30-60% higher risks of ICH in diabetes (3; 4). With more ICH cases than previous studies combined, CKB provides the most robust observational evidence to-date, showing 40% higher risk of ICH in type 2 diabetes. However, previous MR analyses, including approximately 2,200 ICH cases from multiple GWAS, reported no significant association with genetically-predicted type 2 diabetes (OR 1.07, 95% CI 0.95, 1.20 per 1-unit higher log-odds of type 2 diabetes) (17). Likewise, the present study found no clear evidence of a causal association between type 2 diabetes and ICH, suggesting the observational association

might be due chiefly to residual confounding. However, there was limited power to detect an association (0.17), and these data do not completely rule out a modest, causal effect.

We identified inverse associations of genetic predisposition to type 2 diabetes with measures of general and central adiposity. Several type 2 diabetes risk-increasing variants have been associated with lower adiposity (28; 45; 46), potentially reflecting the associations of insulin resistance with higher risk of type 2 diabetes and propensity to visceral, rather than peripheral, adiposity (47). However, caution is required in interpreting the association with some adiposity measures (eg, BMI-adjusted waist-to-hip ratio), given the risk of collider bias (12). Additional adjustment for adiposity (and SBP) and exclusion of SNPs with known associations with lipids and CVD, did not substantially alter the risk estimates, suggesting these factors do not explain the presented findings. However, use of measured phenotypes, rather than genetic associations, may under-estimate their influence.

The strengths of the present study are several fold. In contrast with most previous studies (13; 15-17), the present analyses were based on individual participant data from a single population. Moreover, this is the first study to examine the association of genetically-predicted type 2 diabetes with CVD in a non-European ancestry population. CKB includes large numbers of well-characterised stroke subtypes (~90% of stroke cases have been confirmed by neuroimaging), and stroke adjudication shows high accuracy of diagnoses (~90% verified through medical record review). Utilisation of multiple data sources and outcome adjudication for phenotyping of incident CVD reduced potential limitations inherent in the use of ICD-10 coding (e.g., inadequate granularity of data, inconsistent or incomplete coding), whilst the passive follow-up approach reduced potential reporting, non-response and loss to follow-up biases. Furthermore, as well as enabling assessment of pleiotropic effects of type 2 diabetes-associated variants, extensive phenotyping of CKB participants provided mechanistic insights through investigation of subclinical atherosclerosis. Finally, the large sample size and relatively high stroke incidence facilitated precise

estimates of genetic associations of type 2 diabetes with major CVD types. However, the study also has limitations, including inadequate statistical power to reliably assess the associations of genetically-predicted type 2 diabetes with ICH and lacunar IS (**Supplementary Table 14**). Furthermore, the GRS-T2D may have unidentified pleiotropic effects. However, inclusion of SNPs acting through different pathways should limit the impact of this on causal inferences. Type 2 diabetes genetic risk prediction could be impaired by limited portability of GRS-T2D across diverse populations (48), although this is less likely since the GRS-T2D was based on GWAS-identified SNPs, rather than polygenetic score-based, and single variant effect sizes were consistent across Chinese and European populations (27). Finally, a proportion of diabetes cases will have remained undiagnosed in the study population due to the methods used to identify undiagnosed diabetes at baseline and incident diabetes; this would likely underestimate type 2 diabetes-associated CVD risks in the present study.

In summary, this large study of Chinese adults provides new evidence supporting a causal role for type 2 diabetes in clinical and subclinical ASCVD, consistent with observational epidemiological findings, and highlighting the importance of prevention and appropriate management of type 2 diabetes for reducing the burden of ASCVD. Genetic predisposition to type 2 diabetes was not strongly associated with risk of lacunar IS and ICH, in contrast to observational findings. However, further larger studies examining the associations of genetically-predicted type 2 diabetes with stroke subtypes are needed to clarify these findings.

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Conflicts of interest: We declare that we have no conflict of interest.

Guarantor statement: FB, ZC, WG, and LL are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Data and resource availability: The data that support the findings of this study are from the China Kadoorie Biobank study, whose authors may be contacted at ckbiobank@ndph.ox.ac.uk, but restrictions apply to the availability of these data. No applicable resources were generated or analysed during the current study.

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Table 1. Baseline characteristics of genotyped participants by type 2 diabetes status

Characteristics*	Type 2 diabetes			Total (n= 148,512)
	None (n= 134,799)	Prevalent† (n= 8,886)	Incident (n= 4,827)	
Age and socioeconomic factors				
Men, %	40.8	38.4	38.4	40.5
Age, mean (SD), years	51.5 (10.6)	57.7 (9.5)	54.8 (9.8)	52.0 (10.7)
Living in urban area, %	42.2	55.8	42.6	43.2
Lifestyle factors				
≤6 years of education‡, %	51.4	51.8	51.9	51.4
Annual household income ≤10,000 RMB§, %	29.7	29.2	28.5	29.6
Ever regular smoker, %				
Men	74.5	74.7	74.2	74.6
Women	3.3	3.7	3.7	3.2
Ever regular alcohol drinker, %				
Men	42.7	44.2	44.0	42.7
Women	3.0	2.7	2.2	2.9
Physical activity, mean (SD), MET-h/d	21.3 (14.1)	18.9 (11.8)	20.8 (13.8)	21.2 (14.0)
Physical and blood-based measurements, mean (SD)				
Standing Height¶, cm	158.7 (8.2)	158.8 (8.4)	158.8 (8.3)	158.7 (8.2)
BMI, kg/m ²	23.6 (3.3)	25.0 (3.6)	25.7 (3.7)	23.7 (3.4)
Waist circumference, cm	79.7 (9.6)	84.9 (10.1)	85.6 (10.2)	80.2 (9.8)
Hip circumference, cm	90.7 (6.8)	92.4 (7.8)	93.6 (7.4)	90.9 (7.0)
Waist adjusted for hip, cm	79.9 (6.2)	83.3 (6.4)	82.8 (6.3)	80.2 (6.3)
Waist-to-hip ratio	0.88 (0.07)	0.92 (0.07)	0.91 (0.07)	0.88 (0.07)
Percent body fat, %	27.8 (8.4)	30.5 (8.7)	31.9 (8.8)	28.1 (8.5)
Systolic blood pressure, mmHg	130.7 (20.9)	138.7 (22.5)	136.8 (22.0)	131.4 (21.3)
Diastolic blood pressure, mmHg	77.7 (11.1)	80.6 (11.4)	80.8 (11.3)	77.9 (11.2)
Random plasma glucose, mmol/L	5.6 (1.1)	12.6 (5.6)	6.4 (1.4)	6.1 (2.4)
Total cholesterol#, mmol/L	4.6 (0.9)	4.6 (1.1)	4.2 (1.1)	4.7 (1.0)
Triglycerides#, mmol/L	1.9 (1.4)	2.7 (2.3)	2.3 (2.0)	2.0 (1.6)
LDL-C#, mmol/L	2.4 (0.7)	2.4 (0.7)	2.1 (0.7)	2.4 (0.7)
HDL-C#, mmol/L	1.3 (0.3)	1.1 (0.3)	1.0 (0.3)	1.2 (0.3)
Personal medical history, %				
Diabetes		45.7		3.3
Cardiovascular disease**	4.3	7.6	6.6	4.7
Family history, %				
Diabetes	6.3	18.6	12.2	7.2
Cardiovascular disease**	20.5	22.0	22.9	20.6

*Standardised to age, sex and study area structure of the study population. *p*-values for differences between participants with none, prevalent and incident type 2 diabetes <0.005, unless otherwise indicated

†Self - reported or screen - detected type 2 diabetes at baseline

‡*p*=0.6; §*p*=0.1; ||*p*=0.04; ¶*p*=0.4

#Data available for 8,814 participants

**Coronary heart disease, stroke or transient ischaemic attack

BMI: body mass index; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; MET h/d: metabolic equivalent of task hours per day

Table 2. Association of type 2 diabetes genetic risk score* with cardiovascular risk factors

Outcome	Number of participants	Estimate (95% CI)†	P
Binary traits, cases vs. controls			
Ever regular smoker	47,702 vs. 100,810	1.02 (0.97, 1.08)	0.43
Ever regular alcohol drinker	28,211 vs. 120,301	0.97 (0.93, 1.02)	0.29
≤6 years of education	76,308 vs. 72,204	0.99 (0.96, 1.03)	0.77
Presence of carotid artery plaque‡	6,819 vs. 15,251	1.17 (1.05, 1.29)	3.74×10 ⁻³
Continuous traits			
Physical activity, MET h/d	148,512	-0.04 (-0.23, 0.15)	0.67
Standing height, cm	148,512	0.02 (-0.07, 0.10)	0.70
BMI, kg/m ²	148,511	-0.29 (-0.34, -0.24)	4.55×10 ⁻²⁸
Waist circumference, cm	148,512	-0.58 (-0.73, -0.43)	6.59×10 ⁻¹⁵
WCadjBMI, cm	148,511	0.10 (0.03, 0.17)	3.98×10 ⁻³
Hip circumference, cm	148,512	-0.54 (-0.64, -0.45)	2.26×10 ⁻²⁸
Waist-to-hip ratio (×100)	148,511	-0.08 (-0.18, 0.03)	0.16
WHRadjBMI (×100)	148,512	0.24 (0.16, 0.32)	1.20×10 ⁻⁹
Percentage body fat, %	148,429	-0.44 (-0.54, -0.33)	1.72×10 ⁻¹⁶
Systolic blood pressure, mmHg	148,512	0.33 (0.02, 0.64)	0.04
Diastolic blood pressure, mmHg	148,512	-0.15 (-0.32, 0.03)	0.10
Triglycerides, mmol/L	8,814	0.07 (-0.03, 0.17)	0.17
LDL-C, mmol/L	8,814	0.03 (-0.01, 0.08)	0.12
HDL-C, mmol/L	8,814	0.00 (-0.02, 0.02)	0.78
cIMT§, mm	21,971	0.011 (0.006, 0.016)	1.97×10 ⁻⁵

*Conducted using externally-weighted GRS based on 48 type 2 diabetes related SNPs (GRS-T2D48) in population-based subset of genotyped participants

†Odds ratio for binary traits and beta coefficient for continuous traits (in native units) expressed per 1-unit increase in log-odds of type 2 diabetes risk.

Causal estimates adjusted for age, sex and study area.

‡Observational association of type 2 diabetes with presence of carotid artery plaque: 1.74 (95% CI 1.50, 2.02), $p=2.5\times 10^{-13}$, cases=9,380, controls=14,800

§Observational association of type 2 diabetes with cIMT: 0.015 mm (95% CI 0.009, 0.025 mm), $p=1.51\times 10^{-25}$, n=24,180

Observational estimates stratified by age-at-risk, sex and study area, and adjusted for education, smoking, alcohol consumption, physical activity, systolic blood pressure and BMI

BMI: body mass index; cIMT: carotid intima-media thickness; HDL-C: HDL-cholesterol; LDL-C: LDL-cholesterol; MET h/d: metabolic equivalent of task hours per day; WCadjBMI: waist circumference adjusted for BMI; WHRadjBMI: waist-to-hip ratio adjusted for BMI

Table 3. Association of genetically-predicted type 2 diabetes with major cardiovascular diseases in Chinese and European populations

Outcome	Chinese population			European population			<i>P</i> for heterogeneity
	Cases/ Controls	OR (95% CI)*	<i>P</i>	Cases/ Controls	OR (95% CI)*	<i>P</i>	
Ischaemic stroke	17,097/ 129,684	1.08 (1.02, 1.14)	4.62×10 ⁻³	12,389/ 62,004	1.12 (1.03, 1.22)	7.90×10 ⁻³	0.28
Intracerebral haemorrhage	6,973/ 129,684	1.01 (0.94, 1.10)	0.76	1,545/ 1,481	1.14 (0.93, 1.40)	0.20	0.21
Coronary heart disease	5,081/ 129,684	1.12 (1.02, 1.23)	0.01	60,801/ 123,504	1.09 (1.04, 1.15)	9.32×10 ⁻⁴	0.90

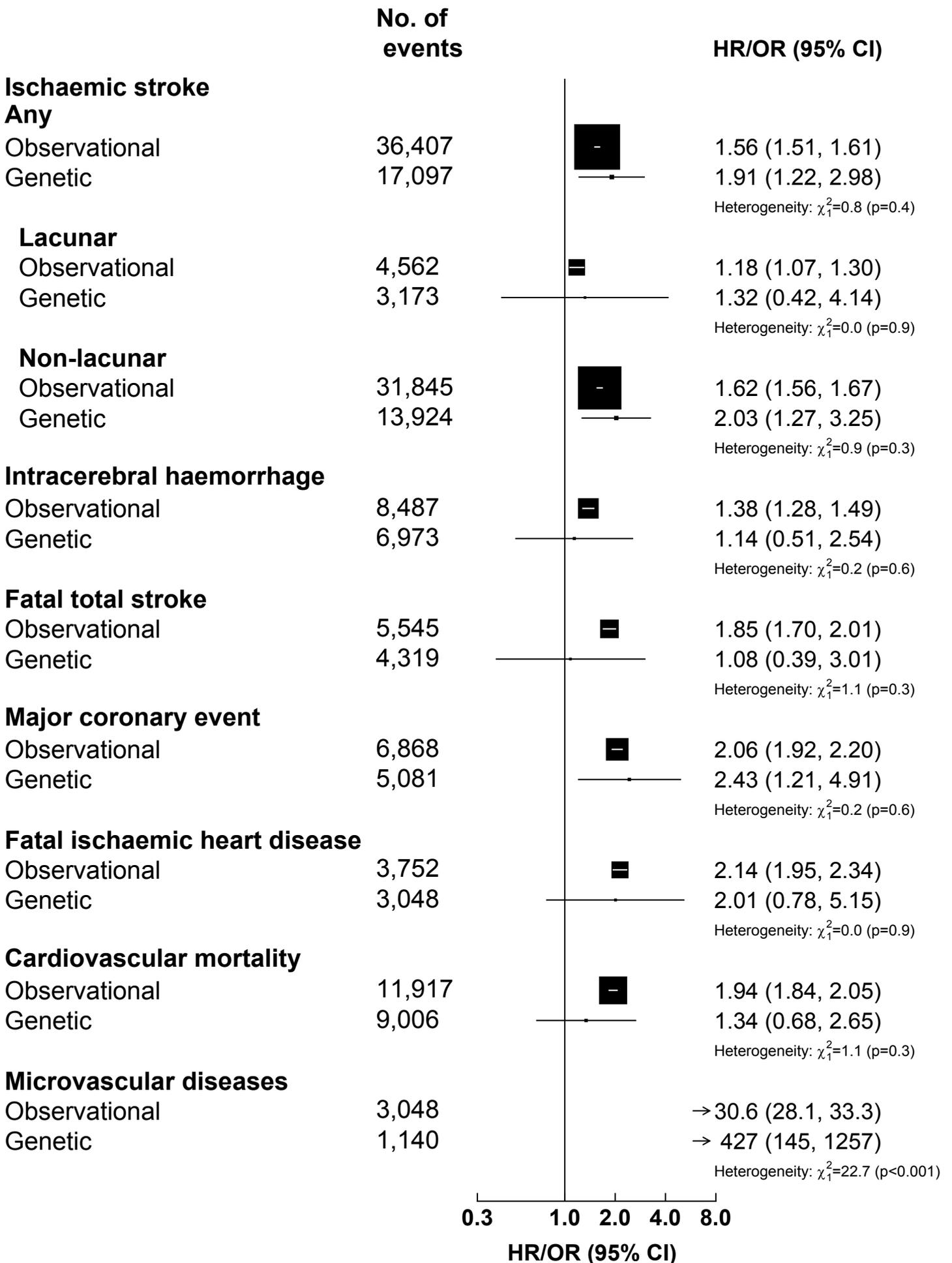
*Expressed as the relative risk per 1-unit higher log-odds of type 2 diabetes risk adjusted for age, sex and study area
OR: odds ratio

Figure legends

Figure 1. Observational and genetic associations of type 2 diabetes with risk of cardiovascular and microvascular diseases

Risk estimates expressed as the relative risk of the outcomes among individuals with type 2 diabetes when compared with individuals without type 2 diabetes. Microvascular diseases defined as diabetic retinopathy (ICD-10 E10.3, E11.3, E12.3, E13.3, E14.3, H36.0), nephropathy (ICD-10 E10.2, E11.2, E12.2, E13.2, E14.2, N08.3) or neuropathy (ICD-10 E10.4, E11.4, E12.4, E13.4, E14.4, G73.0, G99.0, G59.0, G63.2, M14.6). Observational analyses, based on 489,549 participants, stratified by age-at-risk, sex and study area and adjusted for education, smoking, alcohol consumption, physical activity, BMI and systolic blood pressure. Genetic analyses, using externally-weighted GRS based on 48 type 2 diabetes related SNPs (T2D-GRS48w) among 164,815 participants, adjusted for age, sex and study area. Squares represent hazard ratios (HR) or odds ratios (OR), with area inversely proportional to the variance of the log HR/OR. Horizontal lines represent corresponding 95% confidence intervals. Non-fatal MI: observational risk estimate 1.97 (95% CI 1.78,2.18), genetic risk estimate 2.72 (95% CI 0.99, 7.49), *p* for heterogeneity 0.53.

Figure 1. Observational and genetic associations of type 2 diabetes with risk of cardiovascular and microvascular diseases



Online supplemental materials

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Page 25. Supplementary Figure 3. Effect size estimates for type 2 diabetes in China Kadoorie Biobank and trans-ethnic GWAS

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Supplementary Table 1. Allelic effects in European, multi-ethnic and Chinese populations

Nearby Genes	SNP	Chr	BP	R	O	RAF		EUR		TransEthnic		CKB		P_{het} CKB vs. EUR	First reported population	References
						EUR	CKB	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P			
<i>MACF1</i>	rs2296172	1	39835817	G	A	0.19	0.17	1.05 (1.04, 1.07)	2.28×10 ^{-4*}	1.04 (1.02, 1.06)	9.40×10 ^{-3†}	1.06 (1.02, 1.10)	2.31×10 ⁻³	0.73	EU	Albrechtsen et al. (Diabetologia 2013)
<i>FAF1</i>	rs17106184	1	50909985	G	A	0.90	0.90	1.10 (1.08, 1.12)	4.69×10 ^{-6*}	1.11 (1.09, 1.13)	1.90×10 ^{-6†}	1.03 (0.97, 1.08)	0.35	0.04	Multi-ethnic	Mahajan et al. (Nat Genet 2014)
<i>NOTCH2</i>	rs10923931	1	120517959	T	G	0.03	0.03	1.08 (1.06, 1.10)	1.30×10^{-5*}	1.05 (1.03, 1.07)	0.017†	1.11 (1.04, 1.18)	2.72×10⁻³	0.57	EU	Zeggini et al. (Nat Genet 2008)
<i>ATP8B2</i>	rs67156297	1	154336716	A	G	0.25	0.09	1.04 (1.02, 1.06)	0.91§	1.02 (1.00, 1.04)	0.27†	1.02 (0.96, 1.07)	0.53	0.54	EA	Imamura, et al. (Nat Commun 2016)
<i>PROX1</i>	rs340874	1	214159256	C	T	0.39	0.39	1.07 (1.05, 1.08)	1.05×10^{-7*}	1.07 (1.06, 1.09)	1.20×10^{-6†}	1.05 (1.03, 1.08)	2.69×10⁻⁵	0.49	EU	Morris et al. (Nat Genet 2012)
<i>GCKR</i>	rs780094	2	27741237	C	T	0.49	0.49	1.06 (1.05, 1.07)	5.37×10^{-7*}	1.06 (1.05, 1.07)	1.00×10^{-5†}	1.05 (1.03, 1.08)	2.75×10⁻⁵	0.61	EU	Dupuis et al. (Nat Genet 2010)
<i>THADA</i>	rs7578597	2	43732823	T	C	0.99	0.99	1.13 (1.11, 1.16)	2.00×10^{-9*}	1.07 (1.04, 1.10)	5.90×10^{-3†}	1.09 (0.94, 1.26)	0.25	0.59	EU	Morris et al. (Nat Genet 2012)
<i>ASB3</i>	rs9309245	2	53397048	G	C	0.35	0.19	1.01 (1.00, 1.03)	0.50§	1.01 (1.00, 1.02)	0.36†	0.99 (0.96, 1.03)	0.76	0.52	EA	Imamura, et al. (Nat Commun 2016)
<i>CCDC85A</i>	rs1116357	2	57287411	G	A	0.53	0.26	1.01 (1.00, 1.02)	0.47§	1.02 (1.01, 1.03)	0.11†	1.04 (1.00, 1.08)	0.03	0.21	EA	Imamura, et al. (Nat Commun 2016)
<i>BCL11A</i>	rs243021	2	60584819	A	G	0.67	0.67	1.09 (1.07, 1.11)	5.30×10⁻⁶§	1.07 (1.06, 1.08)	1.40×10^{-7†}	1.06 (1.04, 1.09)	3.48×10⁻⁶	0.27	EU	Morris et al. (Nat Genet 2012)
<i>TMEM163</i>	rs998451	2	135429288	G	A	0.66	1.00	1.02 (1.01, 1.03)	0.12*	1.01 (0.99, 1.03)	0.60†	-	-	-	SA	Tabassum R et al (Diabetes 2013)
<i>RBMS1</i>	rs7593730	2	161171454	C	T	0.84	0.84	1.11 (1.09, 1.13)	1.50×10 ⁻⁶ §	1.06 (1.04, 1.08)	4.70×10 ^{-4†}	1.01 (0.98, 1.04)	0.62	4.31×10 ⁻⁴	EU	Qi et al. (Hum Mol Genet 2010)
<i>GRB14</i>	rs3923113	2	165501849	A	C	0.87	0.87	1.07 (1.06, 1.09)	3.28×10^{-8*}	1.08 (1.06, 1.10)	1.50×10^{-6†}	1.01 (0.98, 1.05)	0.47	0.01	SA	Kooner et al. (Nat Genet 2011)
<i>IRS1</i>	rs2943641	2	227093745	C	T	0.93	0.92	1.09 (1.08, 1.11)	2.93×10^{-12*}	1.09 (1.07, 1.11)	2.60×10^{-9†}	1.04 (0.99, 1.09)	0.11	0.06	EU	Morris et al. (Nat Genet 2012)
<i>DNER</i>	rs1861612	2	230522398	A	G	0.55	0.47	1.01 (0.99, 1.03)	0.53	1.01 (1.00, 1.02)	0.33†	1.01 (0.98, 1.04)	0.47	0.96	AA	Hanson RL et al. (Diabetes 2013)
<i>PPARG</i>	rs1801282	3	12393125	C	G	0.95	0.95	1.13 (1.11, 1.15)	1.05×10^{-12*}	1.14 (1.12, 1.16)	5.70×10^{-10†}	1.08 (1.02, 1.14)	8.36×10⁻³	0.13	EU	Voight et al. (Nat Genet 2010); Morris et al. (Nat Genet 2012)
<i>UBE2E2</i>	rs6780569	3	23198484	G	A	0.80	0.80	1.09 (1.06, 1.12)	5.30×10⁻³§	1.10 (1.08, 1.12)	1.10×10^{-8†}	1.10 (1.07, 1.13)	1.35×10⁻⁹	0.81	EA	Yamauchi et al (Nat Genet 2010); Morris et al. (Nat Genet 2012)
<i>PSMD6</i>	rs831571	3	64048297	C	T	0.63	0.63	1.03 (1.01, 1.05)	0.16§	1.05 (1.04, 1.06)	3.70×10^{-4†}	1.07 (1.04, 1.10)	9.27×10⁻⁸	0.12	EA	Cho YS et al. (Nat Genet 2011) Voight et al. (Nat Genet 2010); Morris et al. (Nat Genet 2012)
<i>ADAMTS9</i>	rs4607103	3	64711904	C	T	0.64	0.64	1.08 (1.06, 1.09)	2.93×10^{-8*}	1.04 (1.03, 1.05)	2.10×10^{-3†}	1.02 (0.99, 1.04)	0.18	2.05×10⁻³	EU	Voight et al. (Nat Genet 2010); Morris et al. (Nat Genet 2012)
<i>ADCY5</i>	rs11708067	3	123065778	A	G	1.00	1.00	1.11 (1.10, 1.13)	7.19×10^{-14*}	1.10 (1.08, 1.12)	1.40×10^{-8†}	1.38 (1.08, 1.75)	9.30×10⁻³	0.09	EU	Morris et al. (Nat Genet 2012)
<i>IGF2BP2</i>	rs1470579	3	185529080	C	A	0.26	0.26	1.12 (1.10, 1.14)	7.50×10⁻¹¹§	1.13 (1.12, 1.14)	5.40×10^{-22†}	1.12 (1.09, 1.15)	1.16×10⁻¹⁵	0.86	EU	Morris et al. (Nat Genet 2012)
<i>ST6GAL1</i>	rs16861329	3	186666461	C	T	0.81	0.81	1.03 (1.00, 1.07)	0.39§	1.09 (1.07, 1.11)	8.50×10^{-6†}	1.04 (1.01, 1.07)	0.01	0.80	SA	Kooner et al. (Nat Genet 2011)
<i>LPP</i>	rs6808574	3	187740523	C	T	0.61	0.99	1.07 (1.05, 1.08)	1.40×10 ^{-6*}	1.08 (1.06, 1.10)	4.30×10 ^{-6†}	-	-	-	Multi-ethnic	Mahajan et al. (Nat Genet 2014)
<i>MAEA</i>	rs6815464	4	1309901	C	G	0.58	0.58	1.07 (1.04, 1.11)	0.03*	1.08 (1.06, 1.10)	8.20×10^{-5†}	1.08 (1.06, 1.11)	2.25×10⁻¹¹	0.73	EA	Cho YS et al. (Nat Genet 2011)
<i>WFS1</i>	rs4458523	4	6289986	G	T	0.63	0.94	1.10 (1.09, 1.11)	2.02×10 ^{-15*}	1.09 (1.07, 1.11)	2.10×10 ^{-9†}	1.12 (1.05, 1.20)	7.53×10 ⁻⁴	0.55	EU	Morris et al. (Nat Genet 2012)
<i>TMEM154</i>	rs6813195	4	153520475	C	T	0.71	0.55	1.07 (1.06, 1.09)	5.26×10 ^{-8*}	1.08 (1.07, 1.09)	4.10×10 ^{-9†}	1.07 (1.04, 1.10)	1.53×10 ⁻⁵	0.92	Multi-ethnic	Mahajan et al. (Nat Genet 2014)
<i>ARL15</i>	rs702634	5	53271420	A	G	0.69	0.88	1.06 (1.04, 1.07)	8.48×10 ^{-6*}	1.08 (1.06, 1.10)	3.40×10 ^{-7†}	1.09 (1.04, 1.14)	5.10×10 ⁻⁴	0.30	Multi-ethnic	Mahajan et al. (Nat Genet 2014)
<i>ANKRD55</i>	rs459193	5	55806751	G	A	0.71	0.52	1.08 (1.07, 1.10)	5.99×10 ^{-9*}	1.05 (1.03, 1.07)	8.90×10 ^{-4†}	1.08 (1.04, 1.11)	2.00×10 ⁻⁶	0.87	EU	Morris et al. (Nat Genet 2012)
<i>ZBED3</i>	rs4457053	5	76424949	G	A	0.05	0.05	1.09 (1.08, 1.11)	1.76×10^{-10*}	1.10 (1.07, 1.13)	3.60×10^{-5†}	1.11 (1.06, 1.17)	6.13×10⁻⁵	0.57	EU	Morris et al. (Nat Genet 2012)
<i>PAM</i>	rs35658696	5	102338811	G	A	0.04	0.00	1.23 (1.19, 1.27)	5.70×10 ⁻¹⁰	-	-	-	-	-	EU	Steinthorsdottir V et al. (Nat Genet 2014)
<i>SSR1/RREB1</i>	rs9505118	6	7290437	A	G	0.58	0.58	1.06 (1.05, 1.08)	3.43×10 ^{-7*}	1.06 (1.05, 1.07)	1.90×10 ^{-6†}	1.00 (0.97, 1.03)	0.94	1.75×10 ⁻³	Multi-ethnic	Mahajan et al. (Nat Genet 2014)
<i>CDKAL1</i>	rs7754840	6	20661250	C	G	0.41	0.41	1.13 (1.12, 1.15)	3.99×10^{-25*}	1.15 (1.14, 1.17)	1.20×10^{-26†}	1.18 (1.15, 1.21)	4.31×10⁻⁴⁰	0.03	EU	Voight et al. (Nat Genet 2010); Morris et al. (Nat Genet 2012)
<i>POU5F1/TCF19</i>	rs3132524	6	31136714	C	T	0.78	0.69	1.08 (1.06, 1.10)	4.40×10 ⁻⁵ §	1.07 (1.06, 1.08)	2.50×10 ^{-7†}	1.03 (1.00, 1.07)	0.05	0.08	Multi-ethnic	Mahajan et al. (Nat Genet 2014)
<i>HLA-B</i>	rs2244020	6	31347451	G	A	0.41	0.49	1.07 (1.05, 1.09)	3.60×10 ⁻⁴ §	1.04 (1.02, 1.06)	7.40×10 ^{-3†}	1.01 (0.98, 1.04)	0.73	0.01	AA	Ng M et al. (PLoS Gen 2014)
<i>ZFAND3</i>	rs9470794	6	38106844	C	T	0.32	0.32	0.99 (0.95, 1.03)	0.80§	1.06 (1.04, 1.08)	3.60×10^{-3†}	1.01 (0.99, 1.04)	0.27	0.55	EA	Cho YS et al. (Nat Genet 2011)
<i>KCNK16</i>	rs1535500	6	39284050	T	G	0.49	0.46	1.01 (1.00, 1.02)	0.47§	1.05 (1.04, 1.06)	8.60×10 ^{-5†}	1.04 (1.01, 1.07)	0.01	0.18	EA	Cho YS et al. (Nat Genet 2011)
<i>CENPW</i>	rs11759026	6	126792095	G	A	0.25	0.47	1.12 (1.09, 1.15)	6.45×10 ⁻⁵ ‡	1.12 (1.09, 1.15)	6.45×10 ⁻⁵ ‡	1.06 (1.03, 1.09)	3.04×10 ⁻⁴	0.08	EU	Fuchsberger C et al. (Nature 2016)
<i>DGKB</i>	rs2191349	7	15064309	T	G	0.65	0.66	1.05 (1.04, 1.06)	2.99×10^{-5*}	1.09 (1.08, 1.10)	2.60×10^{-10†}	1.03 (1.00, 1.05)	0.06	0.18	EU	Morris et al. (Nat Genet 2012)
<i>JAZF1</i>	rs864745	7	28180556	T	C	0.77	0.77	1.10 (1.09, 1.11)	2.28×10^{-16*}	1.10 (1.09, 1.11)	6.60×10^{-13†}	1.06 (1.03, 1.09)	1.82×10⁻⁴	0.03	EU	Morris et al. (Nat Genet 2012)
<i>GCK</i>	rs4607517	7	44235668	A	G	0.21	0.21	1.08 (1.06, 1.09)	1.03×10^{-5*}	1.03 (1.01, 1.05)	0.05†	1.03 (1.00, 1.06)	0.03	0.06	EU	Dupuis et al. (Nat Genet 2010)
<i>GCC1-PAX4</i>	rs6467136	7	127164958	G	A	0.78	0.78	0.99 (0.97, 1.01)	0.53§	1.02 (1.00, 1.04)	0.20†	1.02 (0.99, 1.05)	0.31	0.25	EA	Cho YS et al. (Nat Genet 2011)
<i>LEP, MIR129</i>	rs791595	7	127862802	A	G	0.18	0.12	1.01 (0.99, 1.04)	0.69§	1.03 (1.01, 1.05)	0.05†	1.08 (1.04, 1.14)	6.03×10 ⁻⁴	0.04	EA	Hara K et al. (Hum Mol Genet 2013)
<i>KLF14</i>	rs972283	7	130466854	G	A	0.71	0.72	1.04 (1.03, 1.05)	5.97×10^{-4*}	1.05 (1.04, 1.06)	4.50×10^{-4†}	1.05 (1.02, 1.07)	8.99×10⁻⁴	0.83	EU	Voight et al. (Nat Genet 2010)
<i>ANK1</i>	rs515071	8	41519462	G	A	0.77	0.83	1.10 (1.08, 1.12)	1.10×10 ⁻⁶ §	1.08 (1.06, 1.10)	2.00×10 ^{-7†}	1.05 (1.01, 1.10)	0.02</			

Nearby Genes	SNP	Chr	BP	R	O	RAF		EUR		TransEthnic		CKB		P_{het} CKB vs. EUR	First reported population	References
						EUR	CKB	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P			
<i>CDKN2A/B</i>	rs944801	9	22051670	C	G	0.58	0.88	1.08 (1.06, 1.09)	2.42×10 ^{-9*}	1.05 (1.03, 1.07)	2.30×10 ^{-3†}	0.98 (0.94, 1.03)	0.53	1.02×10 ⁻³	EU	Morris et al. (Nat Genet 2012)
<i>CDKN2A/B</i>	rs10811661	9	22134094	T	C	0.54	0.55	1.18 (1.17, 1.20)	3.72×10^{-27*}	1.21 (1.19, 1.23)	1.10×10^{-27†}	1.20 (1.17, 1.23)	7.16×10⁻⁴⁸	0.59	EU	Voight et al. (Nat Genet 2010);Morris et al. (Nat Genet 2012)
<i>DMRTA1</i>	rs1575972	9	22301092	T	A	0.97	0.97	1.20 (1.13, 1.28)	3.20×10 ^{-3§}	1.19 (1.15, 1.24)	4.50×10 ^{-6†}	1.11 (1.01, 1.21)	0.03	0.30	EA	Imamura, et al. (Nat Commun 2016)
<i>TLE4/CHCHD9</i>	rs13292136	9	81952128	C	T	0.91	0.91	1.19 (1.15, 1.23)	8.50×10^{-7§}	1.11 (1.09, 1.13)	6.70×10^{-7†}	1.07 (1.02, 1.12)	2.23×10⁻³	0.01	EU	Voight et al. (Nat Genet 2010)
<i>TLE1</i>	rs2796441	9	84308948	G	A	0.58	0.39	1.07 (1.06, 1.09)	5.39×10 ^{-9*}	1.07 (1.06, 1.09)	1.60×10 ^{-6†}	1.07 (1.04, 1.10)	2.75×10 ⁻⁵	0.82	EU	Morris et al. (Nat Genet 2012)
<i>GPSM1</i>	rs11787792	9	139252148	A	G	0.67	0.96	1.06 (1.04, 1.08)	1.10×10 ^{-4§}	1.02 (0.99, 1.05)	0.55†	1.13 (1.04, 1.24)	5.70×10 ⁻³	0.16	EA	Hara K et al. (Hum Mol Genet 2013)
<i>CDC123</i>	rs10906115	10	12314997	A	G	0.63	0.63	1.04 (1.02, 1.07)	2.80×10^{-4*}	1.07 (1.06, 1.08)	3.70×10^{-5†}	1.10 (1.07, 1.13)	5.42×10⁻¹⁴	3.14×10⁻⁴	EA	Shu et al. (Plos Genet 2010);Morris et al. (Nat Genet 2012)
<i>VPS26A</i>	rs1802295	10	70931474	T	C	0.11	0.11	1.00 (0.99, 1.02)	0.80*	1.05 (1.03, 1.07)	1.40×10^{-3†}	1.03 (0.99, 1.07)	0.19	0.33	SA	Kooner et al. (Nat Genet 2011)
<i>ZMIZ1</i>	rs12571751	10	80942631	A	G	0.55	0.54	1.08 (1.07, 1.09)	1.02×10 ^{-10*}	1.09 (1.08, 1.10)	2.40×10 ^{-10†}	1.04 (1.01, 1.07)	0.02	0.05	EU	Morris et al. (Nat Genet 2012)
<i>HHEX/IDE</i>	rs1111875	10	94462882	C	T	0.28	0.28	1.11 (1.10, 1.12)	1.98×10^{-19*}	1.12 (1.11, 1.13)	3.20×10^{-19†}	1.11 (1.09, 1.14)	7.37×10⁻¹⁶	0.85	EU	Voight et al. (Nat Genet 2010);Morris et al. (Nat Genet 2012)
																Rung et al. (Nat Genet 2009);Voight et al. (Nat Genet 2010);Morris et al. (Nat Genet 2012)
<i>TCF7L2</i>	rs7901695	10	114754088	C	T	0.03	0.04	1.34 (1.33, 1.36)	2.65×10^{-124*}	1.31 (1.29, 1.33)	2.20×10^{-73†}	1.32 (1.24, 1.40)	9.53×10⁻¹⁹	0.53	EU	
<i>GRK5</i>	rs10886471	10	119389891	C	T	0.79	0.80	0.99 (0.97, 1.01)	0.59§	1.01 (0.99, 1.03)	0.61†	1.01 (0.98, 1.05)	0.35	0.31	EA	Li H et al (Diabetes 2012)
<i>DUSP8</i>	rs2334499	11	1696849	T	C	0.43	0.83	1.04 (1.03, 1.05)	1.21×10 ^{-3*}	1.05 (1.03, 1.07)	1.00×10 ^{-3†}	1.00 (0.96, 1.04)	0.94	0.09	EU	Kong AP et al (Nat Genet 2009)
<i>INS-IGF2</i>	rs3842770	11	2178670	A	G	0.00	0.00	-	-	-	-	-	-	-	AA	Ng M et al. (PLoS Gen 2014)
<i>MIR4686</i>	rs7107784	11	2215089	G	A	0.28	0.10	1.05 (1.03, 1.06)	1.14×10 ^{-3*}	1.04 (1.02, 1.06)	0.035†	1.10 (1.04, 1.15)	3.08×10 ⁻⁴	0.12	EA	Imamura, et al. (Nat Commun 2016)
<i>KCNQ1</i>	rs231361	11	2691500	A	G	0.24	0.79	1.09 (1.07, 1.10)	1.21×10 ^{-9*}	1.11 (1.09, 1.13)	2.40×10 ^{-12†}	1.09 (1.04, 1.13)	2.82×10 ⁻⁵	0.99	EU	Morris et al. (Nat Genet 2012)
<i>KCNQ1</i>	rs2237892	11	2839751	C	T	0.68	0.68	1.16 (1.13, 1.19)	3.43×10^{-8*}	1.20 (1.17, 1.23)	7.40×10^{-17†}	1.21 (1.18, 1.24)	6.36×10⁻⁴⁶	0.14	EA	Morris et al. (Nat Genet 2012)
																Voight et al. (Nat Genet 2010);Morris et al. (Nat Genet 2012)
<i>KCNJ11</i>	rs5215	11	17408630	C	T	0.39	0.38	1.07 (1.06, 1.09)	8.50×10^{-10*}	1.09 (1.08, 1.10)	3.20×10^{-11†}	1.07 (1.05, 1.10)	2.12×10⁻⁸	0.90	EU	
																Voight et al. (Nat Genet 2010);Morris et al. (Nat Genet 2012)
<i>ARAP1</i>	rs1552224	11	72433098	A	C	0.92	0.92	1.11 (1.09, 1.12)	1.79×10^{-10*}	1.10 (1.08, 1.12)	1.20×10^{-7†}	1.11 (1.06, 1.16)	3.40×10⁻⁶	0.87	EU	
<i>MTNR1B</i>	rs10830963	11	92708710	G	C	0.43	0.43	1.10 (1.09, 1.12)	5.32×10 ^{-13*}	1.09 (1.07, 1.11)	2.00×10 ^{-7†}	1.00 (0.98, 1.03)	0.83	2.47×10 ⁻⁷	EU	Morris et al. (Nat Genet 2012)
<i>CCND2</i>	rs11063069	12	4374373	G	A	0.20	0.05	1.08 (1.06, 1.10)	3.25×10 ^{-7*}	1.08 (1.06, 1.10)	7.50×10 ^{-4†}	1.00 (0.93, 1.07)	0.96	0.04	EU	Morris et al. (Nat Genet 2012)
<i>CCND2</i>	rs76895963	12	4384844	T	G	0.98	1.00	-	-	-	-	-	-	-	EU	Steinthorsdottir V et al. (Nat Genet 2014)
<i>KLHDC5</i>	rs10842994	12	27965150	C	T	0.79	0.81	1.10 (1.08, 1.11)	6.08×10 ^{-10*}	1.08 (1.06, 1.10)	7.90×10 ^{-6†}	1.03 (0.99, 1.07)	0.16	0.01	EU	Morris et al. (Nat Genet 2012)
<i>FAM60A</i>	rs147538848	12	31466613	A	G	0.00	0.17	-	-	1.10 (1.09, 1.11)	8.21×10 ^{-13†}	1.07 (1.03, 1.12)	9.42×10 ⁻⁴	-	EA	Imamura, et al. (Nat Commun 2016)
<i>HMGA2</i>	rs1531343	12	66174894	C	G	0.10	0.12	1.15 (1.12, 1.18)	4.90×10 ^{-7§}	1.10 (1.08, 1.12)	3.90×10 ^{-7†}	1.06 (1.02, 1.11)	8.18×10 ⁻³	0.03	EU	Morris et al. (Nat Genet 2012)
<i>TSPAN8/LGR5</i>	rs7961581	12	71663102	C	T	0.22	0.22	1.08 (1.06, 1.10)	3.10×10^{-5§}	1.06 (1.04, 1.08)	9.50×10^{-5†}	1.03 (1.00, 1.06)	0.05	0.05	EU	Morris et al. (Nat Genet 2012)
<i>HNF1A</i>	rs483353044	12	121437091	A	G	0.00	0.00	-	-	-	-	-	-	-	Latino	SIGMA, Estrada K et al. (JAMA 2014)
<i>HNF1A</i>	rs7957197	12	121460686	T	A	0.80	1.00	1.08 (1.06, 1.10)	3.31×10 ^{-7*}	1.12 (1.09, 1.15)	9.20×10 ^{-7†}	-	-	-	EU	Voight et al. (Nat Genet 2010)
<i>MPHOSPH9</i>	rs4275659	12	123447928	C	T	0.69	0.65	1.06 (1.05, 1.07)	3.63×10 ^{-6*}	1.06 (1.05, 1.07)	5.50×10 ^{-6†}	1.01 (0.98, 1.04)	0.48	0.02	Multi-ethnic	Mahajan et al. (Nat Genet 2014)
<i>TBC1D4</i>	rs61736969	13	75898521	G	C	0.00	0.00	-	-	-	-	-	-	-	Greenland	Moltke I et al. (Nature 2014)
<i>SPRY2</i>	rs1359790	13	80717156	G	A	0.72	0.72	1.08 (1.06, 1.09)	1.39×10^{-8*}	1.07 (1.05, 1.09)	5.80×10^{-6†}	1.06 (1.03, 1.09)	3.32×10⁻⁵	0.37	EA	Shu et al. (Plos Genet 2010);Morris et al. (Nat Genet 2012)
<i>RASGRP1</i>	rs7403531	15	38530704	T	C	0.35	0.35	1.02 (1.00, 1.04)	0.36§	1.02 (1.01, 1.03)	0.15†	1.04 (1.01, 1.06)	4.77×10⁻³	0.50	EA	Li H et al (Diabetes 2012)
<i>INAFM2</i>	rs67839313	15	40619724	C	T	0.11	0.19	1.02 (1.00, 1.04)	0.36§	1.06 (1.05, 1.07)	1.82×10 ^{-10†}	1.06 (1.01, 1.10)	7.43×10 ⁻³	0.25	EA	Imamura, et al. (Nat Commun 2016)
<i>VPS13C</i>	rs7172432	15	62396389	A	G	0.62	0.62	1.06 (1.04, 1.08)	1.40×10^{-3§}	1.07 (1.06, 1.08)	1.80×10^{-7†}	1.09 (1.06, 1.12)	1.19×10⁻¹¹	0.21	EA	Yamauchi et al (Nat Genet 2010)
																Kooner et al. (Nat Genet 2011);
<i>HMG20A</i>	rs7178572	15	77747190	G	A	0.35	0.35	1.07 (1.06, 1.09)	2.17×10^{-8*}	1.09 (1.08, 1.10)	1.50×10^{-11†}	1.08 (1.05, 1.10)	4.93×10⁻⁹	0.90	SA	Perry et al. (PLoS Genet 2012);
																Morris et al. (Nat Genet 2012)
<i>ZFAND6</i>	rs11634397	15	80432222	G	A	0.09	0.09	1.05 (1.04, 1.06)	1.35×10^{-4*}	1.07 (1.05, 1.09)	1.30×10^{-5†}	1.04 (1.00, 1.09)	0.04	0.89	EU	Voight et al. (Nat Genet 2010)
<i>AP3S2</i>	rs2028299	15	90374257	C	A	0.20	0.20	1.04 (1.02, 1.06)	0.035§	1.07 (1.06, 1.08)	5.20×10^{-7†}	1.05 (1.02, 1.08)	1.42×10⁻³	0.71	SA	Kooner et al. (Nat Genet 2011)
<i>PRC1</i>	rs8042680	15	91521337	A	C	0.33	0.99	1.07 (1.05, 1.08)	1.94×10^{-7*}	1.07 (1.05, 1.09)	6.00×10^{-6†}	0.87 (0.77, 0.98)	0.03	1.33×10⁻³	EU	Morris et al. (Nat Genet 2012)
<i>FTO</i>	rs9939609	16	53820527	A	T	0.12	0.13	1.12 (1.11, 1.13)	9.18×10 ^{-22*}	1.10 (1.09, 1.11)	2.70×10 ^{-18†}	1.14 (1.10, 1.18)	6.25×10 ⁻¹³	0.44	EU	Morris et al. (Nat Genet 2012)
<i>BCAR1</i>	rs7202877	16	75247245	T	G	0.90	0.80	1.12 (1.10, 1.14)	3.50×10 ^{-8*}	1.08 (1.06, 1.10)	5.70×10 ^{-4†}	1.06 (1.02, 1.11)	1.82×10 ⁻³	0.08	EU	Morris et al. (Nat Genet 2012)
<i>SRR</i>	rs4523957	17	2208899	T	G	0.71	0.70	0.99 (0.98, 1.00)	0.39§	1.02 (1.00, 1.04)	0.27†	1.01 (0.99, 1.04)	0.39	0.22	EA	Tsai FJ et al (PLoS Genet 2010)
<i>SLC16A13</i>	rs312457	17	6940393	G	A	0.02	0.11	-	-	1.17 (1.04, 1.32)	0.20†	1.10 (1.05, 1.15)	6.71×10 ⁻⁵	-	EA	Hara K et al. (Hum Mol Genet 2013)

Nearby Genes	SNP	Chr	BP	R	O	RAF		EUR		TransEthnic		CKB		P_{het} CKB vs. EUR	First reported population	References
						EUR	CKB	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P			
<i>HNF1B</i>	<u>rs4430796</u>	17	<u>36098040</u>	G	A	0.28	0.28	<u>1.13 (1.10, 1.16)</u>	<u>2.40×10⁻⁶§</u>	<u>1.10 (1.08, 1.12)</u>	<u>8.90×10⁻¹⁰†</u>	<u>1.08 (1.05, 1.11)</u>	<u>7.72×10⁻⁹</u>	0.14	EU	Morris et al. (Nat Genet 2012)
<i>LAMA1</i>	rs7234998	18	7068724	T	C	0.39	0.70	1.07 (1.05, 1.09)	1.20×10 ⁻³ §	1.06 (1.05, 1.08)	3.50×10 ⁻⁵ †	1.02 (0.99, 1.06)	0.17	0.11	EU	Perry et al. (PLoS Genet 2012)
<i>MC4R</i>	rs12970134	18	57884750	A	G	0.19	0.19	1.08 (1.06, 1.09)	1.19×10 ^{-8*}	1.08 (1.07, 1.10)	2.60×10 ⁻⁸ †	1.08 (1.05, 1.11)	5.92×10 ⁻⁷	0.94	EU	Morris et al. (Nat Genet 2012)
<i>BCL2A</i>	rs12454712	18	60845884	T	C	0.61	0.55	1.04 (1.03, 1.06)	4.45×10 ^{-3*}	1.05 (1.03, 1.07)	3.40×10 ⁻³ †	1.05 (1.02, 1.08)	2.88×10 ⁻³	0.74	Multi-ethnic	Saxena et al. (Am J Hum Genet 2012)
<i>CILP2- GATAD2A</i>	rs10401969	19	19407718	C	T	0.07	0.09	1.10 (1.07, 1.12)	1.50×10 ^{-14*}	1.07 (1.04, 1.10)	9.70×10 ⁻³ †	1.00 (0.95, 1.05)	0.95	1.63×10 ⁻³	EU	Morris et al. (Nat Genet 2012)
<i>PEPD</i>	rs3786897	19	33893008	A	G	0.60	0.54	1.03 (1.01, 1.04)	0.037*	1.05 (1.04, 1.06)	3.30×10 ⁻³ †	1.08 (1.05, 1.12)	6.00×10 ⁻⁷	0.01	EA	Cho YS et al. (Nat Genet 2011)
<i>TOMM40-APOE</i>	rs157582	19	45396219	C	T	0.79	0.81	1.11 (1.07, 1.15)	1.40×10 ⁻³ §	1.13 (1.11, 1.15)	2.80×10 ⁻⁹ †	1.04 (1.00, 1.08)	0.07	0.08	Multi-ethnic	Cook JP, Morris AP (Eur J Hum Genet 2016)
<i>GIPR</i>	rs8108269	19	46158513	G	T	0.30	0.48	1.07 (1.05, 1.08)	4.36×10 ^{-7*}	1.07 (1.05, 1.09)	4.90×10 ⁻⁶ †	1.06 (1.03, 1.09)	3.14×10 ⁻⁴	0.66	EU	Morris et al. (Nat Genet 2012)
<i>HNF4A</i>	<u>rs6017317</u>	20	<u>42946966</u>	G	T	0.43	0.43	<u>1.06 (1.04, 1.09)</u>	<u>0.013§</u>	<u>1.07 (1.06, 1.08)</u>	<u>5.20×10⁻⁷†</u>	<u>1.06 (1.04, 1.09)</u>	<u>8.09×10⁻⁷</u>	0.92	EA	Cho YS et al. (Nat Genet 2011)
<i>MTMR3</i>	rs41278853	22	30416527	A	G	0.94	1.00	1.13 (1.09, 1.17)	1.90×10 ⁻⁴ ‡	1.13 (1.09, 1.17)	2.30×10 ⁻⁴ †	-	-	-	EU	Fuchsberger C et al. (Nature 2016)
<i>DUSP9</i>	rs5945326	23	152899922	A	G	0.79	0.61	1.27 (1.22, 1.32)	3.00×10 ⁻¹⁰ §	-	-	1.11 (1.07, 1.15)	4.10×10 ⁻⁷	-	EU	Voight et al. (Nat Genet 2010)
GRS-T2D48												1.07 (1.07, 1.08)	8.48×10 ⁻²¹⁷			
GRS-T2D48w												1.08 (1.07, 1.08)	4.64×10 ⁻²⁹⁵			
GRS-BC												1.09 (1.09, 1.10)	3.04×10 ⁻²³⁵			
GRS-IR												1.05 (1.04, 1.07)	4.85×10 ⁻¹²			
GRS-T2D86												1.06 (1.05, 1.06)	5.02×10 ⁻¹⁷¹			
GRS-T2D86w												1.06 (1.06, 1.06)	1.00×10 ⁻²¹⁵			

*DIAGRAM metabochip (PMID: 22885922)

†Trans-ethnic meta-analysis of four ethnic groups (East Asians, Europeans, South Asians and Mexicans) (PMID: 24509480)

‡Whole Genome Sequencing +replication (PMID: 27398621)

§DIAGRAMv3 (PMID: 22885922)

||Icelanders (PMID: 24464100)

SNPs included in GRS-T2D48 in bold and underlined

AA: African American; BP: base position; Chr: chromosome; EA: East Asian; EU: European; GRS-BC: beta-cell function genetic risk score; GRS-IR: insulin resistance genetic risk score; GRS-T2D48: unweighted 48 SNP type 2 diabetes genetic risk score; GRS-T2D48w: weighted 48 SNP type 2 diabetes genetic risk score;

GRS-T2D86: unweighted 86 SNP type 2 diabetes genetic risk score; GRS-T2D86w: weighted 86 SNP type 2 diabetes genetic risk score;

O: other allele; OR: odds ratio; R: Risk allele; RAF: risk allele frequency; SA: South Asian; SNP: single nucleotide polymorphisms

Supplementary Table 2. Genetic variants and weights applied to construct type 2 diabetes genetic risk score

SNP	Nearby genes	Chr.	BP	R	O	TransEthnic GWAS*		Note
						β	SE	
rs2296172	<i>MACF1</i>	1	39835817	G	A	0.039	0.015	†
rs17106184	<i>FAF1</i>	1	50909985	G	A	0.104	0.022	
<u>rs10923931</u>	<u>NOTCH2</u>	<u>1</u>	<u>120517959</u>	<u>T</u>	<u>G</u>	<u>0.049</u>	<u>0.020</u>	
rs67156297	<i>ATP8B2</i>	1	154336716	A	G	0.020	0.018	
<u>rs340874</u>	<u>PROX1</u>	<u>1</u>	<u>214159256</u>	<u>C</u>	<u>T</u>	<u>0.068</u>	<u>0.014</u>	‡
<u>rs780094</u>	<u>GCKR</u>	<u>2</u>	<u>27741237</u>	<u>C</u>	<u>T</u>	<u>0.058</u>	<u>0.013</u>	‡§
<u>rs7578597</u>	<u>THADA</u>	<u>2</u>	<u>43732823</u>	<u>T</u>	<u>C</u>	<u>0.068</u>	<u>0.025</u>	‡
rs9309245	<i>ASB3</i>	2	53397048	G	C	0.010	0.011	
rs1116357	<i>CCDC85A</i>	2	57287411	G	A	0.020	0.012	
<u>rs243021</u>	<u>BCL11A</u>	<u>2</u>	<u>60584819</u>	<u>A</u>	<u>G</u>	<u>0.068</u>	<u>0.013</u>	
<u>rs3923113</u>	<u>GRB14</u>	<u>2</u>	<u>165501849</u>	<u>A</u>	<u>C</u>	<u>0.077</u>	<u>0.016</u>	‡§
<u>rs2943641</u>	<u>IRS1</u>	<u>2</u>	<u>227093745</u>	<u>C</u>	<u>T</u>	<u>0.086</u>	<u>0.014</u>	‡§
rs1861612	<i>DNER</i>	2	230522398	A	G	0.010	0.010	
<u>rs1801282</u>	<u>PPARG</u>	<u>3</u>	<u>12393125</u>	<u>C</u>	<u>G</u>	<u>0.131</u>	<u>0.021</u>	§
<u>rs6780569</u>	<u>UBE2E2</u>	<u>3</u>	<u>23198484</u>	<u>G</u>	<u>A</u>	<u>0.095</u>	<u>0.017</u>	
<u>rs831571</u>	<u>PSMD6</u>	<u>3</u>	<u>64048297</u>	<u>C</u>	<u>T</u>	<u>0.049</u>	<u>0.014</u>	§
<u>rs4607103</u>	<u>ADAMTS9</u>	<u>3</u>	<u>64711904</u>	<u>C</u>	<u>T</u>	<u>0.039</u>	<u>0.013</u>	
<u>rs11708067</u>	<u>ADCY5</u>	<u>3</u>	<u>123065778</u>	<u>A</u>	<u>G</u>	<u>0.095</u>	<u>0.017</u>	‡
<u>rs1470579</u>	<u>IGF2BP2</u>	<u>3</u>	<u>185529080</u>	<u>C</u>	<u>A</u>	<u>0.122</u>	<u>0.013</u>	‡
<u>rs16861329</u>	<u>ST6GAL1</u>	<u>3</u>	<u>186666461</u>	<u>C</u>	<u>T</u>	<u>0.086</u>	<u>0.019</u>	‡
<u>rs6815464</u>	<u>MAEA</u>	<u>4</u>	<u>1309901</u>	<u>C</u>	<u>G</u>	<u>0.077</u>	<u>0.020</u>	‡
rs4458523	<i>WFS1</i>	4	6289986	G	T	0.086	0.014	
rs6813195	<i>TMEM154</i>	4	153520475	C	T	0.077	0.013	
rs702634	<i>ARL15</i>	5	53271420	A	G	0.077	0.015	†
rs459193	<i>ANKRD55</i>	5	55806751	G	A	0.049	0.015	†
<u>rs4457053</u>	<u>ZBED3</u>	<u>5</u>	<u>76424949</u>	<u>G</u>	<u>A</u>	<u>0.095</u>	<u>0.023</u>	
rs9505118	<i>SSR1/RREB1</i>	6	7290437	A	G	0.058	0.012	
<u>rs7754840</u>	<u>CDKAL1</u>	<u>6</u>	<u>20661250</u>	<u>C</u>	<u>G</u>	<u>0.140</u>	<u>0.013</u>	‡
rs3132524	<i>POU5F1/TCF19</i>	6	31136714	C	T	0.068	0.013	
rs2244020	<i>HLA-B</i>	6	31347451	G	A	0.039	0.015	†
<u>rs9470794</u>	<u>ZFAND3</u>	<u>6</u>	<u>38106844</u>	<u>C</u>	<u>T</u>	<u>0.058</u>	<u>0.020</u>	
rs1535500	<i>KCNK16</i>	6	39284050	T	G	0.049	0.012	
rs11759026	<i>CENPW</i>	6	126792095	G	A	0.113	0.028	
<u>rs2191349</u>	<u>DGKB</u>	<u>7</u>	<u>15064309</u>	<u>T</u>	<u>G</u>	<u>0.086</u>	<u>0.014</u>	‡
<u>rs864745</u>	<u>JAZF1</u>	<u>7</u>	<u>28180556</u>	<u>T</u>	<u>C</u>	<u>0.095</u>	<u>0.013</u>	
<u>rs4607517</u>	<u>GCK</u>	<u>7</u>	<u>44235668</u>	<u>A</u>	<u>G</u>	<u>0.030</u>	<u>0.015</u>	‡
<u>rs6467136</u>	<u>GCC1-PAX4</u>	<u>7</u>	<u>127164958</u>	<u>G</u>	<u>A</u>	<u>0.020</u>	<u>0.015</u>	‡
rs791595	<i>LEP, MIR129</i>	7	127862802	A	G	0.030	0.015	
<u>rs972283</u>	<u>KLF14</u>	<u>7</u>	<u>130466854</u>	<u>G</u>	<u>A</u>	<u>0.049</u>	<u>0.014</u>	‡§
rs515071	<i>ANK1</i>	8	41519462	G	A	0.077	0.015	
<u>rs896854</u>	<u>TP53INP1</u>	<u>8</u>	<u>95960511</u>	<u>T</u>	<u>C</u>	<u>0.077</u>	<u>0.013</u>	
<u>rs13266634</u>	<u>SLC30A8</u>	<u>8</u>	<u>118184783</u>	<u>C</u>	<u>T</u>	<u>0.131</u>	<u>0.014</u>	‡
<u>rs7041847</u>	<u>GLIS3</u>	<u>9</u>	<u>4287466</u>	<u>A</u>	<u>G</u>	<u>0.058</u>	<u>0.013</u>	‡
<u>rs17584499</u>	<u>PTPRD</u>	<u>9</u>	<u>8879118</u>	<u>T</u>	<u>C</u>	<u>0.010</u>	<u>0.019</u>	
rs944801	<i>CDKN2A/B</i>	9	22051670	C	G	0.049	0.016	
<u>rs10811661</u>	<u>CDKN2A/B</u>	<u>9</u>	<u>22134094</u>	<u>T</u>	<u>C</u>	<u>0.191</u>	<u>0.017</u>	‡

SNP	Nearby genes	Chr.	BP	R	O	TransEthnic GWAS*		Note
						β	SE	
rs1575972	<i>DMRTA1</i>	9	22301092	T	A	0.174	0.038	
<u>rs13292136</u>	<u>TLE4/CHCHD9</u>	<u>9</u>	<u>81952128</u>	<u>C</u>	<u>T</u>	<u>0.104</u>	<u>0.021</u>	
rs2796441	<i>TLE1</i>	9	84308948	G	A	0.068	0.014	
rs11787792	<i>GPSM1</i>	9	139252148	A	G	0.020	0.033	
<u>rs10906115</u>	<u>CDC123</u>	<u>10</u>	<u>12314997</u>	<u>A</u>	<u>G</u>	<u>0.068</u>	<u>0.012</u>	
<u>rs1802295</u>	<u>VPS26A</u>	<u>10</u>	<u>70931474</u>	<u>T</u>	<u>C</u>	<u>0.049</u>	<u>0.015</u>	
rs12571751	<i>ZMIZ1</i>	10	80942631	A	G	0.086	0.014	
<u>rs1111875</u>	<u>HHEX/IDE</u>	<u>10</u>	<u>94462882</u>	<u>C</u>	<u>T</u>	<u>0.113</u>	<u>0.013</u>	‡
<u>rs7901695</u>	<u>TCF7L2</u>	<u>10</u>	<u>114754088</u>	<u>C</u>	<u>T</u>	<u>0.270</u>	<u>0.015</u>	‡
<u>rs10886471</u>	<u>GRK5</u>	<u>10</u>	<u>119389891</u>	<u>C</u>	<u>T</u>	<u>0.010</u>	<u>0.020</u>	
rs7107784	<i>MIR4686</i>	11	2215089	G	A	0.039	0.019	
rs231361	<i>KCNQ1</i>	11	2691500	A	G	0.104	0.015	
<u>rs2237892</u>	<u>KCNQ1</u>	<u>11</u>	<u>2839751</u>	<u>C</u>	<u>T</u>	<u>0.182</u>	<u>0.022</u>	‡
<u>rs5215</u>	<u>KCNJ11</u>	<u>11</u>	<u>17408630</u>	<u>C</u>	<u>T</u>	<u>0.086</u>	<u>0.013</u>	‡
<u>rs1552224</u>	<u>ARAP1</u>	<u>11</u>	<u>72433098</u>	<u>A</u>	<u>C</u>	<u>0.095</u>	<u>0.018</u>	‡
rs11063069	<i>CCND2</i>	12	4374373	G	A	0.077	0.023	
rs10842994	<i>KLHDC5</i>	12	27965150	C	T	0.077	0.017	
rs147538848	<i>FAM60A</i>	12	31466613	A	G	0.095	0.013	
rs1531343	<i>HMGA2</i>	12	66174894	C	G	0.095	0.019	
<u>rs7961581</u>	<u>TSPAN8/LGR5</u>	<u>12</u>	<u>71663102</u>	<u>C</u>	<u>T</u>	<u>0.058</u>	<u>0.015</u>	
rs4275659	<i>MPHOSPH9</i>	12	123447928	C	T	0.058	0.013	†
<u>rs1359790</u>	<u>SPRY2</u>	<u>13</u>	<u>80717156</u>	<u>G</u>	<u>A</u>	<u>0.068</u>	<u>0.015</u>	‡
<u>rs7403531</u>	<u>RASGRP1</u>	<u>15</u>	<u>38530704</u>	<u>T</u>	<u>C</u>	<u>0.020</u>	<u>0.014</u>	
rs67839313	<i>INAFM2</i>	15	40619724	C	T	0.058	0.009	
<u>rs7172432</u>	<u>VPS13C</u>	<u>15</u>	<u>62396389</u>	<u>A</u>	<u>G</u>	<u>0.068</u>	<u>0.013</u>	‡
<u>rs7178572</u>	<u>HMG20A</u>	<u>15</u>	<u>77747190</u>	<u>G</u>	<u>A</u>	<u>0.086</u>	<u>0.013</u>	
<u>rs11634397</u>	<u>ZFAND6</u>	<u>15</u>	<u>80432222</u>	<u>G</u>	<u>A</u>	<u>0.068</u>	<u>0.016</u>	
<u>rs2028299</u>	<u>AP3S2</u>	<u>15</u>	<u>90374257</u>	<u>C</u>	<u>A</u>	<u>0.068</u>	<u>0.013</u>	‡
<u>rs8042680</u>	<u>PRC1</u>	<u>15</u>	<u>91521337</u>	<u>A</u>	<u>C</u>	<u>0.068</u>	<u>0.015</u>	‡
rs7202877	<i>BCAR1</i>	16	75247245	T	G	0.077	0.022	
<u>rs4523957</u>	<u>SRR</u>	<u>17</u>	<u>2208899</u>	<u>T</u>	<u>G</u>	<u>0.020</u>	<u>0.018</u>	‡
rs312457	<i>SLC16A13</i>	17	6940393	G	A	0.157	0.123	
<u>rs4430796</u>	<u>HNF1B</u>	<u>17</u>	<u>36098040</u>	<u>G</u>	<u>A</u>	<u>0.095</u>	<u>0.016</u>	‡
rs7234998	<i>LAMA1</i>	18	7068724	T	C	0.058	0.014	
rs12454712	<i>BCL2</i>	18	60845884	T	C	0.049	0.017	
rs10401969	<i>CILP2-GATAD2A</i>	19	19407718	C	T	0.068	0.026	†
rs3786897	<i>PEPD</i>	19	33893008	A	G	0.049	0.014	†
rs157582	<i>TOMM40-APOE</i>	19	45396219	C	T	0.122	0.021	†
rs8108269	<i>GIPR</i>	19	46158513	G	T	0.068	0.015	†
<u>rs6017317</u>	<u>HNF4A</u>	<u>20</u>	<u>42946966</u>	<u>G</u>	<u>T</u>	<u>0.068</u>	<u>0.013</u>	‡

SNPs included in GRS-T2D48 in bold and underlined

*Trans-ethnic meta-analysis (PMID: 24509480 and PMID: 27398621)

†SNPs associated with blood lipids (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total cholesterol, or triglycerides) at genome-wide significance

‡Beta cell function-related SNPs

§Insulin resistance-related SNPs

||SNPs associated with coronary heart disease at genome-wide significance

BP: base position; O: other allele; R: risk allele; SNP, single nucleotide polymorphisms

Supplementary Table 3. Associations between type 2 diabetes related genetic variants and cardiovascular diseases

Nearby Genes	SNP	R	O	Ischaemic stroke (n=17,097 cases)		Lacunar ischaemic stroke (n=3,173 cases)		Non-lacunar ischaemic stroke (n=13,924 cases)		Intra-cerebral haemorrhage (6,973 cases)		Major coronary event (n= 5,081 cases)		Presence of plaque (n= 6,819 cases)		cIMT, mm (n= 21,971)	
				OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	β (95% CI)	P
<i>MACF1</i>	rs2296172	G	A	1.00 (0.97, 1.04)	0.82	1.00 (0.92, 1.08)	0.96	1.01 (0.97, 1.05)	0.75	1.03 (0.98, 1.09)	0.19	1.11 (1.05, 1.18)	4.25×10 ⁻⁴	1.05 (0.99, 1.12)	0.12	0.004 (0.001, 0.007)	0.02
<i>FAF1</i>	rs17106184	G	A	0.98 (0.94, 1.03)	0.50	1.01 (0.91, 1.12)	0.89	0.98 (0.93, 1.03)	0.38	0.95 (0.89, 1.01)	0.13	0.95 (0.88, 1.02)	0.17	1.10 (1.02, 1.20)	0.02	0.003 (-0.001, 0.007)	0.10
<i>NOTCH2</i>	rs10923931	T	G	1.02 (0.95, 1.09)	0.61	0.94 (0.81, 1.09)	0.42	1.04 (0.97, 1.12)	0.28	1.00 (0.91, 1.11)	0.94	1.08 (0.96, 1.21)	0.19	1.04 (0.91, 1.19)	0.60	-0.006 (-0.013, 0.001)	0.08
<i>ATP8B2</i>	rs67156297	A	G	1.00 (0.95, 1.05)	0.96	1.00 (0.90, 1.12)	0.97	1.00 (0.95, 1.05)	0.95	1.06 (0.99, 1.13)	0.10	0.94 (0.87, 1.02)	0.16	0.99 (0.91, 1.07)	0.78	-0.003 (-0.007, 0.001)	0.18
<i>PROX1</i>	rs340874	C	T	1.01 (0.99, 1.04)	0.28	1.03 (0.98, 1.09)	0.24	1.01 (0.98, 1.04)	0.45	0.99 (0.96, 1.03)	0.69	1.02 (0.98, 1.07)	0.34	1.06 (1.01, 1.11)	0.01	0.001 (-0.001, 0.004)	0.33
<i>GCKR</i>	rs780094	C	T	0.99 (0.96, 1.01)	0.34	0.99 (0.94, 1.05)	0.78	0.99 (0.96, 1.01)	0.35	1.02 (0.98, 1.05)	0.39	0.98 (0.94, 1.03)	0.45	1.01 (0.97, 1.06)	0.59	0.001 (-0.001, 0.003)	0.46
<i>THADA</i>	rs7578597	T	C	1.03 (0.89, 1.19)	0.68	1.13 (0.83, 1.54)	0.45	1.01 (0.87, 1.18)	0.88	0.97 (0.79, 1.18)	0.74	0.96 (0.76, 1.22)	0.75	1.15 (0.85, 1.54)	0.36	0.011 (-0.003, 0.026)	0.11
<i>ASB3</i>	rs9309245	G	C	1.03 (0.99, 1.06)	0.18	1.00 (0.92, 1.08)	0.95	1.03 (0.99, 1.07)	0.12	1.01 (0.96, 1.06)	0.76	1.06 (1.00, 1.13)	0.04	1.00 (0.94, 1.06)	0.97	0.002 (-0.001, 0.005)	0.25
<i>CCDC85A</i>	rs1116357	G	A	1.02 (0.99, 1.06)	0.17	1.10 (1.03, 1.19)	7.08×10 ⁻³	1.01 (0.98, 1.05)	0.53	1.03 (0.98, 1.07)	0.23	1.05 (0.99, 1.11)	0.08	0.99 (0.94, 1.05)	0.85	0.003 (0.000, 0.005)	0.05
<i>BCL11A</i>	rs243021	A	G	1.00 (0.98, 1.03)	0.95	1.02 (0.96, 1.08)	0.51	1.00 (0.97, 1.02)	0.81	0.99 (0.96, 1.03)	0.71	1.04 (0.99, 1.08)	0.11	1.02 (0.97, 1.08)	0.35	0.000 (-0.002, 0.003)	0.82
<i>GRB14</i>	rs3923113	A	C	1.03 (0.99, 1.07)	0.13	1.05 (0.97, 1.14)	0.20	1.02 (0.99, 1.06)	0.22	1.03 (0.98, 1.09)	0.26	1.02 (0.96, 1.08)	0.56	1.02 (0.95, 1.10)	0.53	0.003 (-0.001, 0.006)	0.13
<i>IRS1</i>	rs2943641	C	T	1.01 (0.97, 1.06)	0.55	0.97 (0.88, 1.08)	0.60	1.02 (0.97, 1.08)	0.35	1.05 (0.98, 1.12)	0.18	1.08 (0.99, 1.16)	0.08	0.95 (0.87, 1.04)	0.29	0.000 (-0.005, 0.004)	0.84
<i>DNER</i>	rs1861612	A	G	0.99 (0.97, 1.02)	0.66	1.03 (0.96, 1.09)	0.41	0.99 (0.96, 1.02)	0.40	1.00 (0.96, 1.04)	0.90	1.00 (0.96, 1.05)	0.96	0.99 (0.95, 1.04)	0.71	0.001 (-0.001, 0.003)	0.42
<i>PPARG</i>	rs1801282	C	G	0.98 (0.92, 1.03)	0.35	0.89 (0.80, 1.00)	0.04	1.00 (0.94, 1.06)	0.91	1.00 (0.92, 1.08)	0.97	1.04 (0.95, 1.14)	0.43	1.12 (1.01, 1.25)	0.03	0.002 (-0.004, 0.007)	0.56
<i>UBE2E2</i>	rs6780569	G	A	0.99 (0.96, 1.02)	0.35	0.96 (0.90, 1.03)	0.25	0.99 (0.96, 1.02)	0.55	0.97 (0.93, 1.01)	0.17	1.03 (0.98, 1.09)	0.25	1.01 (0.95, 1.07)	0.83	0.002 (-0.001, 0.005)	0.25
<i>PSMD6</i>	rs831571	C	T	1.02 (0.99, 1.04)	0.15	1.00 (0.94, 1.06)	0.95	1.02 (1.00, 1.05)	0.11	0.99 (0.96, 1.03)	0.63	1.03 (0.99, 1.08)	0.17	1.01 (0.96, 1.06)	0.62	0.003 (0.001, 0.005)	0.01
<i>ADAMTS9</i>	rs4607103	C	T	0.99 (0.96, 1.01)	0.29	0.99 (0.93, 1.04)	0.65	0.98 (0.96, 1.01)	0.23	0.99 (0.96, 1.03)	0.64	0.93 (0.90, 0.98)	1.94×10 ⁻³	0.98 (0.93, 1.03)	0.43	0.005 (0.002, 0.007)	2.19×10 ⁻⁴
<i>ADCY5</i>	rs11708067	A	G	1.02 (0.83, 1.24)	0.86	0.99 (0.66, 1.48)	0.95	1.02 (0.82, 1.27)	0.83	0.97 (0.73, 1.29)	0.84	1.10 (0.78, 1.55)	0.58	1.25 (0.85, 1.84)	0.26	-0.012 (-0.031, 0.007)	0.22
<i>IGF2BP2</i>	rs1470579	C	A	1.03 (1.00, 1.06)	0.04	1.00 (0.94, 1.06)	0.92	1.04 (1.01, 1.07)	0.02	1.00 (0.96, 1.04)	0.95	1.04 (0.99, 1.09)	0.10	1.01 (0.96, 1.07)	0.70	0.002 (0.000, 0.005)	0.11
<i>ST6GAL1</i>	rs16861329	C	T	1.00 (0.97, 1.03)	0.99	1.02 (0.95, 1.09)	0.60	1.00 (0.96, 1.03)	0.81	0.99 (0.94, 1.03)	0.57	1.00 (0.95, 1.06)	0.88	1.03 (0.97, 1.09)	0.31	0.000 (-0.003, 0.003)	0.92
<i>MAEA</i>	rs6815464	C	G	1.00 (0.98, 1.03)	0.73	0.98 (0.93, 1.03)	0.40	1.01 (0.99, 1.04)	0.39	1.02 (0.98, 1.05)	0.40	1.04 (1.00, 1.08)	0.07	1.02 (0.97, 1.07)	0.45	0.001 (-0.001, 0.003)	0.33
<i>WFS1</i>	rs4458523	G	T	1.05 (0.98, 1.11)	0.15	0.90 (0.78, 1.04)	0.14	1.07 (1.00, 1.15)	0.04	0.99 (0.92, 1.07)	0.85	0.98 (0.89, 1.08)	0.64	1.08 (0.98, 1.19)	0.11	0.005 (0.000, 0.010)	0.05
<i>TMEM154</i>	rs6813195	C	T	1.00 (0.97, 1.03)	0.80	1.04 (0.98, 1.11)	0.18	0.99 (0.96, 1.02)	0.40	0.98 (0.94, 1.01)	0.21	1.04 (1.00, 1.09)	0.07	0.99 (0.95, 1.04)	0.78	0.002 (-0.001, 0.004)	0.20
<i>ARL15</i>	rs702634	A	G	1.03 (0.98, 1.07)	0.22	1.04 (0.94, 1.15)	0.44	1.02 (0.98, 1.07)	0.32	1.00 (0.95, 1.06)	0.94	1.06 (0.99, 1.14)	0.09	0.93 (0.87, 1.00)	0.06	-0.002 (-0.006, 0.001)	0.23
<i>ANKRD55</i>	rs459193	G	A	1.02 (0.99, 1.05)	0.11	1.00 (0.94, 1.06)	0.98	1.03 (1.00, 1.06)	0.10	0.99 (0.95, 1.03)	0.57	1.00 (0.95, 1.05)	0.96	1.02 (0.97, 1.07)	0.45	0.001 (-0.001, 0.003)	0.43
<i>ZBED3</i>	rs4457053	G	A	1.02 (0.96, 1.07)	0.53	0.99 (0.87, 1.12)	0.83	1.02 (0.96, 1.08)	0.46	1.07 (0.99, 1.16)	0.07	0.99 (0.90, 1.09)	0.86	0.98 (0.88, 1.08)	0.68	0.001 (-0.004, 0.006)	0.65
<i>SSR1/RREB1</i>	rs9505118	A	G	1.00 (0.97, 1.03)	0.95	0.96 (0.90, 1.02)	0.21	1.01 (0.98, 1.04)	0.64	1.00 (0.96, 1.04)	0.95	1.00 (0.96, 1.05)	0.99	1.01 (0.96, 1.06)	0.66	0.000 (-0.003, 0.002)	0.74
<i>CDKAL1</i>	rs7754840	C	G	1.01 (0.99, 1.04)	0.34	1.00 (0.95, 1.06)	0.99	1.02 (0.99, 1.04)	0.26	0.97 (0.94, 1.01)	0.14	1.02 (0.98, 1.06)	0.38	1.04 (0.99, 1.09)	0.08	0.005 (0.003, 0.007)	3.15×10 ⁻⁵
<i>POU5F1/TCF19</i>	rs3132524	C	T	0.99 (0.96, 1.02)	0.40	0.98 (0.91, 1.05)	0.51	0.99 (0.96, 1.02)	0.50	0.98 (0.94, 1.02)	0.39	0.99 (0.94, 1.04)	0.68	0.99 (0.94, 1.04)	0.58	-0.003 (-0.006, -0.001)	0.01
<i>HLA-B</i>	rs2244020	G	A	0.97 (0.95, 1.00)	0.06	1.01 (0.95, 1.07)	0.77	0.96 (0.94, 0.99)	0.02	1.04 (1.00, 1.08)	0.04	0.96 (0.92, 1.01)	0.08	1.03 (0.98, 1.08)	0.26	-0.001 (-0.003, 0.001)	0.38
<i>ZFAND3</i>	rs9470794	C	T	1.02 (0.99, 1.05)	0.17	1.03 (0.97, 1.09)	0.35	1.02 (0.99, 1.05)	0.26	1.02 (0.98, 1.06)	0.32	0.98 (0.93, 1.02)	0.29	1.02 (0.97, 1.07)	0.40	0.000 (-0.003, 0.002)	0.71
<i>KCNK16</i>	rs1535500	T	G	1.01 (0.98, 1.04)	0.40	0.99 (0.93, 1.05)	0.74	1.02 (0.99, 1.05)	0.29	1.00 (0.96, 1.04)	0.90	0.98 (0.94, 1.03)	0.47	1.02 (0.97, 1.06)	0.53	-0.001 (-0.003, 0.002)	0.54
<i>CENPW</i>	rs11759026	G	A	0.99 (0.96, 1.02)	0.35	0.98 (0.92, 1.05)	0.62	0.99 (0.96, 1.02)	0.47	0.94 (0.91, 0.98)	2.13×10 ⁻³	1.00 (0.95, 1.04)	0.89	1.04 (0.99, 1.09)	0.11	0.003 (0.001, 0.005)	9.89×10 ⁻³
<i>DGKB</i>	rs2191349	T	G	1.01 (0.98, 1.03)	0.68	1.04 (0.98, 1.10)	0.20	1.00 (0.97, 1.03)	0.83	1.04 (1.00, 1.09)	0.04	1.01 (0.96, 1.06)	0.67	0.97 (0.93, 1.02)	0.28	0.002 (0.000, 0.005)	0.10
<i>JAZF1</i>	rs864745	T	C	0.99 (0.96, 1.02)	0.60	0.95 (0.90, 1.01)	0.12	1.00 (0.97, 1.03)	0.91	1.03 (0.99, 1.07)	0.20	1.02 (0.97, 1.07)	0.35	1.06 (1.00, 1.12)	0.05	0.001 (-0.002, 0.004)	0.40
<i>GCK</i>	rs4607517	A	G	1.00 (0.97, 1.03)	0.87	0.97 (0.91, 1.04)	0.37	1.00 (0.97, 1.03)	0.89	0.96 (0.92, 1.01)	0.09	1.01 (0.96, 1.06)	0.77	1.00 (0.94, 1.06)	0.97	0.002 (-0.001, 0.005)	0.25
<i>GCC1-PAX4</i>	rs6467136	G	A	1.01 (0.98, 1.04)	0.63	1.01 (0.95, 1.08)	0.68	1.00 (0.97, 1.03)	0.86	1.02 (0.97, 1.06)	0.48	0.96 (0.92, 1.01)	0.12	0.95 (0.90, 1.01)	0.10	0.000 (-0.003, 0.003)	0.86
<i>LEP, MIR129</i>	rs791595	A	G	1.00 (0.96, 1.05)	0.98	0.93 (0.84, 1.03)	0.17	1.01 (0.97, 1.06)	0.57	1.02 (0.96, 1.08)	0.59	1.00 (0.93, 1.07)	0.96	1.01 (0.94, 1.08)	0.87	0.000 (-0.004, 0.004)	0.98
<i>KLF14</i>	rs972283	G	A	1.02 (0.99, 1.04)	0.27	0.97 (0.91, 1.03)	0.28	1.03 (1.00, 1.06)	0.07	1.03 (0.99, 1.07)	0.18	1.00 (0.96, 1.05)	0.95	1.01 (0.96, 1.06)	0.78	-0.001 (-0.003, 0.002)	0.69
<i>ANK1</i>	rs515071	G	A	1.02 (0.98, 1.06)	0.43	1.00 (0.92, 1.09)	0.92	1.02 (0.98, 1.06)	0.39	1.00 (0.95, 1.06)	0.88	0.98 (0.92, 1.04)	0.43	0.99 (0.93, 1.06)	0.81	0.000 (-0.003, 0.003)	0.89
<i>TP53INP1</i>	rs896854	T	C	1.02 (1.00, 1.05)	0.07	1.04 (0.98, 1.10)	0.18	1.02 (0.99, 1.05)	0.11	1.00 (0.96, 1.03)	0.82	1.02 (0.98, 1.07)	0.31	0.99 (0.94, 1.04)	0.67	0.001 (-0.002, 0.003)	0.48
<i>SLC30A8</i>	rs13266634	C	T	1.03 (1.00, 1.05)	0.02	1.02 (0.97, 1.07)	0.50	1.03 (1.00, 1.06)	0.02	1.05 (1.02, 1.09)	4.85×10 ⁻³	1.04 (1.00, 1.08)	0.05	1.02 (0.98, 1.07)	0.38	0.000 (-0.002, 0.003)	0.79
<i>GLIS3</i>	rs7041847	A	G	1.01 (0.99, 1.03)	0.45	1.04 (0.98, 1.09)	0.19	1.00 (0.98, 1.03)	0.73	1.02 (0.98, 1.05)	0.37	1.00 (0.96, 1.05)	0.88	1.00 (0.95, 1.05)	0.96	0.000 (-0.003, 0.002)	0.75
<i>PTPRD</i>	rs17584499	T	C	0.98 (0.94, 1.02)	0.22	1.01 (0.92, 1.10)	0.86	0.97 (0.93, 1.01)	0.16	1.01 (0.95, 1.07)	0.75	0.96 (0.89, 1.03)	0.21	1.04 (0.96, 1.12)	0.31	-0.001 (-0.005, 0.003)	0.52

Nearby Genes	SNP	R	O	Ischaemic stroke (n=17,097 cases)		Lacunar ischaemic stroke (n=3,173 cases)		Non-lacunar ischaemic stroke (n=13,924 cases)		Intra-cerebral haemorrhage (6,973 cases)		Major coronary event (n= 5,081 cases)		Presence of plaque (n= 6,819 cases)		cIMT, mm (n= 21,971)	
				OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	β (95% CI)	P
<i>CDKN2A/B</i>	rs944801	C	G	1.01 (0.97, 1.06)	0.59	0.96 (0.88, 1.06)	0.45	1.02 (0.98, 1.07)	0.33	0.97 (0.91, 1.02)	0.25	1.10 (1.02, 1.18)	0.01	1.08 (1.01, 1.16)	0.04	0.002 (-0.002, 0.005)	0.37
<i>CDKN2A/B</i>	rs10811661	T	C	1.02 (1.00, 1.04)	0.12	1.00 (0.95, 1.06)	0.95	1.02 (1.00, 1.05)	0.08	0.99 (0.95, 1.02)	0.41	1.01 (0.97, 1.05)	0.67	0.97 (0.92, 1.01)	0.15	0.000 (-0.002, 0.002)	0.89
<i>DMRTA1</i>	rs1575972	T	A	0.97 (0.89, 1.05)	0.48	1.06 (0.87, 1.28)	0.56	0.95 (0.87, 1.04)	0.29	1.02 (0.91, 1.14)	0.77	1.01 (0.88, 1.15)	0.92	1.00 (0.88, 1.15)	0.95	0.000 (-0.006, 0.007)	0.96
<i>TLE4/CHCHD9</i>	rs13292136	C	T	0.99 (0.95, 1.04)	0.79	0.99 (0.90, 1.08)	0.76	1.00 (0.95, 1.04)	0.93	1.01 (0.95, 1.08)	0.65	1.00 (0.93, 1.07)	0.91	0.96 (0.88, 1.04)	0.31	-0.002 (-0.006, 0.002)	0.28
<i>TLE1</i>	rs2796441	G	A	1.01 (0.98, 1.04)	0.73	1.01 (0.94, 1.07)	0.83	1.01 (0.97, 1.04)	0.76	0.99 (0.95, 1.03)	0.52	1.06 (1.01, 1.11)	0.02	0.99 (0.94, 1.04)	0.63	0.001 (-0.002, 0.003)	0.47
<i>GPSM1</i>	rs11787792	A	G	1.07 (0.99, 1.16)	0.10	1.10 (0.92, 1.30)	0.29	1.06 (0.97, 1.16)	0.17	1.01 (0.91, 1.12)	0.89	1.03 (0.90, 1.18)	0.70	1.06 (0.93, 1.20)	0.41	0.002 (-0.004, 0.009)	0.46
<i>CDC123</i>	rs10906115	A	G	1.00 (0.98, 1.03)	0.77	1.03 (0.97, 1.09)	0.33	1.00 (0.97, 1.03)	0.90	0.99 (0.96, 1.03)	0.62	1.00 (0.96, 1.05)	0.86	1.01 (0.97, 1.06)	0.54	0.002 (0.000, 0.004)	0.11
<i>VPS26A</i>	rs1802295	T	C	0.97 (0.94, 1.01)	0.20	0.98 (0.89, 1.07)	0.59	0.97 (0.93, 1.02)	0.21	1.00 (0.94, 1.06)	0.95	1.02 (0.96, 1.09)	0.52	0.95 (0.88, 1.02)	0.16	0.000 (-0.003, 0.004)	0.86
<i>ZMIZ1</i>	rs12571751	A	G	1.02 (0.99, 1.05)	0.23	1.00 (0.94, 1.07)	0.90	1.02 (0.99, 1.05)	0.21	0.98 (0.95, 1.02)	0.42	1.03 (0.98, 1.08)	0.21	1.07 (1.02, 1.12)	5.24×10 ⁻³	0.003 (0.001, 0.005)	0.02
<i>HHEX/IDE</i>	rs1111875	C	T	1.03 (1.01, 1.06)	0.01	0.98 (0.92, 1.04)	0.47	1.05 (1.02, 1.08)	2.30×10 ⁻³	1.00 (0.96, 1.04)	0.93	0.97 (0.93, 1.02)	0.26	0.99 (0.93, 1.04)	0.58	0.001 (-0.002, 0.003)	0.59
<i>TCF7L2</i>	rs7901695	C	T	0.99 (0.92, 1.05)	0.67	1.04 (0.90, 1.20)	0.60	0.98 (0.91, 1.05)	0.50	0.98 (0.89, 1.08)	0.71	0.95 (0.85, 1.07)	0.40	1.09 (0.96, 1.24)	0.17	0.005 (-0.001, 0.011)	0.12
<i>GRK5</i>	rs10886471	C	T	1.01 (0.98, 1.04)	0.40	1.01 (0.95, 1.08)	0.73	1.01 (0.98, 1.05)	0.50	1.01 (0.97, 1.06)	0.55	1.00 (0.95, 1.05)	0.92	1.02 (0.96, 1.08)	0.47	-0.001 (-0.004, 0.002)	0.64
<i>MIR4686</i>	rs7107784	G	A	1.02 (0.97, 1.07)	0.41	1.07 (0.96, 1.18)	0.21	1.01 (0.96, 1.06)	0.70	1.03 (0.96, 1.09)	0.40	1.03 (0.95, 1.11)	0.45	1.06 (0.98, 1.14)	0.17	0.005 (0.001, 0.009)	8.70×10 ⁻³
<i>KCNQ1</i>	rs231361	A	G	1.00 (0.96, 1.03)	0.89	0.99 (0.92, 1.07)	0.80	1.00 (0.96, 1.04)	0.97	1.01 (0.96, 1.06)	0.70	1.04 (0.98, 1.10)	0.20	0.95 (0.90, 1.01)	0.09	-0.001 (-0.004, 0.001)	0.34
<i>KCNQ1</i>	rs2237892	C	T	1.00 (0.97, 1.03)	0.96	1.00 (0.95, 1.06)	0.92	1.00 (0.97, 1.03)	0.91	1.00 (0.97, 1.04)	0.89	1.03 (0.98, 1.08)	0.20	1.05 (1.00, 1.11)	0.04	0.001 (-0.001, 0.004)	0.37
<i>KCNJ11</i>	rs5215	C	T	1.01 (0.98, 1.03)	0.65	1.04 (0.98, 1.10)	0.17	1.00 (0.97, 1.03)	0.98	0.99 (0.96, 1.03)	0.75	1.01 (0.97, 1.05)	0.71	1.01 (0.96, 1.06)	0.80	0.001 (-0.001, 0.004)	0.23
<i>ARAP1</i>	rs1552224	A	C	1.00 (0.96, 1.04)	0.96	1.00 (0.91, 1.10)	0.94	1.00 (0.95, 1.04)	0.89	0.97 (0.91, 1.03)	0.33	1.06 (0.98, 1.14)	0.15	1.01 (0.93, 1.10)	0.85	0.005 (0.001, 0.010)	0.01
<i>CCND2</i>	rs11063069	G	A	0.96 (0.90, 1.03)	0.23	0.99 (0.86, 1.14)	0.90	0.96 (0.89, 1.03)	0.20	1.03 (0.94, 1.12)	0.58	0.95 (0.85, 1.05)	0.31	1.00 (0.90, 1.11)	0.96	-0.002 (-0.007, 0.004)	0.55
<i>KLHDC5</i>	rs10842994	C	T	0.99 (0.96, 1.03)	0.76	0.94 (0.87, 1.02)	0.16	1.00 (0.96, 1.04)	0.93	0.97 (0.93, 1.02)	0.26	1.04 (0.98, 1.10)	0.24	0.98 (0.92, 1.04)	0.50	0.001 (-0.002, 0.004)	0.68
<i>FAM60A</i>	rs147538848	A	G	1.04 (1.00, 1.09)	0.03	1.04 (0.96, 1.14)	0.35	1.05 (1.00, 1.09)	0.04	1.04 (0.99, 1.10)	0.12	0.99 (0.93, 1.06)	0.83	1.01 (0.95, 1.08)	0.79	-0.002 (-0.005, 0.001)	0.16
<i>HMGA2</i>	rs1531343	C	G	0.94 (0.90, 0.98)	8.42×10 ⁻³	0.96 (0.87, 1.06)	0.40	0.94 (0.89, 0.99)	0.01	0.96 (0.91, 1.02)	0.20	0.93 (0.87, 1.00)	0.06	1.00 (0.93, 1.07)	0.97	0.000(-0.003, 0.004)	0.96
<i>TSPAN8/LGR5</i>	rs7961581	C	T	0.98 (0.95, 1.01)	0.18	0.99 (0.93, 1.06)	0.76	0.98 (0.95, 1.01)	0.16	1.00 (0.95, 1.04)	0.87	0.97 (0.92, 1.02)	0.26	0.99 (0.94, 1.05)	0.83	-0.001 (-0.004, 0.002)	0.43
<i>MPHOSPH9</i>	rs4275659	C	T	0.97 (0.95, 1.00)	0.09	0.98 (0.92, 1.05)	0.64	0.97 (0.94, 1.01)	0.12	0.95 (0.91, 0.99)	9.40×10 ⁻³	0.98 (0.93, 1.03)	0.42	1.01 (0.96, 1.06)	0.82	0.001 (-0.002, 0.003)	0.60
<i>SPRY2</i>	rs1359790	G	A	1.01 (0.98, 1.03)	0.58	1.01 (0.96, 1.08)	0.63	1.01 (0.98, 1.04)	0.64	1.02 (0.98, 1.06)	0.39	1.01 (0.96, 1.06)	0.71	1.04 (0.99, 1.10)	0.11	0.000 (-0.002, 0.003)	0.83
<i>RASGRP1</i>	rs7403531	T	C	1.02 (1.00, 1.05)	0.08	1.06 (1.00, 1.12)	0.05	1.01 (0.98, 1.04)	0.40	1.01 (0.97, 1.05)	0.74	1.02 (0.98, 1.07)	0.32	1.02 (0.97, 1.07)	0.38	0.000 (-0.002, 0.003)	0.89
<i>INAFM2</i>	rs67839313	C	T	0.98 (0.94, 1.02)	0.26	0.90 (0.83, 0.99)	0.02	1.00 (0.96, 1.04)	0.92	0.99 (0.94, 1.04)	0.57	1.00 (0.94, 1.06)	0.95	1.01 (0.95, 1.07)	0.81	0.001 (-0.002, 0.004)	0.34
<i>VPS13C</i>	rs7172432	A	G	1.00 (0.97, 1.02)	0.77	0.96 (0.91, 1.02)	0.18	1.00 (0.98, 1.03)	0.84	0.99 (0.96, 1.03)	0.68	0.99 (0.95, 1.03)	0.56	1.05 (1.00, 1.10)	0.07	0.000 (-0.002, 0.003)	0.75
<i>HMG20A</i>	rs7178572	G	A	0.99 (0.97, 1.02)	0.55	0.98 (0.92, 1.03)	0.43	1.00 (0.97, 1.02)	0.74	1.00 (0.96, 1.04)	0.90	0.98 (0.94, 1.03)	0.44	1.02 (0.97, 1.07)	0.46	-0.002 (-0.004, 0.001)	0.20
<i>ZFAND6</i>	rs11634397	G	A	0.99 (0.95, 1.04)	0.75	1.06 (0.97, 1.16)	0.23	0.98 (0.93, 1.02)	0.33	1.01 (0.95, 1.07)	0.87	0.96 (0.90, 1.04)	0.31	0.97 (0.90, 1.05)	0.49	-0.001 (-0.005, 0.004)	0.80
<i>AP3S2</i>	rs2028299	C	A	1.01 (0.98, 1.04)	0.49	1.01 (0.95, 1.08)	0.73	1.01 (0.98, 1.04)	0.60	0.99 (0.95, 1.03)	0.65	0.97 (0.92, 1.02)	0.20	1.08 (1.02, 1.15)	7.02×10 ⁻³	0.003 (0.000,0.006)	0.07
<i>PRC1</i>	rs8042680	A	C	0.98 (0.88, 1.11)	0.78	0.94 (0.74, 1.19)	0.62	1.00 (0.88, 1.14)	0.94	0.92 (0.79, 1.09)	0.34	1.11 (0.90, 1.36)	0.32	1.11 (0.87, 1.42)	0.41	-0.006 (-0.018, 0.006)	0.33
<i>FTO</i>	rs9939609	A	T	1.05 (1.02, 1.09)	5.47×10 ⁻³	0.98 (0.90, 1.06)	0.57	1.07 (1.03, 1.11)	9.02×10 ⁻⁴	1.05 (1.00, 1.11)	0.06	1.03 (0.97, 1.10)	0.36	0.99 (0.93, 1.07)	0.87	-0.002 (-0.005, 0.002)	0.29
<i>BCAR1</i>	rs7202877	T	G	1.00 (0.97, 1.04)	0.81	1.05 (0.97, 1.14)	0.25	1.00 (0.96, 1.04)	0.84	1.03 (0.98, 1.08)	0.21	1.01 (0.95, 1.07)	0.81	1.04 (0.98, 1.11)	0.17	0.003 (0.000, 0.006)	0.07
<i>SRR</i>	rs4523957	T	G	0.95 (0.93, 0.98)	2.79×10 ⁻⁴	0.98 (0.93, 1.04)	0.59	0.95 (0.92, 0.98)	3.45×10 ⁻⁴	0.92 (0.89, 0.96)	8.97×10 ⁻⁵	0.99 (0.94, 1.03)	0.59	1.00 (0.95, 1.06)	0.86	0.001 (-0.001, 0.004)	0.37
<i>SLC16A13</i>	rs312457	G	A	0.98 (0.94, 1.02)	0.33	0.92 (0.84, 1.02)	0.11	0.99 (0.94, 1.04)	0.67	1.00 (0.94, 1.06)	0.96	1.01 (0.94, 1.08)	0.83	1.01 (0.94, 1.09)	0.74	-0.002 (-0.005, 0.002)	0.39
<i>HNF1B</i>	rs4430796	G	A	1.00 (0.97, 1.03)	0.94	0.99 (0.93, 1.05)	0.73	1.00 (0.97, 1.03)	0.83	0.96 (0.92, 1.00)	0.05	1.00 (0.95, 1.05)	0.97	0.99 (0.94, 1.05)	0.82	0.000 (-0.002, 0.003)	0.86
<i>LAMA1</i>	rs7234998	T	C	1.01 (0.98, 1.04)	0.45	1.07 (1.00, 1.15)	0.05	1.00 (0.97, 1.04)	0.95	0.99 (0.94, 1.03)	0.50	0.96 (0.92, 1.01)	0.15	0.99 (0.94, 1.04)	0.60	0.000 (-0.003, 0.002)	0.76
<i>MC4R</i>	rs12970134	A	G	1.00 (0.97, 1.04)	0.77	0.99 (0.93, 1.06)	0.88	1.01 (0.97, 1.04)	0.70	1.01 (0.96, 1.05)	0.79	1.01 (0.96, 1.07)	0.66	1.04 (0.98, 1.10)	0.22	0.002 (-0.001, 0.005)	0.12
<i>BCL2</i>	rs12454712	T	C	1.01 (0.98, 1.04)	0.53	1.03 (0.96, 1.09)	0.43	1.01 (0.98, 1.04)	0.64	1.05 (1.01, 1.09)	0.02	1.00 (0.96, 1.05)	0.87	1.01 (0.96, 1.06)	0.66	0.000 (-0.002, 0.003)	0.68
<i>CILP2-GATAD2A</i>	rs10401969	C	T	0.99 (0.94, 1.04)	0.62	1.01 (0.90, 1.13)	0.87	0.99 (0.93, 1.04)	0.59	0.96 (0.90, 1.02)	0.21	1.01 (0.93, 1.09)	0.88	0.98 (0.91, 1.07)	0.69	0.001 (-0.003, 0.005)	0.50
<i>PEPD</i>	rs3786897	A	G	1.02 (0.99, 1.05)	0.22	1.05 (0.98, 1.11)	0.17	1.01 (0.98, 1.04)	0.42	1.02 (0.98, 1.06)	0.32	1.00 (0.96, 1.05)	0.84	1.07 (1.02, 1.12)	6.98×10 ⁻³	0.005 (0.003, 0.008)	1.14×10 ⁻⁵
<i>TOMM40-APOE</i>	rs157582	C	T	1.01 (0.97, 1.05)	0.57	0.96 (0.88, 1.04)	0.29	1.02 (0.98, 1.06)	0.33	0.98 (0.93, 1.03)	0.42	0.96 (0.90, 1.02)	0.15	1.11 (1.04, 1.18)	7.74×10 ⁻⁴	0.007 (0.004, 0.010)	1.65×10 ⁻⁶
<i>GIPR</i>	rs8108269	G	T	1.00 (0.97, 1.03)	0.98	0.99 (0.93, 1.06)	0.86	1.00 (0.97, 1.03)	0.93	1.02 (0.98, 1.06)	0.36	0.97 (0.93, 1.02)	0.19	1.01 (0.96, 1.06)	0.64	0.000 (-0.003, 0.002)	0.86
<i>HNF4A</i>	rs6017317	G	T	1.00 (0.97, 1.02)	0.83	1.04 (0.98, 1.10)	0.17	0.99 (0.96, 1.02)	0.40	1.01 (0.98, 1.05)	0.56	1.03 (0.99, 1.08)	0.13	0.98 (0.93, 1.03)	0.37	-0.002 (-0.004, 0.001)	0.17

O: other allele; OR: odds ratio; R: risk allele; SNP: single nucleotide polymorphisms

Supplementary Table 4. Baseline characteristics of participants by type 2 diabetes status in full study population

Characteristics*	Type 2 diabetes			Total (n=512,678)
	None (n=466,083)	Prevalent† (n=30,264)	Incident (n=16,331)	
Age and socioeconomic factors				
Men, %	41.4	39.4	39.5	41.0
Age, mean (SD), years	51.5 (10.6)	58.2 (9.6)	55.2 (9.8)	52.0 (10.7)
Living in urban area, %	43.3	57.2	41.2	44.1
Lifestyle factors				
≤6 years of education‡, %	50.8	50.8	51.6	50.8
Annual household income ≤10,000 RMB, %	28.3	27.5	27.7	28.2
Ever regular smoker, %				
Men§	74.2	73.7	73.6	74.4
Women	3.3	3.6	3.7	3.2
Ever regular alcohol drinker, %				
Men	41.9	43.4	42.1	42.0
Women	3.0	2.5	2.8	2.9
Physical activity, mean (SD), MET-h/d	21.2 (13.9)	18.9 (11.9)	20.4 (13.8)	21.1 (13.9)
Physical and blood-based measurements, mean (SD)				
Standing Height, cm	158.7 (8.3)	158.8 (8.4)	159.0 (8.3)	158.7 (8.3)
BMI, kg/m ²	23.5 (3.3)	24.9 (3.6)	25.6 (3.6)	23.7 (3.4)
Waist circumference, cm	79.8 (9.6)	84.9 (10.0)	85.8 (10.1)	80.3 (9.8)
Hip circumference, cm	90.8 (6.8)	92.3 (7.6)	93.7 (7.2)	90.9 (6.9)
Waist adjusted for hip, cm	80.0 (6.2)	83.4 (6.4)	82.8 (6.3)	80.3 (6.3)
Waist-to-hip ratio	0.88 (0.07)	0.92 (0.07)	0.91 (0.07)	0.88 (0.07)
Percent body fat, %	27.7 (8.3)	30.4 (8.7)	31.7 (8.7)	27.9 (8.4)
Systolic blood pressure, mmHg	130.4 (20.9)	138.3 (22.6)	136.6 (22.1)	131.1 (21.3)
Diastolic blood pressure, mmHg	77.6 (11.1)	80.5 (11.4)	80.7 (11.3)	77.8 (11.2)
Random plasma glucose, mmol/L	5.7 (1.1)	12.6 (5.6)	6.4 (1.4)	6.1 (2.3)
Total cholesterol , mmol/L	4.6 (1.0)	4.8 (1.2)	4.6 (1.0)	4.7 (1.0)
Triglycerides , mmol/L	1.9 (1.5)	2.8 (2.3)	2.5 (1.8)	2.0 (1.6)
LDL-C , mmol/L	2.4 (0.7)	2.4 (0.8)	2.3 (0.7)	2.4 (0.7)
HDL-C , mmol/L	1.2 (0.3)	1.1 (0.3)	1.1 (0.3)	1.2 (0.3)
Personal medical history, %				
Diabetes		45.7		3.2
Cardiovascular disease§	4.1	7.7	6.3	4.5
Family history, %				
Diabetes	6.2	18.9	12.6	7.1
Cardiovascular disease¶	20.5	22.5	23.0	20.7

*Standardised to age, sex and study area structure of the study population. *p*-values for differences between participants with no, prevalent and incident type 2 diabetes <0.005, unless otherwise indicated.

†Self-reported or screen-detected type 2 diabetes at baseline

‡*p*=0.1; §*p*=0.04

||Data available for 18,175 participants

¶Coronary heart disease, stroke or transient ischaemic attack

BMI: body mass index; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; MET h/d: metabolic equivalent of task hours per day

Supplementary Table 5. Genetic correlation between type 2 diabetes and cardiovascular diseases in China Kadoorie Biobank*

Outcome	Genetic correlation (SE)	<i>P</i>
Ischaemic stroke	0.14 (0.05)	0.0020
Lacunar	0.01 (0.07)	0.93
Non-lacunar	0.18 (0.05)	0.00016
Intracerebral haemorrhage	0.08 (0.04)	0.050
Major coronary event	0.15 (0.05)	0.0028

*Estimated using LD score regression (PMID: 25642630) among the full genome-wide genotyped CKB population (n=96,217)

Supplementary Table 6. Estimates of the association between genetically-predicted type 2 diabetes and cardiovascular diseases

Outcome	No. of cases	Model 1*		Model 2†		Model 3‡	
		Risk estimate (95% CI)§	P	Risk estimate (95% CI)§	P	Risk estimate (95% CI)§	P
Ischaemic stroke	17,097	1.08 (1.02, 1.14)	4.62×10 ⁻³	1.09 (1.04, 1.15)	3.85×10 ⁻⁴	1.07 (1.02, 1.13)	8.74×10 ⁻³
Lacunar	3,173	1.03 (0.91, 1.16)	0.63	1.05 (0.95, 1.17)	0.35	1.02 (0.90, 1.14)	0.78
Non-lacunar	13,924	1.09 (1.03, 1.16)	3.06×10 ⁻³	1.10 (1.04, 1.16)	3.19×10 ⁻⁴	1.08 (1.02, 1.15)	5.99×10 ⁻³
Intracerebral haemorrhage	6,973	1.01 (0.94, 1.10)	0.76	1.02 (0.95, 1.09)	0.65	1.00 (0.92, 1.09)	0.97
Fatal total stroke	4,319	1.01 (0.91, 1.11)	0.88	1.01 (0.92, 1.10)	0.83	1.01 (0.92, 1.09)	0.91
Major coronary event	5,081	1.12 (1.02, 1.23)	0.01	1.12 (1.03, 1.22)	9.24×10 ⁻³	1.11 (1.01, 1.22)	0.02
Non-fatal myocardial infarction	2,033	1.15 (1.00, 1.32)	0.05	1.15 (1.02, 1.31)	0.03	1.14 (1.00, 1.31)	0.06
Fatal ischaemic heart disease	3,048	1.09 (0.97, 1.22)	0.15	1.08 (0.97, 1.19)	0.17	1.08 (0.96, 1.21)	0.19
Small vessel disease	9,986	1.02 (0.95, 1.09)	0.60	1.03 (0.96, 1.09)	0.43	1.01 (0.94, 1.08)	0.83
Large vessel disease¶	18,249	1.10 (1.04, 1.15)	5.24×10 ⁻⁴	1.10 (1.05, 1.16)	5.60×10 ⁻⁵	1.09 (1.03, 1.15)	1.43×10 ⁻³
Presence of plaque	6,819	1.17 (1.05, 1.29)	3.74×10 ⁻³	1.15 (1.05, 1.27)	3.18×10 ⁻³	1.16 (1.05, 1.29)	4.52×10 ⁻³
cIMT, mm	21,971	0.011 (0.006, 0.016)	1.97×10 ⁻⁵	0.011 (0.007, 0.016)	1.67×10 ⁻⁶	0.011 (0.006, 0.015)	5.68×10 ⁻⁶
Cardiovascular mortality	9,006	1.03 (0.96, 1.11)	0.40	1.03 (0.96, 1.10)	0.40	1.02 (0.95, 1.10)	0.56
Microvascular diseases	1,140	2.80 (2.33, 3.36)	4.48×10 ⁻²⁸	2.65 (2.24, 3.14)	4.88×10 ⁻³⁰	2.75 (2.29, 3.29)	1.43×10 ⁻²⁷

*Adjusted for age, sex and study area

†Adjusted for age, sex, study area, BMI, waist circumference and body fat percentage

‡Adjusted for age, sex, study area and systolic blood pressure

§Odds ratio for binary outcomes and beta coefficient for cIMT (in native units), expressed per 1-unit higher log-odds of type 2 diabetes risk

||Lacunar stroke and intra-cerebral haemorrhage

¶Non-lacunar ischaemic stroke plus major coronary event

Genetic analyses conducted using externally-weighted GRS calculated based on 48 T2D related SNPs (T2D-GRS48w)

cIMT: carotid intima-media thickness

Supplementary Table 7. Sensitivity analyses using 48 SNP type 2 diabetes genetic risk score

Outcome	Dataset*	No. of cases	Externally-weighted		Unweighted		Internally-weighted with 1000-fold cross validation		Excluding 5 lipid and/or CVD associated SNPs	
			Estimate† (95% CI)	P	Estimate† (95% CI)	P	Estimate† (95% CI)	P	Estimate† (95% CI)	P
Ischaemic stroke										
	Pop+	17,097	1.08 (1.02, 1.14)	4.62×10 ⁻³	1.07 (1.00, 1.14)	0.03	1.08 (1.02, 1.14)	4.92×10 ⁻³	1.08 (1.02, 1.14)	4.93×10 ⁻³
	Pop	13,362	1.09 (1.02, 1.15)	6.86×10 ⁻³	1.09 (1.01, 1.16)	0.02	1.08 (1.02, 1.15)	7.59×10 ⁻³	1.08 (1.02, 1.15)	9.94×10 ⁻³
Lacunar										
	Pop+	3,173	1.03 (0.91, 1.16)	0.63	1.06 (0.92, 1.22)	0.41	1.03 (0.91, 1.15)	0.67	1.03 (0.92, 1.16)	0.61
	Pop	2,587	0.99 (0.87, 1.13)	0.92	1.03 (0.89, 1.20)	0.68	0.99 (0.87, 1.12)	0.84	0.99 (0.87, 1.13)	0.88
Non-lacunar										
	Pop+	13,924	1.09 (1.03, 1.16)	3.06×10 ⁻³	1.07 (1.00, 1.14)	0.05	1.09 (1.03, 1.15)	2.98×10 ⁻³	1.09 (1.03, 1.15)	3.73×10 ⁻³
	Pop	10,775	1.11 (1.04, 1.18)	2.00×10 ⁻³	1.10 (1.02, 1.18)	0.02	1.10 (1.04, 1.18)	1.20×10 ⁻³	1.10 (1.03, 1.17)	3.26×10 ⁻³
Intracerebral haemorrhage										
	Pop+	6,973	1.01 (0.94, 1.10)	0.76	1.01 (0.92, 1.11)	0.85	1.00 (0.92, 1.08)	0.99	0.99 (0.91, 1.07)	0.76
	Pop	2,682	1.00 (0.88, 1.13)	1.00	1.00 (0.87, 1.16)	0.95	0.99 (0.88, 1.12)	0.88	0.98 (0.87, 1.10)	0.71
Major coronary event										
	Pop+	5,081	1.12 (1.02, 1.23)	0.01	1.09 (0.98, 1.22)	0.10	1.13 (1.03, 1.23)	0.01	1.13 (1.03, 1.23)	0.01
	Pop	2,775	1.11 (0.98, 1.25)	0.10	1.09 (0.94, 1.25)	0.26	1.11 (0.98, 1.25)	0.10	1.10 (0.97, 1.24)	0.14
Presence of plaque										
	Pop	6,819	1.17 (1.05, 1.29)	3.74×10 ⁻³	1.19 (1.06, 1.34)	4.51×10 ⁻³	1.17 (1.05, 1.29)	3.37×10 ⁻³	1.17 (1.05, 1.29)	3.25×10 ⁻³
cIMT, mm										
	Pop	21,971	0.011 (0.006, 0.016)	1.97×10 ⁻⁵	0.013 (0.007, 0.018)	3.38×10 ⁻⁵	0.011 (0.006, 0.016)	1.15×10 ⁻⁵	0.011 (0.006, 0.016)	1.75×10 ⁻⁵

*Pop: randomly selected population-based sample of 148,512 participants; Pop+: Pop supplemented with cases of disease of interest.

†Adjusted for age, sex, and study area. Odds Ratio (95% CI) for binary outcomes and beta coefficient (95%CI) for cIMT (in native units), expressed per 1-unit higher log-odds of type 2 diabetes risk

Supplementary Table 8. Sensitivity analyses using 86 SNP type 2 diabetes genetic risk score

Outcome	Dataset*	No. of Cases	Externally-weighted		Unweighted		Internally-weighted with 1000-fold cross validation		Excluding 14 lipid and/or CVD associated SNPs	
			Estimate† (95% CI)	P	Estimate† (95% CI)	P	Estimate† (95% CI)	P	Estimate† (95% CI)	P
Ischaemic stroke										
	Pop+	12,953	1.06 (1.00, 1.12)	0.04	1.07 (1.01, 1.14)	0.03	1.08 (1.02, 1.14)	0.01	1.08 (1.02, 1.14)	0.01
	Pop	9,218	1.07 (1.00, 1.14)	0.04	1.08 (1.00, 1.17)	0.04	1.08 (1.02, 1.16)	0.01	1.07 (1.00, 1.15)	0.05
Lacunar										
	Pop+	2,410	1.00 (0.88, 1.14)	0.96	1.06 (0.92, 1.22)	0.42	1.02 (0.90, 1.15)	0.76	1.03 (0.91, 1.17)	0.65
	Pop	1,824	0.96 (0.83, 1.10)	0.55	1.02 (0.87, 1.20)	0.77	0.97 (0.84, 1.11)	0.65	0.96 (0.83, 1.11)	0.58
Non-lacunar										
	Pop+	10,543	1.07 (1.01, 1.14)	0.02	1.07 (1.00, 1.15)	0.04	1.09 (1.02, 1.15)	5.98×10 ⁻³	1.09 (1.02, 1.16)	7.91×10 ⁻³
	Pop	7,394	1.10 (1.02, 1.18)	0.01	1.10 (1.01, 1.19)	0.03	1.11 (1.04, 1.19)	2.89×10 ⁻³	1.10 (1.02, 1.18)	0.01
Intracerebral haemorrhage										
	Pop+	6,383	0.95 (0.88, 1.03)	0.22	0.98 (0.90, 1.07)	0.68	0.96 (0.89, 1.04)	0.32	0.95 (0.88, 1.03)	0.15
	Pop	2,091	0.93 (0.82, 1.06)	0.28	0.96 (0.84, 1.11)	0.62	0.95 (0.84, 1.08)	0.42	0.91 (0.80, 1.04)	0.17
Major coronary event										
	Pop+	4,383	1.06 (0.97, 1.16)	0.20	1.08 (0.97, 1.19)	0.17	1.07 (0.98, 1.18)	0.12	1.08 (0.99, 1.19)	0.09
	Pop	2,077	1.06 (0.93, 1.20)	0.42	1.07 (0.93, 1.24)	0.34	1.05 (0.92, 1.19)	0.49	1.05 (0.92, 1.20)	0.48
Presence of plaque										
	Pop	6,705	1.23 (1.12, 1.35)	2.29×10 ⁻⁵	1.26 (1.13, 1.40)	2.86×10 ⁻⁵	1.21 (1.10, 1.32)	6.51×10 ⁻⁵	1.16 (1.06, 1.28)	1.94×10 ⁻³
cIMT, mm										
	Pop	21,971	0.014 (0.009, 0.018)	1.12×10 ⁻⁵	0.016 (0.010, 0.021)	5.74×10 ⁻⁹	0.014 (0.009, 0.018)	5.67×10 ⁻⁹	0.011 (0.006, 0.016)	4.02×10 ⁻⁶

*Pop: randomly selected population-based sample of 79,919 participants; Pop+: Pop supplemented with cases of disease of interest.

†Adjusted for age, sex, and study area. Odds Ratio (95% CI) for binary outcomes and beta coefficient (95%CI) for cIMT (in native units), expressed per 1-unit higher log-odds of type 2 diabetes risk

Supplementary Table 9. Estimates of the association between genetically-predicted type 2 diabetes and adiposity

Adiposity measure	GRS-BC*		GRS-IR†		GRS-Un‡		P_{het} BC vs IR
	β (95% CI)	<i>P</i>	β (95% CI)	<i>P</i>	β (95% CI)	<i>P</i>	
BMI, kg/m ²	-0.30 (-0.35, -0.24)	1.7×10^{-24}	-0.39 (-0.64, -0.14)	2.30×10^{-3}	-0.22 (-0.36, -0.09)	1.36×10^{-3}	0.49
Waist circumference, cm	-0.55 (-0.71, -0.39)	3.1×10^{-11}	-1.04 (-1.75, -0.33)	3.90×10^{-3}	-0.61 (-1.00, -0.23)	1.97×10^{-3}	0.18
Hip circumference, cm	-0.56 (-0.66, -0.45)	1.9×10^{-24}	-0.77 (-1.23, -0.30)	1.28×10^{-3}	-0.43 (-0.69, -0.17)	1.02×10^{-3}	0.39
WCadjHC, cm	0.06 (-0.04, 0.16)	0.26	-0.20 (-0.64, 0.23)	0.36	-0.14 (-0.39, 0.10)	0.24	0.25
Waist-to-hip ratio	-0.03 (-0.14, 0.09)	0.62	-0.41 (-0.92, 0.10)	0.11	-0.20 (-0.48, 0.08)	0.15	0.15
Percentage body fat, %	-0.38 (-0.49, -0.26)	1.20×10^{-10}	-1.51 (-2.01, -1.01)	3.70×10^{-9}	-0.39 (-0.66, -0.11)	6.12×10^{-3}	1.60×10^{-5}

*GRS comprises 24 SNPs

†GRS comprises 6 SNPs

‡GRS comprises 18 SNPs

GRS-BC: beta-cell function genetic risk score; GRS-IR: insulin resistance genetic risk score; GRS-Un: undefined T2D genetic risk score; WCadjHC: waist circumference adjusted for hip circumference

Supplementary Table 10. Estimates of the association between genetically-predicted type 2 diabetes and cardiovascular diseases using summary statistics-based two-sample Mendelian randomisation approaches in China Kadoorie Biobank*

Mendelian randomisation method	Ischaemic stroke		Lacunar ischaemic stroke		Non-lacunar ischaemic stroke		Haemorrhagic stroke		Major coronary event	
	Estimate (95% CI)†	P	Estimate (95% CI)†	P	Estimate (95% CI)†	P	Estimate (95% CI)†	P	Estimate (95% CI)†	P
48 type 2 diabetes variants										
Conventional‡	1.07 (1.02, 1.13)	7.33×10 ⁻³	1.03 (0.92, 1.14)	0.62	1.08 (1.02, 1.14)	6.15×10 ⁻³	1.01 (0.94, 1.09)	0.78	1.11 (1.02, 1.21)	0.02
Weighted median	1.07 (0.99, 1.16)	0.07	1.01 (0.87, 1.18)	0.88	1.11 (1.02, 1.2)	0.02	0.97 (0.87, 1.08)	0.57	1.14 (1.00, 1.29)	0.05
Weighted mode	1.06 (0.97, 1.16)	0.22	1.02 (0.87, 1.19)	0.85	1.04 (0.95, 1.15)	0.38	0.94 (0.84, 1.05)	0.3	1.15 (1.00, 1.32)	0.06
MR-Egger	1.11 (1.00, 1.24)	0.06	0.94 (0.75, 1.18)	0.59	1.16 (1.03, 1.30)	0.02	1.02 (0.87, 1.21)	0.77	1.22 (1.02, 1.46)	0.04
Intercept§	0.00 (-0.01, 0.01)	0.45	0.01 (-0.01, 0.03)	0.39	-0.01 (-0.02, 0.00)	0.22	0.00 (-0.02, 0.01)	0.86	-0.01 (-0.03, 0.01)	0.26
86 type 2 diabetes variants										
Conventional‡	1.05 (1.01, 1.10)	0.02	1.01 (0.92, 1.10)	0.88	1.06 (1.01, 1.12)	0.01	0.98 (0.92, 1.05)	0.6	1.09 (1.00, 1.18)	0.04
Weighted median	1.07 (1.00, 1.14)	0.05	1.01 (0.88, 1.16)	0.88	1.04 (0.97, 1.12)	0.27	0.94 (0.86, 1.04)	0.26	1.09 (0.97, 1.21)	0.14
Weighted mode	1.04 (0.97, 1.13)	0.29	0.99 (0.85, 1.15)	0.87	1.03 (0.95, 1.12)	0.42	0.94 (0.84, 1.04)	0.22	1.12 (0.98, 1.28)	0.09
MR-Egger	1.06 (0.96, 1.16)	0.26	0.87 (0.72, 1.06)	0.17	1.10 (0.99, 1.22)	0.08	0.93 (0.81, 1.08)	0.34	1.10 (0.93, 1.31)	0.28
Intercept§	0.00 (-0.01, 0.01)	0.95	0.01 (0.00, 0.03)	0.1	0.00 (-0.01, 0.01)	0.48	0.00 (-0.01, 0.02)	0.43	0.00 (-0.02, 0.01)	0.87

*Genetic estimates for T2D were derived from TransEthnic GWAS of T2D and genetic estimates for CVD were obtained from the CKB study

†Odds Ratio (95%CI) expressed as the relative risk of outcome per 1-unit higher log-odds of type 2 diabetes risk

‡Summary-statistics-based inverse-variance weighted two-sample Mendelian randomisation

§Intercept denotes the average pleiotropic effect across all variants, a non-zero intercept suggesting the presence of directional pleiotropy

Supplementary Table 11. Estimates of the association between genetically-predicted type 2 diabetes and cardiovascular diseases

Outcome	No. of Cases	GRS-BC*		GRS-IR†		GRS-Un‡	
		Risk Estimate (95% CI)§	<i>P</i>	Risk Estimate (95% CI)§	<i>P</i>	Risk Estimate (95% CI)§	<i>P</i>
Ischaemic stroke	17,097	1.10 (1.04, 1.17)	1.10×10 ⁻³	1.14 (0.86, 1.50)	0.36	0.97 (0.84, 1.11)	0.62
Lacunar	3,173	1.07 (0.94, 1.22)	0.32	0.70 (0.39, 1.29)	0.26	0.97 (0.72, 1.32)	0.86
Non-lacunar	13,924	1.11 (1.04, 1.18)	1.36×10 ⁻³	1.28 (0.95, 1.73)	0.11	0.96 (0.83, 1.12)	0.61
Intracerebral haemorrhage	6,973	0.99 (0.91, 1.09)	0.91	1.41 (0.94, 2.13)	0.10	1.00 (0.81, 1.22)	0.98
Major coronary event	5,081	1.13 (1.02, 1.25)	0.02	1.43 (0.88, 2.31)	0.15	1.02 (0.81, 1.30)	0.84
Presence of Plaque	6,819	1.16 (1.03, 1.30)	0.01	1.47 (0.86, 2.52)	0.16	1.14 (0.87, 1.48)	0.35
cIMT, mm	21,971	0.011 (0.005, 0.017)	1.37×10 ⁻⁴	0.026 (0.000, 0.053)	0.05	0.007 (-0.006, 0.020)	0.28

P for heterogeneity between associations of GRS-BC and GRS-IR >0.08 for all cardiovascular disease outcomes

*GRS comprises 24 SNPs

†GRS comprises 6 SNPs

‡GRS comprises 18 SNPs

§Adjusted for age, sex, and study area. Odds Ratio (95% CI) for binary outcomes and beta coefficient (95%CI) for cIMT (in native units), expressed per 1-unit higher log-odds of type 2 diabetes risk
 cIMT: carotid intima media thickness; GRS-BC: beta-cell function related SNPs; GRS-IR: insulin resistance related SNPs; GRS-Un: undefined SNPs

Supplementary Table 12. Estimates of the association between genetically-predicted type 2 diabetes and cardiovascular diseases using two-sample Mendelian randomisation approaches in European ancestry populations*

Mendelian randomisation method	Ischaemic stroke		Small vessel stroke		Large artery stroke		Intracerebral haemorrhage		Coronary heart disease	
	Estimate (95% CI)†	<i>P</i>	Estimate (95% CI)†	<i>P</i>	Estimate (95% CI)†	<i>P</i>	Estimate (95% CI)†	<i>P</i>	Estimate (95% CI)†	<i>P</i>
48 type 2 diabetes variants										
Conventional‡	1.12 (1.03, 1.22)	7.90×10 ⁻³	1.15 (0.97, 1.35)	0.11	1.24 (1.07, 1.44)	4.53×10 ⁻³	1.14 (0.93, 1.40)	0.20	1.09 (1.04, 1.15)	9.32×10 ⁻⁴
Weighted median	1.10 (0.96, 1.25)	0.17	1.20 (0.93, 1.55)	0.17	1.29 (1.02, 1.63)	0.03	1.00 (0.75, 1.34)	1.00	1.10 (1.04, 1.17)	5.99×10 ⁻⁴
Weighted mode	1.06 (0.91, 1.25)	0.46	1.19 (0.87, 1.64)	0.28	1.22 (0.92, 1.61)	0.18	1.03 (0.76, 1.39)	0.86	1.08 (0.98, 1.19)	0.15
MR-Egger	1.11 (0.96, 1.28)	0.18	1.20 (0.91, 1.59)	0.20	1.18 (0.92, 1.52)	0.19	1.01 (0.72, 1.44)	0.94	1.11 (1.01, 1.21)	0.03
Intercept	0.00 (-0.01, 0.01)	0.82	-0.01 (-0.03, 0.02)	0.67	0.00 (-0.02, 0.03)	0.65	0.01 (-0.02, 0.04)	0.42	0.00 (-0.01, 0.01)	0.71
86 type 2 diabetes variants										
Conventional‡	1.13 (1.05, 1.21)	5.13×10 ⁻⁴	1.19 (1.04, 1.38)	0.01	1.32 (1.16, 1.50)	2.27×10 ⁻⁵	1.12 (0.94, 1.34)	0.21	1.11 (1.05, 1.17)	7.72×10 ⁻⁵
Weighted median	1.10 (0.98, 1.24)	0.11	1.20 (0.94, 1.54)	0.14	1.30 (1.03, 1.64)	0.03	1.01 (0.76, 1.33)	0.96	1.10 (1.05, 1.16)	3.67×10 ⁻⁴
Weighted mode	1.05 (0.90, 1.23)	0.53	1.18 (0.87, 1.60)	0.30	1.35 (1.03, 1.77)	0.04	1.08 (0.80, 1.44)	0.62	1.08 (0.97, 1.20)	0.15
MR-Egger	1.12 (0.99, 1.26)	0.07	1.19 (0.93, 1.53)	0.17	1.20 (0.96, 1.50)	0.12	0.99 (0.73, 1.36)	0.97	1.08 (0.99, 1.19)	0.10
Intercept	0.00 (-0.01, 0.01)	0.84	0.00 (-0.02, 0.02)	0.99	0.01 (-0.01, 0.03)	0.31	0.01 (-0.01, 0.04)	0.36	0.00 (0.00, 0.01)	0.48

*Based on summary statistics from DIAGRAMv.4, CARDIoGRAMplusC4D GWAS consortium, ISGC consortium

†Odds Ratio (95%CI) expressed as the relative risk of outcome per 1-unit higher log-odds of type 2 diabetes risk

‡Inverse variance weighted MR

Supplementary Table 13. Sensitivity analyses of the association of genetically-predicted type 2 diabetes and cardiovascular diseases, stratified by study area

Outcome	Dataset*	Estimate† (95% CI)	<i>P</i>	<i>P</i> _{het‡}
Ischaemic stroke	Pop+	1.08 (1.03, 1.14)	3.86×10 ⁻³	0.38
	Pop	1.09 (1.03, 1.16)	5.84×10 ⁻³	0.52
Lacunar	Pop+	1.03 (0.91, 1.16)	0.62	0.56
	Pop	0.99 (0.87, 1.14)	0.93	0.21
Non-lacunar	Pop+	1.10 (1.03, 1.16)	2.47×10 ⁻³	0.28
	Pop	1.11 (1.04, 1.19)	1.71×10 ⁻³	0.62
Intracerebral haemorrhage	Pop+	1.01 (0.94, 1.10)	0.72	0.12
	Pop	1.00 (0.88, 1.14)	0.97	0.06
Major coronary event	Pop+	1.13 (1.03, 1.24)	0.01	0.48
	Pop	1.11 (0.98, 1.26)	0.09	0.56
Presence of plaque	Pop	1.17 (1.05, 1.30)	4.51×10 ⁻³	0.72
	Pop	0.011 (0.006, 0.016)	9.35×10 ⁻⁶	0.37

*Pop: randomly selected population-based sample of 148,512 participants; Pop+: Pop supplemented with cases of disease of interest

†Adjusted for age, sex and study area in the first-stage regression of GRS-T2D48w with type 2 diabetes, and, in the second-stage regression of GRS-T2D48w with risk of cardiovascular diseases, adjusted for age and sex and inverse variance weighted meta-analysed over study areas. Odds Ratio (95% CI) for binary outcomes and beta coefficient (95% CI) for cIMT (in native units), expressed per 1-unit higher log-odds of type 2 diabetes risk.

‡*p* for heterogeneity of effect estimate across 10 regions

Supplementary Table 14. Power estimates for detection of associations between genetically-predicted type 2 diabetes and cardiovascular diseases

Outcome	No. of events	OR	Power
Ischaemic stroke	17,097	1.08	0.86
Lacunar	3,173	1.03	0.08
Non-lacunar	13,924	1.09	0.87
Intracerebral haemorrhage	6,973	1.04	0.17
Major coronary event	5,081	1.12	0.72

OR: odds ratio of cardiovascular disease outcome per 1-unit higher log-odds of type 2 diabetes risk
 Total participants: 159,528
 Log-odds ratio of type 2 diabetes per 1 SD higher T2D-GRS48w:0.32

Supplementary Table 15. Estimates of the association between genetically-predicted type 2 diabetes (based on SNPs associated with type 2 diabetes at genome-wide significance level) and cardiovascular diseases

Outcome	No. of cases	Model 1*		Model 2†		Model 3‡	
		Risk estimate (95% CI)§	P	Risk estimate (95% CI)§	P	Risk estimate (95% CI)§	P
Ischaemic stroke	17,097	1.08 (1.02, 1.15)	7.78×10 ⁻³	1.09 (1.04, 1.16)	9.38×10 ⁻⁴	1.08 (1.01, 1.14)	0.02
Lacunar	3,173	0.99 (0.87, 1.13)	0.86	1.01 (0.90, 1.14)	0.86	0.97 (0.86, 1.11)	0.69
Non-lacunar	13,924	1.10 (1.04, 1.17)	2.29×10 ⁻³	1.11 (1.05, 1.18)	2.90×10 ⁻⁴	1.09 (1.03, 1.17)	5.28×10 ⁻³
Intracerebral haemorrhage	6,973	0.97 (0.89, 1.05)	0.46	0.98 (0.90, 1.06)	0.55	0.95 (0.87, 1.04)	0.28
Major coronary event	5,081	1.11 (1.00, 1.22)	0.05	1.10 (1.00, 1.21)	0.04	1.09 (0.99, 1.21)	0.09
Small vessel disease	9,986	0.97 (0.90, 1.05)	0.47	0.98 (0.92, 1.05)	0.63	0.96 (0.89, 1.03)	0.29
Large vessel disease¶	18,249	1.10 (1.04, 1.16)	1.24×10 ⁻³	1.10 (1.05, 1.16)	2.01×10 ⁻⁴	1.09 (1.03, 1.15)	3.34×10 ⁻³
Presence of plaque	6,819	1.13 (1.01, 1.26)	0.04	1.12 (1.01, 1.24)	0.03	1.12 (1.00, 1.25)	0.05
cIMT, mm	21,971	0.009 (0.004, 0.015)	7.49×10 ⁻⁴	0.010 (0.005, 0.015)	8.16×10 ⁻⁵	0.009 (0.004, 0.014)	2.58×10 ⁻⁴
Microvascular diseases	1,140	2.96 (2.42, 3.61)	3.28×10 ⁻²⁶	2.79 (2.32, 3.35)	1.19×10 ⁻²⁷	2.92 (2.39, 3.56)	7.85 ×10 ⁻²⁶

*Adjusted for age, sex and study area

†Adjusted for age, sex, study area, BMI, waist circumference and body fat percentage

‡Adjusted for age, sex, study area and systolic blood pressure

§Odds ratio for binary outcomes and beta coefficient for cIMT (in native units), expressed per 1-unit higher log-odds of type 2 diabetes risk

||Lacunar stroke and intra-cerebral haemorrhage

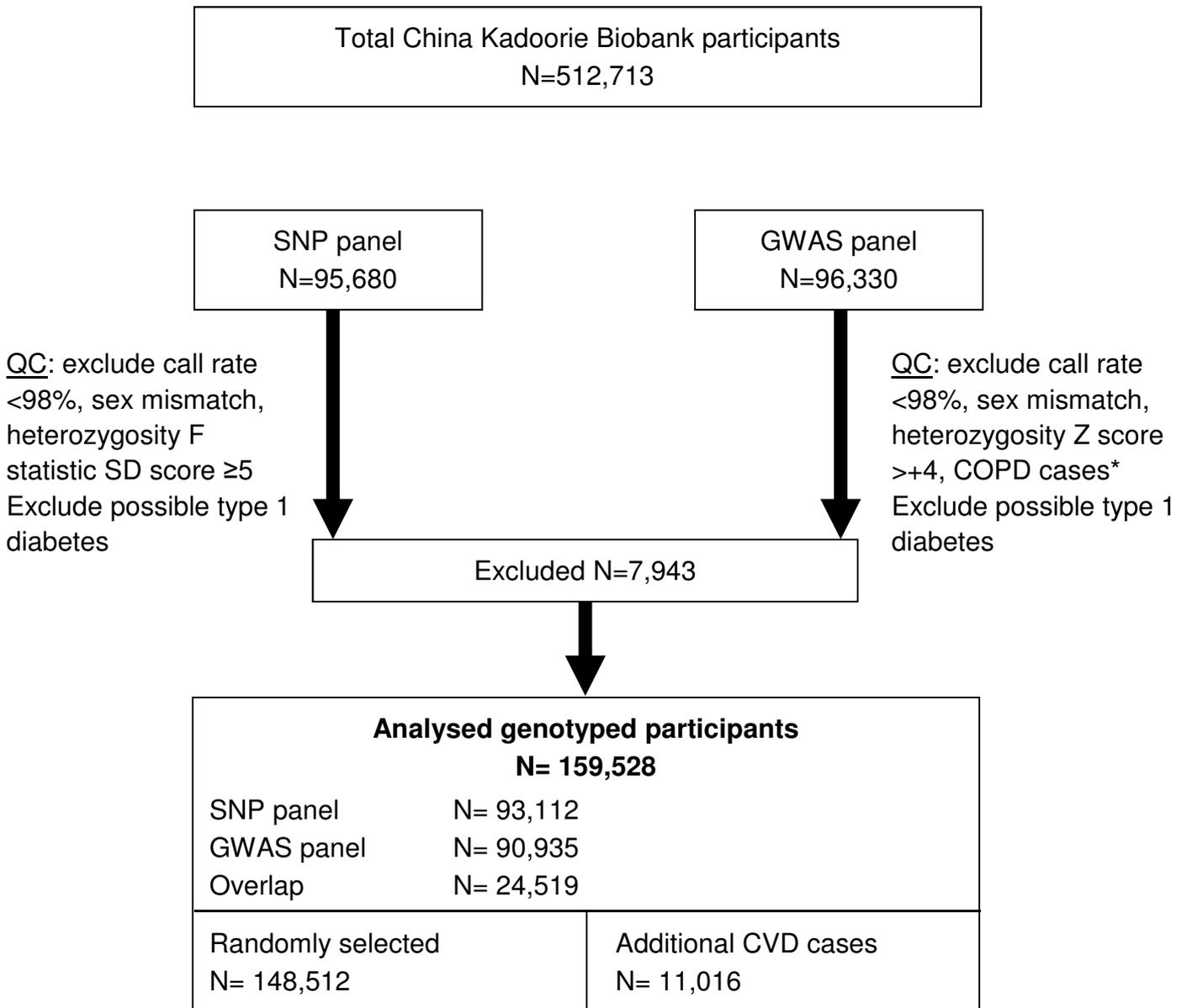
¶Non-lacunar ischaemic stroke plus major coronary event

Genetic analyses conducted using externally-weighted GRS calculated based on 14 SNPs associated with type 2 diabetes at the genome-wide significance level ($p < 5 \times 10^{-8}$) (excluding rs9939609 within FTO locus)

cIMT: carotid intima-media thickness

Supplementary Figure 1. Study participant flowchart

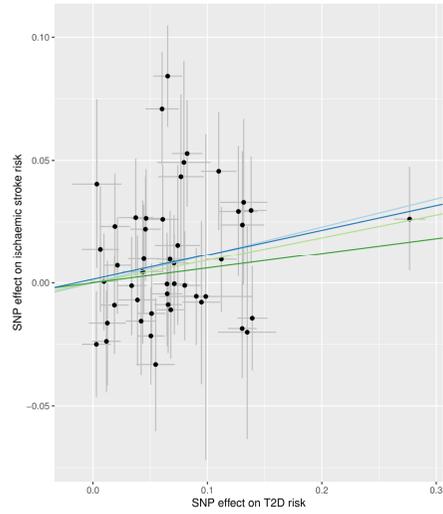
*Nested case control study of COPD included in GWAS genotyping



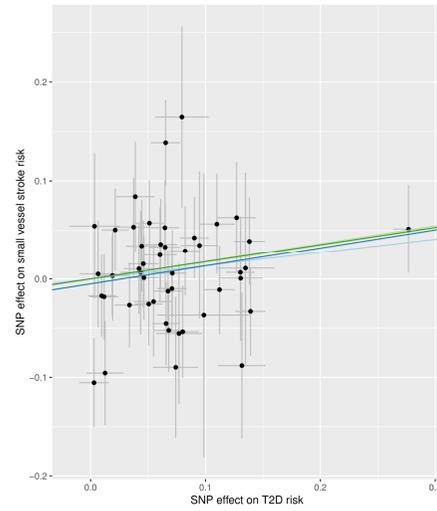
Supplementary Figure 2. Regression coefficients for associations of type 2 diabetes related genetic variants (included in 48 SNP type 2 diabetes genetic risk score) with type 2 diabetes and cardiovascular diseases in European ancestry populations*

*Based on summary statistics from DIAGRAMv.4, CARDIoGRAMplusC4D GWAS consortium, ISGC consortium

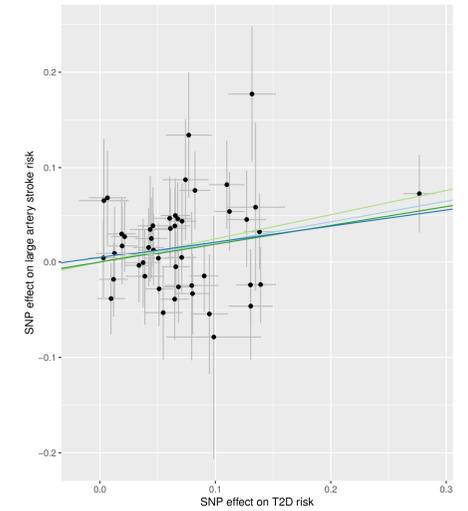
A. Ischaemic stroke



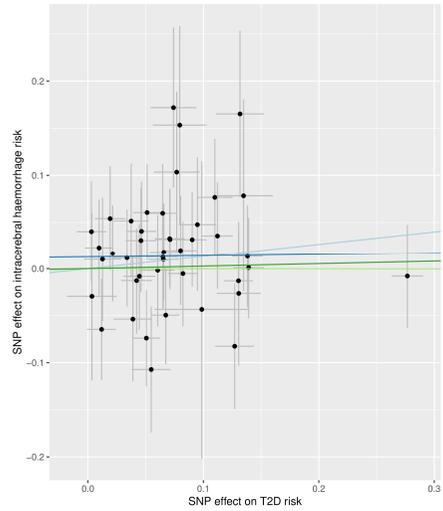
B. Small vessel stroke



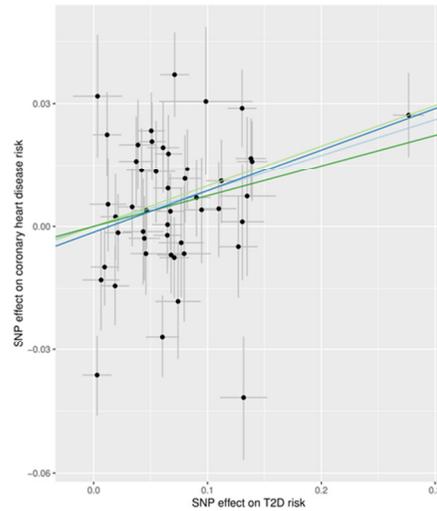
C. Large vessel stroke



D. Intracerebral haemorrhage



E. Coronary heart disease



MR Test

- Inverse variance weighted
- MR Egger
- Weighted median
- Weighted mode

**Supplementary Figure 3. Effect size estimates for type 2 diabetes in China
Kadoorie Biobank and trans-ethnic GWAS**
Solid line represents line of equality

