Genetic Predisposition to Type 2 Diabetes and Risk of Subclinical Atherosclerosis and Cardiovascular Diseases Among 160,000 Chinese Adults

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In observational studies, type 2 diabetes is associated with two- to fourfold higher risk of cardiovascular diseases (CVD). Using data from the China Kadoorie Biobank (CKB), 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 (odds ratio 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 ischemic stroke (IS) (1.08 [1.02, 1.14]; *n* = 17,097), nonlacunar 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 hemorrhage (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 randomization analyses based on summary statistics from European population genome-wide association studies (*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 two- to fourfold higher risks of CVD, in particular various types of atherosclerotic CVD (ASCVD), such as coronary heart disease (CHD), ischemic 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 hemorrhagic stroke (2–4,8), are less well understood. Although randomized controlled trials can assess causality, existing trial evidence for the effects of intensive glycemic control in diabetes (9), and of interventions to reduce or delay progression of prediabetes to diabetes (10,11), on risk of CVD is inconclusive.

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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 randomization" (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 hemorrhagic stroke (17), and subclinical atherosclerosis (18,19). The characteristically high rates of stroke, with a higher proportion of hemorrhagic stroke, in Chinese, compared with Western, populations (20) provide 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 *1*) examine the association of genetically predicted type 2 diabetes with different CVD and with subclinical atherosclerosis and *2*) 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 previously been published (21). Briefly, 512,713 Chinese adults (210,205 men, 302,508 women), aged 30–79 years at enrollment, 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 Center for Disease Control and Prevention (China CDC), and the 10 study areas' local CDCs.

Data Collection

Participants were interviewed by trained health workers using laptop-based questionnaires, collecting information on sociodemographic and lifestyle factors (e.g., 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 nonfasting 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). Individuals with an RPG level $\geq$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 analyzer; Beckman-Coulter) (Wolfson Laboratories, Oxford Clinical Trial Service Unit and Epidemiological Studies Unit [CTSU], Oxford, U.K.) 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 5-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 2013–2014 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 ($<$5%) without recent prior medical attention, was determined through verbal autopsy. Information on disease diagnoses resulting in, and during, hospitalizations was obtained through linkage, via unique national identification number, to established disease registries (for CHD, stroke, diabetes, and cancer) and to the national health insurance system ($>$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 diabetes or screen-detected diabetes (no prior diabetes diagnosis with a plasma glucose concentration $\geq$7.8 mmol/L and fasting time $\geq$8 h, a plasma glucose concentration $\geq$11.1 mmol/L and fasting time $<$8 h, or a fasting plasma glucose concentration $\geq$7.0 mmol/L) at baseline (excluding individuals with possible type 1 diabetes, defined as diagnosis at $<$30 years of age and use of insulin [n = 35]) (24). Incident type 2 diabetes included diabetes diagnoses (ICD-10 E11–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 end points for the current study were IS (ICD-10 I63, I69.3) (further classified into lacunar and nonlacunar), intracerebral hemorrhage (ICH) (ICD-10: I61, I69.1), and major coronary event (MCE) (nonfatal 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 (22,25,26). Additional analyses examined fatal total stroke (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 noncase samples were genotyped in the same batches, and assays were conducted blind to case status. After application of quality control criteria, 159,528 participants remained for inclusion in the current analyses (Supplementary Fig. 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.

A total of 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: β-cell dysfunction (GRS-BC) (24 SNPs), insulin resistance (GRS-IR) (6 SNPs), or unclassified (18 SNPs) (27). Sensitivity analyses included *1*) analyses excluding SNPs associated with plasma lipids, stroke, and CHD (Supplementary Table 2); *2*) analyses using internal weights calculated through 1000-fold cross-validation; *3*) analyses restricted to the population-based genotyped sample; *4*) 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; *5*) summary statistics–based analyses using SNP–type 2 diabetes effect estimates derived from transethnic type 2 diabetes GWAS (28,29) and SNP-CVD effect estimates derived from CKB; and *6*) 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, standardized by 5-year age-group, sex, and study area. Observational analyses excluded individuals with prior CVD (CHD, stroke, or transient ischemic attack; $n = 23,129$) or missing BMI ($n = 2$). After application of 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 time scale, 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, and 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 transethnic 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, with adjustment for the same variables. Linear regression was applied to the second stage in testing of associations with continuous traits. Further analyses additionally adjusted for known CVD risk factors (SBP and adiposity). For comparison with observational estimates, genetic estimates of the odds of CVD associated with type 2 diabetes were calculated using the following formula: $\mathrm{OR} = 1 + \frac{1 - \exp(\beta)}{(\exp(\beta) - \exp(1)) \times A}$ 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 the Cochran 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 DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) (26,676 type 2 diabetes case and 132,532 control subjects) (30), CARDIoGRAMplusC4D (Coronary ARtery DIsease Genome wide Replication and Meta-analysis (CARDIoGRAM) plus The Coronary Artery Disease (C4D) Genetics) (60,801 CHD case and 123,504 control subjects) (31), and the International Stroke Genetics Consortium (ISGC) (12,389 IS case and 62,004 control subjects, with 1,545 ICH case and 1,481 control subjects) (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). The Cochran 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 *1*) MR-Egger (36), *2*) weighted median MR (37), and *3*) weighted-mode MR (38).

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

Data and Resource Availability

The data that support the findings of this study are from the CKB 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 analyzed during the current study.

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, nonlacunar (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]) (Fig. 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]).

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 cutoff 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 ($\beta = 0.33$ [95% CI 0.02, 0.64] per 1-unit higher log-odds type 2 diabetes, $P = 0.04$) (Table 2). It was inversely associated with general adiposity (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 adiposity (waist circumference $\beta = -0.58$ [95% CI −0.73, −0.43], $P = 6.59 \times 10^{-15}$) 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] 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), nonlacunar IS (1.09 [95% CI 1.03–1.16]; n = 13,924) but not

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

Characteristics*	No type 2 diabetes (n = 134,799)	Prevalent type 2 diabetes (n = 8,886)†	Incident type 2 diabetes (n = 4,827)	Total (n = 148,512)
Age and socioeconomic factors				
Men, %	40.8	38.4	38.4	40.5
Age, years, mean (SD)	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, MET h/day, mean (SD)	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)
SBP, 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)
RPG, 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 cholesterol, mmol/L#	2.4 (0.7)	2.4 (0.7)	2.1 (0.7)	2.4 (0.7)
HDL cholesterol, 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
CVD**	4.3	7.6	6.6	4.7
Family history, %				
Diabetes	6.3	18.6	12.2	7.2
CVD**	20.5	22.0	22.9	20.6

*Standardized 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 = 0.6; §P = 0.1; ‖P = 0.04; ¶P = 0.4. #Data available for 8,814 participants. **CHD, stroke, or transient ischemic attack.

lacunar IS (1.03 [95% CI 0.91, 1.16]; n = 3,173), fatal total stroke (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. For comparison with observational associations, genetic estimates of the odds of CVD associated with type 2 diabetes, versus with no type 2 diabetes, were estimated (Fig. 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 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 nonsignificantly stronger than those of β-cell dysfunction–related variants (GRS-BC) for any and nonlacunar 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

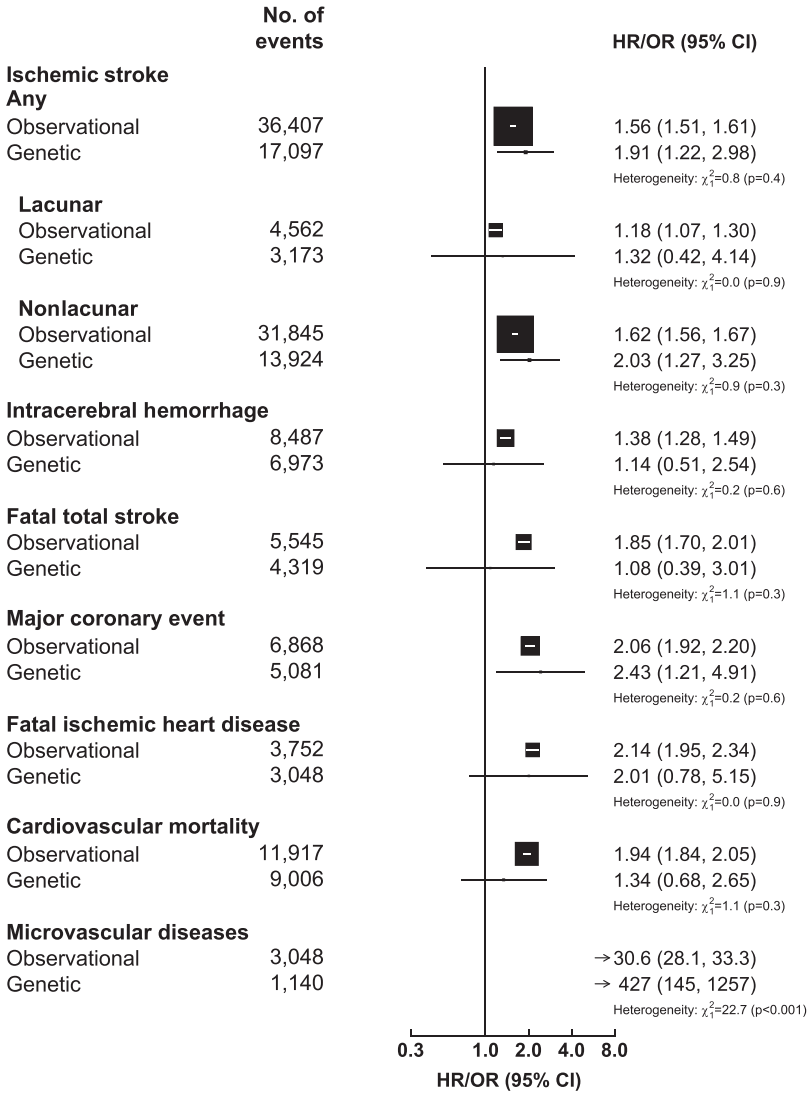

Figure 1—Observational and genetic associations of type 2 diabetes with risk of cardiovascular and microvascular diseases. Risk estimates expressed as the relative risk of the outcomes among individuals with type 2 diabetes compared with individuals without type 2 diabetes. Microvascular diseases defined 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 SBP. 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 HRs or ORs, with area inversely proportional to the variance of the log HR/OR. Horizontal lines represent corresponding 95% CIs. Nonfatal myocardial infarction: 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.

(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 and 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 Fig. 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

Table 2—Association of type 2 diabetes GRS* with cardiovascular risk factors

Outcome	Number of participants	Estimate (95% CI)†	*P*
Binary traits, case vs. control subjects			
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/day	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}
WC_{adjBMI}, 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
WHR_{adjBMI} (×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}
SBP, 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 cholesterol, mmol/L	8,814	0.03 (−0.01, 0.08)	0.12
HDL cholesterol, 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}

Observational estimates stratified by age at risk, sex, and study area and adjusted for education, smoking, alcohol consumption, physical activity, SBP, and BMI. WC_{adjBMI}, waist circumference adjusted for BMI; WHR_{adjBMI}, waist-to-hip ratio adjusted for BMI. *Conducted using externally weighted GRS based on 48 type 2 diabetes–related SNPs (GRS-T2D48) in population-based subset of genotyped participants. †OR for binary traits and β-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), $P = 2.5 \times 10^{-13}$, case subjects = 9,380, control subjects = 14,800. §Observational association of type 2 diabetes with cIMT: 0.015 mm (95% CI 0.009, 0.025), $P = 1.51 \times 10^{-25}$, $n = 24,180$.

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 two- to fourfold 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 current 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 with inclusion of a number of stroke cases similar to that of the current 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 current study, in general, we found nonsignificantly 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 U.S. 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

Table 3—Association of genetically predicted type 2 diabetes with major CVD in Chinese and European populations

Outcome	Case/control subjects in Chinese population	OR (95% CI) in Chinese population*	*P* in Chinese population	Case/control subjects in European population	OR (95% CI) in European population*	*P* in European population	*P* for heterogeneity
IS	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
ICH	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
CHD	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.

lacunar IS (n = 2,191) associated with genetically predicted type 2 diabetes (17), while 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, nonsignificant, association of genetically predicted type 2 diabetes with lacunar IS (1.03). Widespread use of computed tomography and MRI 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 nonlacunar IS in CKB (1.09) lies between previous estimates of the association of genetically predicted type 2 diabetes with large-vessel (atherosclerotic) IS (1.28 [95% CI 1.16, 1.40]) and cardioembolic IS (1.06 [95% CI 0.97, 1.15]) (15), the two major nonlacunar 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 ~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 current 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 (e.g., 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 underestimate their influence.

The strengths of the current 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-characterized 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). Utilization 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), while the passive follow-up approach reduced potential reporting, nonresponse, 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 current 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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