Type 2 Diabetes and Adiposity Induce Different Lipid Profile Disorders: A Mendelian Randomization Analysis

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Context: Type 2 diabetes and obesity often coexist, so it is difficult to judge whether diabetes or obesity induce certain types of hyperlipidemia due to mutual confounds and reverse causation. We used Mendelian randomization analyses to explore the causal relationships of diabetes and adiposity with lipid profiles.

Design, Setting, and Main Outcome Measures: From 23 sites in East China, 9798 participants were enrolled during 2014 to 2016. We calculated two weighted genetic risk scores as instrumental variables for type 2 diabetes and body mass index (BMI). These scores were used to measure the causal relationships of diabetes and BMI with lipid profiles that included total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TGs).

Results: The causal regression coefficients (β_{IV}) of genetically determined diabetes for the total cholesterol, LDL-C, and $\log_{10}$TG were 0.130 [95% confidence interval (CI): 0.020, 0.240; $P = 0.014$], 0.125 (96% CI: 0.041, 0.209; $P = 0.001$), and 0.019 (95% CI: –0.001, 0.039; $P = 0.055$), respectively. The β_{IV} for HDL-C was –0.008 (95% CI: –0.032. 0.016), which was not significant ($P = 0.699$). The causal regression coefficients of a genetically determined 10 kg/m^2 increase in BMI for HDL-C and $\log_{10}$TG were –0.409 (96% CI: –0.698, –0.120; $P = 0.004$) and 0.227 (95% CI: 0.039, 0.415; $P = 0.026$), respectively. The β_{IV}s for TGs and LDL-C were not significant.

Conclusions: This study has provided evidence for the biologically plausible causal effects of diabetes and adiposity by BMI on different elements of the lipid profile using Mendelian randomization analyses. ***(J Clin Endocrinol Metab* 103: 2016–2025, 2018)**

Atherosclerotic cardiovascular disease (CVD) is the leading cause of death worldwide (1). The incidence and prevalence of CVD are continuously increasing in parallel with the increase in dyslipidemia, especially in low- and middle-income countries such as China (1). According to the Coronary Heart Disease Policy Model-China, total cholesterol (TC) increases of 0.58 mmol/L (22.4 mg/dL) and 0.55 mmol/L (21.6 mg/dL) in Chinese men and women, respectively, from 2010 to 2030 would lead to approximately 960 million new CVD events in total, which represents the largest increase in CVD events among all modeled risk factors, including diabetes and body mass index (BMI) (2).

Many well-designed epidemiological studies have demonstrated the associations of diabetes and obesity with lipid profile (3–5). Previous studies have reported

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Abbreviations: BMI, body mass index; BMI_GRS, body mass index genetic risk score; CI, confidence interval; CVD, cardiovascular disease; DM_GRS, diabetes mellitus genetic risk score; FPG, fasting plasma glucose; GRS, genetic risk score; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; IV, instrumental variable; LDL-C, low-density lipoprotein cholesterol; MR, Mendelian randomization; OR, odds ratio; SD, standard deviation; SNP, single-nucleotide polymorphism; SPECT, Survey on Prevalence in East China for metabolic diseases and risk factors; TC, total cholesterol; TG, triglyceride.

that the most common pattern of dyslipidemia in patients with type 2 diabetes includes elevated triglyceride (TG) levels and decreased high-density lipoprotein cholesterol (HDL-C) levels (6). The concentration of low-density lipoprotein cholesterol (LDL-C) exhibits no significant increase (6). In obesity, hypercholesterolemia, hypertriglyceridemia, and high LDL-C and low HDL-C levels are very common (5). However, diabetes and obesity have often coexisted in the samples of previous studies, so it is difficult to judge whether diabetes or obesity induces certain types of hyperlipidemia due to mutual confounds, reverse causation, and other issues with conventional observational studies that ultimately lead to imprecision in the estimation of both the directions and magnitudes of the effects (7).

An alternative to classical observational studies are Mendelian randomization (MR) studies. MR uses genetic variants associated with an intermediate phenotype (in the current study, diabetes and BMI) as instrumental variables (IVs) in nonexperimental data to make causal inferences about the effect of an exposure on an outcome (Fig. 1) (8). Because genetic variants are assumed to be randomly distributed within a population and exist before the outcome, the IV is regarded as independent of the confounders that affect the exposure-outcome relationship and guide definite causal direction (9). In this study, if type 2 diabetes and BMI causally induce certain types of hyperlipidemia, then genetic variants associated with type 2 diabetes and BMI could be expected to affect certain types of hyperlipidemia.

Based on the large community-based sample of Chinese participants from the Survey on Prevalence in East China for metabolic diseases and risk factors (SPECT)-China study (www.chictr.org.cn; registration no. ChiCTR-ECS-14005052), we performed MR analyses to explore the causal associations of diabetes and BMI with lipid profiles, including TC, LDL-C, HDL-C, and TG. Diabetes mellitus genetic risk scores (DM_GRSs) and BMI genetic risk scores (BMI_GRSs) were constructed to represent genetic susceptibility, and we evaluated the causal links of genetically determined diabetes and genetically determined BMI with lipid profiles.

Methods

Study design and participants

Figure 1 presents the study design. We analyzed the observed associations between the measured variables (residual confounds and reverse causation) and the genetic associations between genotypes and the measured variables (no residual confounds or reverse causation). First, we assessed the association between type 2 diabetes mellitus–related genetic variants and present diabetes (Fig. 1A) and the relation between BMI-related genetic variants and measured BMI (Fig. 1A). Second, we measured the effects of genetic variants associated with type 2 diabetes and BMI on the changes in lipid profiles, including TC, LDL-C, HDL-C, and TG (Fig. 1C). Third, we performed observational assessments of the relation between present diabetes and lipid profile and between BMI and lipid profile (Fig. 1B).

The data were taken from the ongoing SPECT-China study, which is a cross-sectional investigation of the prevalence of metabolic diseases and risk factors in East China. Recruitment and enrollment have previously been described in detail (10–12). Chinese citizens ≥18 years old who had lived in their current area for ≥6 months were included. From 2014 to 2016, 12,666 subjects who were 18 to 93 years old from 23 sites in the Shanghai, Zhejiang, Jiangsu, Anhui, and Jiangxi provinces were recruited into the SPECT-China study. Among these participants, genotype information was available for 10,516 (83.0%). We excluded participants with missing information on more than two single-nucleotide polymorphism (SNP) genotypes (n = 297), missing lipid profile values (n = 3), and missing measured BMI (n = 242) and those who were using lipid-lowering drugs (n = 176). In total, 9,798 participants were involved in the final analyses.

The study protocol was approved by the Ethics Committee of Shanghai Ninth People's Hospital, Shanghai JiaoTong University School of Medicine. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in the *a priori* approval by the appropriate institutional review committee. Informed consent was obtained from all participants included in the study.

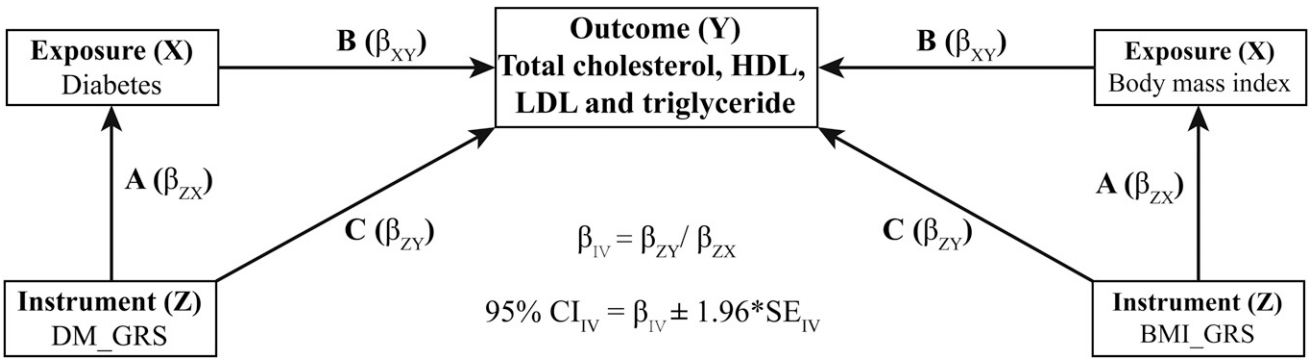

Figure 1. Study design and tested associations. BMI_GRS, body mass index genetic risk score; DM_GRS, diabetes mellitus genetic risk score.

Procedures

A single-assessment protocol was adopted by trained staff during the interviews and the collection of biological specimens at each study site. Blood samples were obtained between 7:00 AM and 10:00 AM after fasting for at least 8 hours. The blood was refrigerated immediately after phlebotomy. After 2 to 4 hours, the blood was centrifuged, and the serum was aliquoted and frozen in a central laboratory. Glycated hemoglobin (HbA1c) was measured by high-performance liquid chromatography (MQ-2000PT; Medconn, Shanghai, China). Fasting plasma glucose (FPG), TG, TC, HDL-C, and LDL-C were measured with a Beckman Coulter AU680 (Brea, CA). BMI was calculated as the weight in kilograms divided by the height in meters squared. Body weight, height, and blood pressure were measured using standard methods as described previously (13).

Diabetes was defined by the following criteria (1): a self-reported previous diagnosis by a health care professional (13), (2) an FPG level of 7.0 mmol/L or higher, or (3) an HbA1c concentration of 6.5% or more. Hypertension was assessed as a systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, or a self-reported previous diagnosis of hypertension by a physician. The 16 study sites were categorized into high and low economic status according to the gross domestic product per capita of the whole nation in 2013 (10).

DNA was extracted from white bloods cells using a blood genomic DNA extraction kit (DP603; TIANGEN BIOTECH CO, LTD, Beijing, China) on an automated nucleic acid extraction instrument (YOSE-S32; TIANGEN BIOTECH CO, LTD, Beijing, China). Specific assays were designed using Geneious Pro (version 4.8.3; www.geneious.com/, Auckland, New Zealand). Mass determination was performed with JUNO, and data acquisition was performed using Fluidigm SNP Genotyping Analysis version 4.1.3 software (Fluidigm Corporation, San Francisco, CA) (14). The researchers were masked to the data regarding present diabetes, BMI, and phenotype. The call rates of all SNPs were higher than 98%.

For the selection of the diabetes- and BMI-related SNPs, we mainly considered the SNPs that have been identified in genome-wide association studies or replicated in Asians and then successfully used in two Chinese MR studies (15, 16). For diabetes, we *a priori* selected 18 SNPs that were identified and validated in meta-analyses including genome-wide association studies in East Asians (17, 18). A previous Chinese MR study (15) included 34 SNPs. To minimize the pleiotropic effects, we further selected the 18 SNPs that exhibited no significant associations with BMI or systolic and diastolic blood pressure in that study (15). These SNPs were *TCF2* (*HNF1B*) rs4430796, *GCC1/PAX4* rs6467136, *MAEA* rs6815464, *GLIS3* rs7041847, *C2CD4A/C2CD4B* rs7172432, *TCF7L2* rs7903146, *ZFAND3* rs9470794, *CDKN2A/B* rs10811661, *CDC123/CAMK1D* rs12779790, *PROX1* rs340874, *SRR* rs391300, *PSMD6* rs831571, *JAZF1* rs864745, *TP53INP1* rs896854, *SPRY2* rs1359790, *PPARG* rs1801282, *KCNQ1* rs2237892, and *IRS1* rs2943641. For BMI, 14 SNPs from a previous MR study (16) that were selected from genome-wide association studies in East Asians (19, 20) were adopted. These SNPs included *TFAP2B* rs4715210, *MAP2K5* rs4776970, *ADCY3-DNAJC27* rs6545814, *MC4R* rs6567160, *CDKAL1* rs9356744, *GNPDA2* rs10938397, *SMC5-KLF9* rs11142387, *GIPR-QPCTL* rs11671664, *GP2* rs12597579, *FTO* rs17817449, *BDNF* rs6265, *PCSK1* rs261967, *SEC16B* rs574367, and *PAX6* rs652722. There were no linkage disequilibrium relationships ($r^2 = 0$) among the previous diabetes and BMI SNPs (15, 16). The full list of each SNP is presented in Supplemental Table 1.

Statistical analysis

The data analyses were performed using IBM SPSS Statistics version 22 (IBM Corporation, Armonk, NY). All analyses were two sided. A P value <0.05 indicated significance. Continuous variables are expressed as the mean ± the standard deviation (SD), and categorical variables are expressed as percentages (%). Serum TG was logarithmically transformed before the analysis. The P values for trends of the characteristics according to the genetic risk score (GRS) quintiles were calculated with one-way analysis of variance and χ^2 tests.

The additive genetic model for each SNP (coded as 0-2) was used to construct the DM_GRS and BMI_GRS. The scores were defined as the sum of the number of BMI-increasing and diabetes risk-increasing alleles at each locus multiplied by the respective β coefficient as reported from the meta-analysis. Next, the total scores were divided by the average effect sizes of these SNPs. Those who were missing one or two SNPs were imputed by the regression method using covariates. The missing rates of one or two diabetes- and BMI-related SNPs were 16.4% and 15.5%, respectively. There were also 82 missing blood pressure values, which were not imputed.

For our analyses of the association between DM_GRS and present diabetes and that between BMI_GRS and measured BMI (Fig. 1A), we used logistic and linear regression analyses. The data were adjusted for age, sex, BMI (only in the DM_GRS model), diabetes (only in the BMI_GRS model), hypertension, and economic status. To assess the reliabilities and strengths of the GRSs as instruments, the F statistic was adopted ($F = [R^2 \times (n–2)]/[1–R^2]$) (21). An F value greater than 10 indicates that the instrument is sufficiently strong as an IV, and the R^2 is the proportion of variation in the respective phenotype that is explained by the genotype (22).

We used regression analyses to calculate the β coefficients for the associations of present diabetes and BMI with lipid profile, including TC, LDL-C, HDL-C, and TG (Fig. 1B). Then, we also investigated the associations of the DM_GRS and BMI_GRS with lipid profile (Fig. 1C) by linear regressions that were adjusted for age, sex, BMI (only in the DM_GRS model), diabetes (only in the BMI_GRS model), hypertension, and economic status. The association of each individual SNP with lipid profile was analyzed by linear regression analysis with an unadjusted model.

Next, we calculated the IV estimates of the genetically determined β coefficients with the Wald-type estimator (7, 22). For abnormal lipid profile trends due to present diabetes and increased BMI, the computational formulae were $\beta_{IV(DM\text{-}lipid)} = \beta_{DM\_GRS\text{-}lipid}/\beta_{DM\_GRS\text{-}DM}$ and $\beta_{IV(BMI\text{-}lipid)} = \beta_{BMI\_GRS\text{-}lipid}/\beta_{BMI\_GRS\text{-}BMI}$, respectively. The standard errors and confidence intervals (CIs) for the IV estimators were estimated by the δ method. The formulae are:

$$SE_{IV} = abs(\beta_{IV})\sqrt{\left(\frac{SE_{GRS\_exposure}}{\beta_{GRS\_exposure}}\right)^2 + \left(\frac{SE_{GRS\_eoutcome}}{\beta_{GRS\_outcome}}\right)^2}$$

$$95\%\ CI_{IV} = \beta_{IV} \pm 1.96 \times SE_{IV}$$

According to a previous study, a 10 kg/m^2 BMI increment was used because this increment roughly reflects a shift from normal weight to obesity. Thus, to increase the parity between the observational and genetic estimates, the effect of the BMI_GRS was extrapolated to correspond to a 10 kg/m^2 increase in BMI for the genetic analyses.

A GRS as an IV should meet three assumptions (23). First, the GRS should be associated with the exposure. This assumption is confirmed in the aforementioned Fig. 1A. Second, the GRS should be independent of the confounding factors. Thus, we also measured the associations of each individual SNP and GRS with BMI, blood pressure, FPG, HbA1c, and age. Third, the two GRSs should have effects on lipid profile that are mediated solely through diabetes and BMI (*i.e.*, there are no pleiotropic effects) (23). However, this is only an idealized view and could only be verified to a limited extent. We additionally adjusted the HbA1c or BMI in the previous models to observe the changes in the associations of the DM_GRS or BMI_GRS with the lipid profiles.

In the sensitivity analysis, because the BMI_GRS exhibited significant associations with age and hypertension, in consideration of pleiotropy, we constructed a BMI_GRS$_{12SNP}$ that excluded the most obvious loci that may have been involved in the regulation of other traits (*i.e.*, *FTO* rs17817449 and *MC4R* rs6567160) (24).

Results

Associations of SNPs with exposure and outcome

We tested the associations of the diabetes- and BMI-related SNPs with exposure (present diabetes and measured BMI) and outcome (lipid profile). The unstandardized coefficients (95% CIs) and odds ratios (ORs) are presented in Tables 1 and 2 and Supplemental Figs. 1 and 2. Among the 18 diabetes-related SNPs, seven SNPs located at the *GLIS3*, *CDKN2A/B*, *CDC123/CAMK1D*, *TP53INP1*, *PPARG*, *KCNQ1*, and *IRS1* loci were significantly associated with present diabetes (Supplemental Fig. 1). Among the 14 BMI-related SNPs, eight SNPs located at the *MAP2K5*, *ADCY3-DNAJC27*, *MC4R*, *CDKAL1*, *GIPR-QPCTL*, *FTO*, *BDNF*, and *SEC16B* loci were significantly associated with BMI (Supplemental Fig. 2).

Most of the diabetes-related SNPs did not exhibit significant associations with lipid profile; the exceptions were rs4430796, rs6467136, rs12779790, rs831571, rs864745, rs7041847, and rs2943641 (Table 1). Most of the BMI-related SNPs also did not exhibit significant relationships with lipid profile; the exceptions were rs17817449, rs4776970, rs6567160, rs6265, and rs574367 (Table 2). However, additional adjustments for HbA1c and BMI greatly attenuated the associations of most of these exceptive SNPs with lipid profile.

Pleiotropic effects of SNPs

We measured the potential associations of the SNPs with BMI, systolic and diastolic blood pressure, FPG, HbA1c, and age using an additive model (Supplemental Figs. 3 and 4). Three of the diabetes-related SNPs exhibited an association with at least one trait at the nominal P value ≤ 0.05. Two SNPs (rs4430796 and rs391300) were associated with systolic and diastolic blood pressure, and two SNPs (rs4430796 and rs896854) were associated with age. Seven of the BMI-related SNPs exhibited a significant association with at least one trait. Seven SNPs were associated with blood pressure (rs4776970, rs12597579, rs17817449, rs261967, rs4715210, rs6567160, and rs574367), two SNPs were associated with FPG (rs4715210 and rs6545814), and two SNPs were associated with age (rs4715210 and rs17817449).

Table 1. Association of the 18 Diabetes-Related SNPs With Lipid Profile

Gene	SNP	TC	LDL-C	HDL-C	$\log_{10}$TG
TCF2 (*HNF1B*)	rs4430796	0.047 (0.009, 0.085)	0.031 (0.004, 0.059)	−0.002 (−0.013, 0.009)	0.003 (−0.005, 0.011)
GCC1/PAX4	rs6467136	0.077 (0.028, 0.125)	0.042 (0.008, 0.077)	0.014 (0.001, 0.028)	0.003 (−0.007, 0.014)
MAEA	rs6815464	−0.016 (−0.052, 0.019)	−0.009 (−0.035, 0.016)	0.007 (−0.003, 0.017)	0.001 (−0.006, 0.009)
GLIS3	rs7041847	0.031 (−0.003, 0.066)	0.027 (0.002, 0.051)	0.005 (−0.005, 0.014)	0.001 (−0.006, 0.008)
C2CD4A/C2CD4B	rs7172432	0.001 (−0.034, 0.036)	0.010 (−0.015, 0.035)	−0.002 (−0.012, 0.008)	−0.002 (−0.010, 0.005)
TCF7L2	rs7903146	0.036 (−0.056, 0.129)	0.043 (−0.024, 0.109)	0.006 (−0.020, 0.032)	−0.006 (−0.025, 0.014)
ZFAND3	rs9470794	−0.017 (−0.054, 0.020)	−0.002 (−0.029, 0.024)	−0.007 (−0.018, 0.004)	0.004 (−0.003, 0.012)
CDKN2A/B	rs10811661	0.018 (−0.016, 0.053)	0.017 (−0.007, 0.042)	0.004 (−0.006, 0.014)	0.004 (−0.003, 0.011)
CDC123/CAMK1D	rs12779790	0.050 (0.004, 0.096)	0.017 (−0.016, 0.050)	0.003 (−0.010, 0.016)	0.003 (−0.007, 0.012)
PROX1	rs340874	0.008 (−0.028, 0.043)	0.005 (−0.021, 0.030)	0.008 (−0.002, 0.018)	0.002 (−0.005, 0.010)
SRR	rs391300	0.004 (−0.033, 0.042)	0.011 (−0.015, 0.038)	−0.001 (−0.011, 0.010)	0.000 (−0.008, 0.008)
PSMD6	rs831571	0.038 (0.001, 0.074)	0.038 (0.012, 0.064)	0.003 (−0.007, 0.014)	0.003 (−0.004, 0.011)
JAZF1	rs864745	0.043 (0.003, 0.084)	0.032 (0.003, 0.061)	−0.001 (−0.013, 0.010)	0.000 (−0.004, 0.011)
TP53INP1	rs896854	0.016 (−0.022, 0.053)	0.006 (−0.021, 0.033)	0.003 (−0.008, 0.014)	0.004 (−0.004, 0.012)
SPRY2	rs1359790	−0.011 (−0.050, 0.028)	−0.014 (−0.042, 0.014)	−0.005 (−0.016, 0.006)	−0.007 (−0.016, 0.001)
PPARG	rs1801282	0.013 (−0.061, 0.087)	0.011 (−0.042, 0.064)	0.014 (−0.007, 0.035)	0.015 (0.000, 0.031)
KCNQ1	rs2237892	0.014 (−0.023, 0.051)	0.014 (−0.012, 0.040)	−0.002 (−0.013, 0.008)	0.001 (−0.007, 0.009)
IRS1	rs2943641	0.012 (−0.057, 0.081)	−0.011 (−0.061, 0.038)	−0.019 (−0.039, 0.001)	0.017 (0.003, 0.032)

The data are presented as unstandardized coefficients and 95% CIs using linear regression analyses. The model was unadjusted.

Table 2. Association of the 14 BMI-Related SNPs With Lipid Profile

Gene	SNP	TC	LDL-C	HDL-C	log_{10}TG
TFAP2B	rs4715210	0.002 (−0.044, 0.049)	0.015 (−0.019, 0.049)	−0.002 (−0.015, 0.012)	0.006 (−0.004, 0.016)
MAP2K5	rs4776970	−0.004 (−0.044, 0.036)	0.001 (−0.028, 0.030)	−0.015 (−0.027, −0.004)	0.005 (−0.003, 0.014)
ADCY3-DNAJC27	rs6545814	−0.007 (−0.042, 0.027)	0.019 (−0.006, 0.045)	−0.007 (−0.017, 0.003)	−0.002 (−0.010, 0.005)
MC4R	rs6567160	0.019 (−0.023, 0.060)	0.025 (−0.005, 0.055)	−0.014 (−0.026, –0.002)	0.008 (−0.001, 0.017)
CDKAL1	rs9356744	−0.019 (−0.053, 0.015)	−0.020 (−0.045, 0.005)	0.001 (−0.008, 0.011)	−0.001 (−0.008, 0.006)
GNPDA2	rs10938397	0.024 (−0.012, 0.060)	0.012 (−0.014, 0.038)	0.007 (−0.004, 0.017)	−0.002 (−0.010, 0.005)
SMC5-KLF9	rs11142387	−0.012 (−0.048, 0.025)	−0.002 (−0.029, 0.025)	0.001 (−0.009, 0.012)	0.005 (−0.003, 0.012)
GIPR-QPCTL	rs11671664	0.001 (−0.032, 0.035)	−0.004 (−0.028, 0.021)	0.002 (−0.007, 0.012)	0.003 (−0.004, 0.010)
GP2	rs12597579	0.014 (−0.023, 0.052)	0.008 (−0.019, 0.035)	−0.004 (−0.015, 0.007)	0.006 (−0.002, 0.014)
FTO	rs17817449	0.033 (−0.020, 0.086)	0.029 (−0.009, 0.068)	−0.015 (−0.031, 0.000)	0.017 (0.005, 0.028)
BDNF	rs6265	−0.015 (−0.048, 0.019)	0.008 (−0.016, 0.033)	−0.012 (−0.022, −0.002)	−0.003 (−0.010, 0.004)
PCSK1	rs261967	−0.020 (−0.054, 0.014)	−0.003 (−0.028, 0.022)	−0.009 (−0.019, 0.001)	0.005 (−0.003, 0.012)
SEC16B	rs574367	0.027 (−0.016, 0.07)	0.006 (−0.025, 0.037)	−0.013 (−0.025, 0.000)	0.008 (−0.002, 0.017)
PAX6	rs652722	0.002 (−0.033, 0.037)	0.002 (−0.023, 0.028)	0.000 (−0.010, 0.010)	0.000 (−0.008, 0.007)

The data are presented as unstandardized coefficients and 95% CIs using linear regression analyses. The model was unadjusted.

Study characteristics based on the DM_GRS and BMI_GRS

As expected, with increases in the DM_GRS, the FPG, HbA1c, and prevalence of diabetes significantly increased. The BMI_GRS was also significantly associated with an increase in BMI (all $P < 0.001$; Table 3).

The OR_{ZX} of the observed association between DM_GRS (per 1 SD increase) and diabetes was 1.231 (95% CI: 1.159, 1.307) with an F statistic of 69. The β_{ZX} regression coefficient between BMI_GRS (per 1 SD increase) and BMI was 0.215 (95% CI: 0.147, 0.284) with an F statistic of 39. The F statistics greater than 10 commonly suggest these two GRSs are sufficiently strong as IVs.

Regarding the pleiotropic effects, the DM_GRS quintiles were not significantly associated with BMI or hypertension, and each 1 SD increment of the DM_GRS also did not exhibit a significant association with BMI or

Table 3. Characteristics of the Study Participants According to the DM_GRS and the BMI_GRS (n = 9798)

Characteristic	Q1	Q2	Q3	Q4	Q5	*P* for Trend
DM_GRS	≤18.013	18.014–19.740	19.741–21.312	21.313–23.011	≥23.012	
n	1959	1961	1958	1961	1959	
Age, y	54.3 (13.0)	55.0 (12.9)	55.4 (12.5)	54.3 (13.0)	54.4 (12.9)	0.669
Men, %	40.3	40.1	39.0	39.9	40.0	0.850
BMI, kg/m^2	24.7 (3.5)	24.8 (3.7)	24.6 (3.6)	24.6 (3.7)	24.5 (3.5)	0.176
TC, mmol/L	5.19 (1.20)	5.15 (1.00)	5.25 (1.04)	5.23 (1.08)	5.24 (1.21)	0.010
TGs, mmol/L	1.65 (1.51)	1.63 (1.22)	1.67 (1.44)	1.67 (1.54)	1.68 (1.55)	0.220
HDL-C, mmol/L	1.40 (0.32)	1.39 (0.32)	1.40 (0.33)	1.41 (0.32)	1.40 (0.31)	0.726
LDL-C, mmol/L	3.17 (0.79)	3.18 (0.78)	3.25 (0.82)	3.23 (0.81)	3.22 (0.82)	0.010
FPG, mmol/L	5.5 (1.39)	5.6 (1.35)	5.7 (1.53)	5.7 (1.54)	5.8 (1.65)	3.9E-7
HbA1c, %	5.5 (0.9)	5.6 (0.9)	5.6 (1.0)	5.6 (1.0)	5.7 (1.1)	3.4E-8
Diabetes, %	11.7	13.7	14.2	15.5	18.3	2.9E-8
Hypertension, %	48.3	49.7	48.3	47.0	46.2	0.052
Economic status, low %/high %	32.7/67.3	34.6/65.4	33.7/66.3	35.1/64.9	35.6/64.4	0.062
BMI_GRS	≤8.186	8.187–9.404	9.405–10.621	10.622–12.007	≥12.008	
n	2358	1857	1855	1849	1879	
Age, y	54.8 (12.9)	54.8 (13.0)	55.1 (12.6)	54.6 (12.9)	54.0 (13.0)	0.036
Men, %	40.5	39.1	39.3	41.3	38.9	0.702
BMI, kg/m^2	24.4 (3.6)	24.5 (3.5)	24.7 (3.7)	24.8 (3.5)	25.0 (3.6)	3.5E-9
TC, mmol/L	5.19 (1.07)	5.21 (1.10)	5.23 (1.06)	5.25 (1.24)	5.18 (1.07)	0.906
TGs, mmol/L	1.64 (1.57)	1.65 (1.47)	1.63 (1.23)	1.71 (1.46)	1.68 (1.49)	0.019
HDL-C, mmol/L	1.41 (0.33)	1.41 (0.32)	1.41 (0.32)	1.39 (0.32)	1.38 (0.31)	0.005
LDL-C, mmol/L	3.19 (0.81)	3.20 (0.78)	3.23 (0.81)	3.23 (0.81)	3.21 (0.81)	0.197
FPG, mmol/L	5.7 (1.6)	5.6 (1.5)	5.6 (1.4)	5.6 (1.6)	5.7 (1.5)	0.953
HbA1c, %	5.6 (1.0)	5.6 (1.0)	5.6 (1.0)	5.6 (1.0)	5.7 (1.0)	0.367
Diabetes, %	14.6	14.3	15.6	13.8	15.1	0.864
Hypertension, %	46.9	46.6	47.3	48.9	49.9	0.022
Economic status, low %/high %	34.1/65.9	32.7/67.3	35.0/65.0	35.6/64.4	34.4/65.6	0.313

The data are summarized as the means (SD) for continuous variables and as numerical proportions for categorical variables. The *P* values for the trends were as calculated with analysis of variance and χ^2 tests.

hypertension in the adjusted model. The BMI_GRSs quintiles were associated with age and hypertension (Table 3). Therefore, in the sensitivity analyses, we constructed a BMI_GRS_{12SNP} that excluded *FTO* rs17817449 and *MC4R* rs6567160, which were the two most obvious loci that had pleiotropic effects.

Association of diabetes and DM_GRS with lipid profile

Next, we analyzed the associations of present diabetes and DM_GRS with lipid profile including TC, HDL-C, LDL-C, and TG (Table 4). In this cross-sectional study, present diabetes (β_{XY}) was significantly associated with $\log_{10}$TG (β = 0.078; 95% CI: 0.066, 0.091) and HDL-C (β = –0.067; 95% CI: –0.085, –0.049) but not with TC or LDL-C. However, the DM_GRS (β_{ZY}) was significantly related to TC (β = 0.027; 95% CI: 0.005, 0.048) and LDL-C (β = 0.026; 95% CI: 0.011, 0.042) and marginally related to $\log_{10}$TG (β = 0.004; 95% CI: 0.000, 0.009) but not to HDL-C.

In the IV analysis, the causal regression coefficients (β_{IV}) of genetically determined diabetes for TC, LDL-C, and $\log_{10}$TG were 0.130 (95% CI: 0.020, 0.240; P = 0.014), 0.125 (96% CI: 0.041, 0.209; P = 0.001), and 0.019 (95% CI: –0.001, 0.039; P = 0.055), respectively. The β_{IV} for HDL-C was –0.005 (95% CI: –0.033, 0.023), which was not significant (P = 0.699).

Association of BMI and the BMI_GRS with lipid profile

The associations of measured BMI and the BMI_GRS with lipid profile are presented in Table 4. A 10 kg/m^2 increase in measured BMI (β_{XY}) was significantly associated with TC (β = 0.281; 95% CI: 0.219, 0.343), LDL-C (β = 0.328: 95% CI: 0.284, 0.373), HDL-C (β = –0.212; 95% CI: –0.230, –0.195), and $\log_{10}$TG (β = 0.169; 95% CI: 0.157, 0.182). However, the BMI_GRS (β_{ZY}) was only significantly associated with HDL-C (β = –0.009; 95% CI: –0.015, –0.003) and $\log_{10}$TG (β = 0.005; 95% CI: 0.001, 0.010).

In the IV analysis, the causal regression coefficients (β_{IV}) of a genetically determined 10 kg/m^2 higher BMI for HDL-C and $\log_{10}$TG were –0.409 (96% CI: –0.698, –0.120; P = 0.004) and 0.227 (95% CI: 0.039, 0.415; P = 0.026), respectively. The β_{IV} for TC and LDL-C was not significant.

Sensitivity analysis

Considering pleiotropy, we constructed a GRS that excluded *FTO* rs17817449 and *MC4R* rs6567160, which were no longer significantly associated with age (P = 0.155) or hypertension (P = 0.091). A genetically determined 10 kg/m^2 greater BMI was still causally related to HDL (β = –0.361; 95% CI: –0.675, –0.047; P = 0.024) and marginally related to $\log_{10}$TG (β = 0.227; 95% CI: –0.001, 0.455; P = 0.051).

Three assumptions for IV in MR

First, the GRSs were strongly associated with exposure with F statistics that were considerably greater than 10, which indicated that these GRSs were adequate IVs. Second, a GRS should not be associated with any confounder of the exposure-outcome association. In our study, the BMI_GRSs quintiles were associated with age and hypertension; therefore, the BMI_GRS_{12SNP} was constructed, and the BMI determined by the BMI_GRS_{12SNP} was still causally associated with HDL. Third, a GRS should be independent of the outcome, except possibly through its association with the exposure. This assumption means that the only causal route from the genetic variants to the outcome should be through the exposure (*i.e.*, there should be no other routes between the DM_GRS and BMI_GRS and hyperlipidemia) (23). However, this assumption is only an idealized view and quite untestable because it is possible that a causal association is due to other diabetes characteristics as a

Table 4. Causal Coefficients From the MR Analysis for the Associations of Type 2 Diabetes and BMI With Lipid Profile

	TC	LDL-C	HDL-C	$\log_{10}$TG
DM				
β_{XY} (present diabetes)	0.019 (–0.043, 0.082)	0.029 (–0.016, 0.073)	−0.067 (–0.085, –0.049)	0.078 (0.066, 0.091)
β_{ZY} (per SD increase in DM_GRS)	0.027 (0.005, 0.048)	0.026 (0.011, 0.042)	−0.001 (–0.007, 0.005)	0.004 (0.000, 0.009)
β_{IV} (present diabetes)	0.130 (0.020, 0.240)	0.125 (0.041, 0.209)	−0.005 (–0.033, 0.023)	0.019 (–0.001, 0.039)
BMI				
β_{XY} (per 10 kg/m^2 increase in BMI)	0.281 (0.219, 0.343)	0.328 (0.284, 0.373)	−0.212 (–0.230, –0.195)	0.169 (0.157, 0.182)
β_{ZY} (per SD increase in BMI_GRS)	−0.002 (–0.024, 0.019)	0.008 (–0.008, 0.023)	−0.009 (–0.015, –0.003)	0.005 (0.001, 0.010)
β_{IV} (per 10 kg/m^2 increase in BMI)	−0.091 (–1.071, 0.889)	0.364 (–0.365, 1.083)	−0.409 (–0.698, –0.120)	0.227 (0.039, 0.415)

The data are presented as regression coefficients (β) and 95% CIs. In this MR framework, the IV estimator is $\beta_{IV} = \beta_{ZY}/\beta_{ZX}$, which equals the causal coefficients of diabetes and BMI (per 10 kg/m^2 increase) for changes in lipid parameters. The data were adjusted for age, sex, BMI (only in the the BMI_GRS model), hypertension, and economic status.

Abbreviation: DM, diabetes mellitus.

direct consequence of being diabetic (15), and biologic pathways are complex and interconnected. Additional adjustments for HbA1c or BMI could greatly attenuate most of the associations of DM_GRS and BMI_GRS with lipid profile, which verified the third assumption to a limited extent.

Discussion

In this cross-sectional survey that included almost 10,000 community-dwelling Chinese adults, we used an MR design to examine the causal associations between adiposity, as assessed by an elevated BMI, and lipid profile and between diabetes and lipid profile. The current study is, to our knowledge, the first MR study to measure the effect of diabetes on elements of the lipid profile. This is an old topic, but the MR design seems to reveal results that differ from conventional opinions. We demonstrated evidence for causal relationships (1) between diabetes and higher TC and LDL-C but not lower HDL-C and (2) between obesity and lower HDL-C and higher TG but not higher TC and LDL-C. Our findings do not fully accord with those of conventional observational studies. However, the setting of our study was different: We assessed the effects of lifelong exposure to diabetes risks and high BMI on hyperlipidemia.

Many previous studies have demonstrated that hyperlipidemia is more prevalent in individuals with diabetes and obesity than it is in their nondiabetic and nonobese counterparts (25). The features of dyslipidemia in patients with diabetes have been reported to be high TG levels and decreased HDL-C levels, but the concentration of LDL-C can be in the normal range, and small dense LDL-C can be increased (6). However, our study found that type 2 diabetes may induce a significant elevation of LDL-C but not a decrease of HDL-C. This finding further indicates the important role of diabetes in the formation of atherosclerosis because LDL-C level is recommended for use as the primary lipid analysis for screening, risk estimation, diagnosis, and management (25). Interestingly, in our study, the observed associations of diabetes with lipid profile were significant for HDL-C and TG but not for TC or LDL-C, which might reflect the flaws of conventional observational studies. Additional independent MR studies of this association should be performed.

In obesity, elevations of TC, LDL-C, and TG levels and decreased HDL-C levels are very common (5). There are two additional MR studies that have measured the associations of BMI with lipid profile (7, 26). We replicated the results of Fall *et al.* (7) from individuals of European descent. Using the *FTO* locus as the IV, these authors also observed an unfavorable effect of BMI on decreased HDL-C levels and increased TG levels and not on LDL-C or TC (7). However, another study that used 14 BMI-associated SNPs reported that a 1 kg/m^2 increase in BMI reduced HDL-C by –0.02 mmol/L (95% CI: –0.03, –0.01) and, interestingly, LDL-C by –0.04 mmol/L (95% CI: –0.07, –0.01) in individuals of European descent (26). We found that the IV estimates for the effects of BMI on HDL-C and TG were greater than those calculated from standard linear regressions. As suggested in previous studies (7), possible explanations include the following: the cross-sectional nature of a study that could result in reverse causation and confounds, and the notion that the lifelong effects of SNPs on adiposity are not entirely captured by a single BMI measurement (27).

CVD is the main cause of death in patients with type 2 diabetes and obesity (28, 29). Hyperlipidemia may be one important pathway linking diabetes and obesity to cardiovascular outcomes. Obesity could lead to dyslipidemia, which further induces and aggravates CVD (25, 30). Furthermore, a sustainable weight loss of 5 to 8 kg results in a mean LDL-C reduction of 5 mg/dL and a mean HDL-C increase of 2 to 3 mg/dL (30). Additionally, weight loss is also expected to decrease TG (30). However, an MR study did not identify evidence of a causal relationship between BMI and coronary heart disease (OR: 1.01; 95% CI: 0.94, 1.08) (26), and this issue requires further evidence. Although type 2 diabetes is regarded as a risk factor for CVD, the effect of intensive glucose-lowering therapies on the prevention of CVD is controversial. Some studies have found no benefit of intensive glucose-lowering therapy (31, 32), whereas one meta-analysis of randomized controlled trials indicated that intensive glycemic control resulted in a 15% reduction in coronary heart disease events (33). Moreover, a very recent MR study revealed a causal association between diabetes and increased arterial stiffness (OR: 1.24; 95% CI: 1.06, 1.47) in a Chinese population, which indicates that long-term treatment of diabetes may be beneficial to the prevention of the development of arterial stiffening (15). Our study suggests that diabetes could induce an elevation of LDL-C, which is the core element of the lipid profile in the development of atherosclerosis. Thus, we suspect that long-term treatment of diabetes may have benefits for atherosclerosis prevention that are partly mediated through LDL-C reduction.

The strengths of our study include the well-defined community setting and the use of MR to delineate the genetically determined relations between diabetes, BMI, and lipid profile. Second, the IVs we used for the MR were strong ($F > 10$). Last, our participants were all of Asian descent, which eliminated population admixture as a potential drawback. This study also has some limitations. All of the participants were of Asian origin. Therefore,

our findings may not be applicable to other ethnicities. Second, the lipid profiles were measured only once at baseline. Hence, we were not able to control for intra-individual variability. Third, the self-reported diagnoses of hypertension and diabetes may not have been completely accurate; however, in an Asian population study, the self-reported medical histories were generally accurate, including self-reported hypertension and diabetes (34). Finally, we built our GRSs based only on common variants that are considered to represent limited diabetes and BMI heritability. We were unable to assess the potential contribution of rare variants. It was also difficult to use the GRSs to completely discriminate the effects of diabetes and obesity from the effects of other risk factors on changes in lipid profile because of the possible pleiotropic effects of SNPs, especially regarding the BMI_GRS.

In conclusion, this analysis has provided evidence for the biologically plausible causal relationships of genetically determined type 2 diabetes with higher TC and LDL-C and genetically determined obesity with lower HDL-C and higher TG in a Chinese population. Diabetes and adiposity seem to cause different types of hyperlipidemia. Our study suggests that early diagnosis and long-term treatment of type 2 diabetes may be beneficial for LDL-C, which is the lipid element with the most strongly confirmed involvement in atherosclerosis development, and thus lower LDL-C levels could aid the prevention of CVD. Independent MR studies are needed to validate our findings in other ethnicities.

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