Original Article
EPIDEMIOLOGY/GENETICS

Obesity

Causal Association of Overall Obesity and Abdominal Obesity with Type 2 Diabetes: A Mendelian Randomization Analysis

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Objective: This study aimed to compare the causal effect of overall obesity and abdominal obesity on type 2 diabetes among Chinese Han individuals.

Methods: The causal relationship of BMI and waist-to-hip ratio (WHR) with the risk of glucose deterioration and glycemic traits was compared using two different genetic instruments based on 30 BMI loci and 6 WHR loci with Mendelian randomization (MR) in three prospective cohorts ($n = 6,476$).

Results: Each 1-SD genetically instrumented higher WHR was associated with a 65.7% higher risk of glucose deterioration (95% CI = 1.069-2.569, $P = 0.024$), whereas no significant association of BMI with glucose deterioration was observed. Furthermore, a causal relationship was found only between BMI and homeostatic model assessment β-cell function (HOMA-B) ($\beta = 0.143$, $P = 0.001$), and there was a nominal association with Stumvoll second-phase insulin secretion traits ($\beta = 0.074$, $P = 0.022$). The significance level did not persist in sensitivity analyses, except in the causal estimate of WHR on the Gutt index in MR-Egger ($\beta = -0.379$, $P = 0.022$) and the causal estimate of BMI on homeostatic model assessment β-cell function in weighted median MR ($\beta = 0.128$, $P = 0.017$).

Conclusions: The data from this study support the potential causal relationship between abdominal obesity and hyperglycemia, which may be driven by aggravated insulin resistance, in contrast with the potential causal relationship between overall obesity and insulin secretion.

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Introduction

The prevalence and incidence of obesity are currently increasing worldwide. It is predicted that more than 1.12 billion individuals will have obesity by 2030 (1). The epidemic burst of obesity undoubtedly imposes a challenging burden for a clustering of metabolic disorders including type 2 diabetes. The link to type 2 diabetes is attributed not only to the amount of body fat but also its distribution. Specifically, subjects with abdominal obesity, quantified by waist circumference (WC) or waist-to-hip ratio (WHR), have shown increased sensitivity to type 2 diabetes independent of overall obesity (quantified by BMI) in observational epidemiological studies (2,3).

The obesity epidemic is due to a combination of genetic and environmental factors (4,5). Because measures of overall obesity and abdominal obesity are highly correlated with each other ($r^2 = 0.9$ between BMI and WC, $r^2 = 0.6$ between BMI and WHR) (6), observational studies have shown no advantage in assessing the effects on numerous metabolic and immunological diseases accounting for BMI and WHR.

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The Mendelian randomization (MR) approach could facilitate a robust causal inference using a single genetic variant or a genetic risk score (GRS) that summarizes the susceptibility of the overall contribution of all genetic variants related to a trait as the instrument. Because a GRS combines information from multiple variants, the summary measurement is more important to each individual variant and is robust to imperfect linkage for any one variant. The recent development of MR, together with the large number of BMI- and WHR-related loci, has allowed a far more detailed causal investigation of obesity-related diseases than was previously known (7-9). In particular, more recent published MR studies have indicated that both overall obesity and abdominal obesity had causal effects on type 2 diabetes in individuals of European ancestry, in which a total of 97 established BMI variants and 48 WHR variants were used as the instruments (10,11). East Asian individuals demonstrate unique characteristics with type 2 diabetes onset, including lower BMI and earlier β-cell dysfunction compared with European populations. However, conclusive and sufficient evidence for the influence of BMI and WHR on type 2 diabetes risk in East Asian populations is lacking. Moreover, type 2 diabetes is characterized by insulin resistance accompanied by a progressive loss of β-cell function. The present evidence presents mixed findings regarding the impact of a predisposition to BMI on β-cell function (12-14). Whether there is difference in the causal effects of elevated BMI and WHR on insulin secretion and insulin resistance remains unknown.

Accordingly, our study aimed to compare the causal effects of overall obesity and abdominal obesity on type 2 diabetes development, insulin secretion, and insulin resistant traits in a population-based prospective cohort.

Methods

Subjects

For the present study, we analyzed three cohorts from Chinese Han individuals (Figure 1). In general, the following criteria were required for inclusion in the combined analysis: age > 20 years; absence of type 2 diabetes at baseline; and complete data available for BMI, WHR, and genotype information.

The Shanghai Diabetes Study (SHDS) was a community-based survey of diabetes including 5,994 participants aged > 15 years from two communities in Shanghai, Huayang and Caoyang, in 1998 to 2001 (15). A total of 5,355 subjects participated in two follow-up examinations during 2003 to 2004 and 2010 to 2012. Here, we analyzed 2,547 subjects free of diabetes with genotype available from this cohort, also referred to as the 9-year cohort (Figure 1A).

The SHDS II was another independent community-based survey of diabetes in Shanghai (16). Baseline surveys were performed for 5,372 participants aged 14 to 79 years from six communities (Huayang, Linfeng, Tianmu, Pengpu, Gongye, and Anting) between 2007 and 2008. The subjects from the SHDS and SHDS II cohorts did not overlap, as they were involved in different communities or different residential areas in the Huayang community. The subjects from the Anting and Huayang communities were selected in our study because they received a complete follow-up examination in 2011 to 2012 ($n = 1,985$). Subjects with malignant tumors, severe disability, or psychiatric disturbances or those from other ethnic groups were excluded ($n = 5$). Here, we enrolled 1,853 subjects with genotype information available for the analysis. The Fat Distribution and Disease (FADE) cohort was a survey of metabolic syndrome in China. Between 2009 and 2010, a total of 2,958 subjects aged 15 to 79 years were enrolled at baseline and then underwent two follow-up examinations in 2011 to 2012 and in 2013 to 2014. Subjects with malignant tumors, severe disability, or psychiatric disturbances or those from other ethnic groups were ineligible ($n = 114$). Here, we enrolled 2,830 subjects with genotype data information available for the analysis. Since these two cohorts were completed within a similar period, we performed combined analysis by pooling data with genotype available ($n = 4,683$) and excluded the subjects with type 2 diabetes at baseline ($n = 754$). Therefore, the total sample size in the merged cohorts, also referred to as the combined 3-year cohort, was 3,929 (Figure 1B).

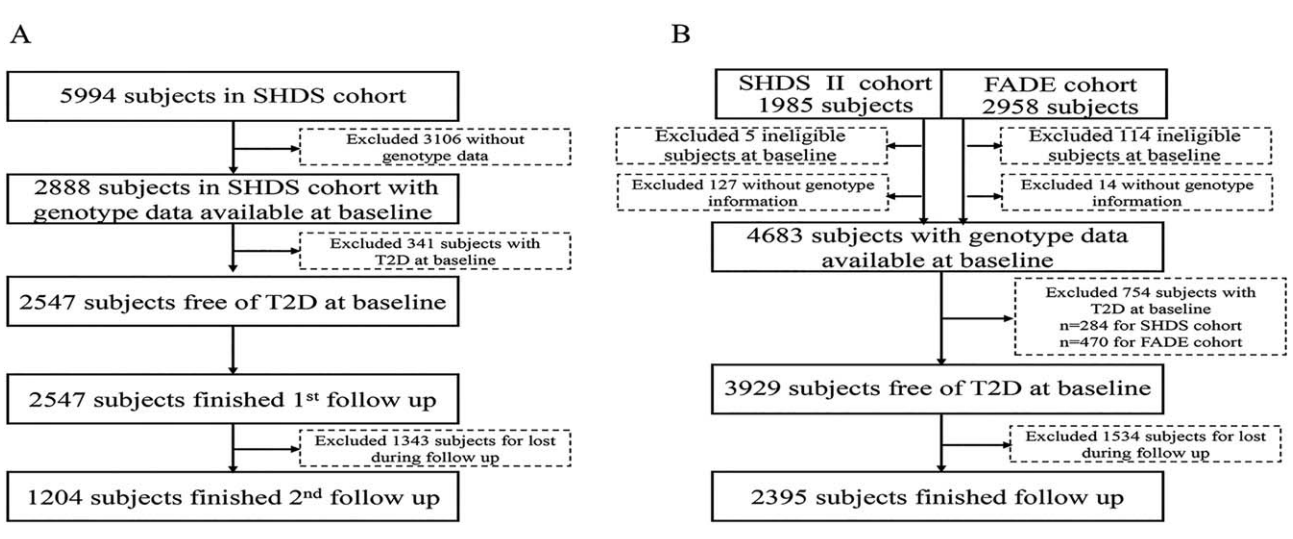

Figure 1 Flow diagram of the subjects (**A**) in the 9-year cohort and (**B**) in the combined 3-year cohort.

Finally, a total of 6,476 subjects initially free of type 2 diabetes with genotype available were included ($n = 2,547$ for the 9-year cohort; $n = 3,929$ for the combined 3-year cohort). Subjects provided written informed consent. All procedures were performed in accordance with the Declaration of Helsinki and the Institutional Review Board of Shanghai Jiao Tong University Affiliated Sixth People's Hospital.

Examinations

The subjects completed a standardized questionnaire to collect information on their health and lifestyle and their anthropometric and clinical measurements at baseline and follow-up. BMI was calculated as weight (kilograms) divided by height (meters squared). WC was measured at the horizontal plane between the inferior costal margin and the iliac crest on the midaxillary line. WHR was calculated as WC (centimeters) divided by hip circumference (centimeters). Body fat percentage (percent) was measured with the TBF-410 Tanita Body Composition Analyzer (Tanita, Tokyo, Japan). Subjects underwent a 75-g oral glucose tolerance test after an 8-hour overnight fast, except for those with a validated history of diabetes. Blood samples were obtained at the fasting, 30-minute, and 2-hour time points. Glucose levels were measured with the glucose oxidase method, and plasma insulin levels were assayed by radioimmunoassay (Linco Research, St Charles, Missouri) in a specific center. Glycated hemoglobin (HbA_{1c}) level was tested using high-performance liquid chromatography (VARIANT II; Bio-Rad, Hercules, California). Insulin sensitivity and secretion were estimated according to the homeostatic model assessments of insulin resistance and β-cell function (HOMA-IR and HOMA-B) and computations proposed by Stumvoll et al. and Gutt et al. (Stumvoll first-phase and second-phase insulin secretion and Gutt index, respectively) (17,18).

Outcome

Diabetes was diagnosed in accordance with the criteria of the American Diabetes Association in 2010 (19). Diabetes was diagnosed as a fasting plasma glucose (FPG) concentration ≥ 7 mmol/L, 2-hour plasma glucose ≥ 11.1 mmol/L, or $HbA_{1c} \geq 6.5\%$ or from a diabetes history. Prediabetes was defined as an FPG concentration of 5.6 to 6.9 mmol/L, a 2-hour plasma glucose concentration of 7.8 to 11.1 mmol/L, or an HbA_{1c} level of 5.7% to 6.4%. The diagnoses of diabetes without clinical symptoms were evaluated by clinical specialists and a confirmatory test was made if necessary. A "positive event" indicating blood glucose deterioration was classified as a transition from normal glucose tolerance to prediabetes or diabetes or a transition from prediabetes to diabetes.

Genotyping and calculating GRS

As reported in a previous study (20), we selected 30 established BMI single-nucleotide polymorphisms (SNPs) and 6 WHR-associated SNPs, which were established among East Asians by genome-wide association studies. There is no overlap between the 30 BMI SNPs and 6 WHR SNPs. A total of 36 SNPs were genotyped using the MassARRAY compact analyzer (Sequenom, San Diego, California). The SNP characteristics are presented in Supporting Information Table S1. The weighted GRS was derived from the sum of BMI- or WHR-increasing alleles weighted by the effect size for BMI and WHR from previous genome-wide association studies conducted in East Asians, which were totally independent of our study. For missing data, only subjects whose data were missing for more than 15% of the total SNPs (i.e., four SNPs for BMI and one SNP for WHR) were excluded. The GRS of the remaining subjects with missing data was standardized to those of subjects with complete data.

Statistical analysis

Data are presented as the mean ± SD, *n* (%), or odds ratio (OR) with 95% CI. All quantitative traits with a skewed distribution were logarithmically transformed to approximate univariate normality (i.e., Stumvoll first-phase insulin secretion, Stumvoll second-phase insulin secretion, HOMA-B, HOMA-IR, and Gutt index). Calculations of allele frequencies and tests of SNPs for Hardy-Weinberg equilibrium were performed by using PLINK (http://www.cog-genomics.org/plink/1.9/). Multiple logistic regressions were conducted to assess the association of BMI and WHR with glucose deterioration risk, and linear regressions were used to assess the association of BMI and WHR with quantitative traits at follow-up. The causal effects of BMI and WHR on glucose deterioration and quantitative traits were examined by the two-stage least squares estimator method (also termed conventional MR), which uses predicted values of BMI or WHR per allele and regresses each outcome against these predicted values. Separate models were tested for each outcome variable, which included adjustment for age, sex, BMI, and the baseline value of the outcome, if appropriate. Subgroup analysis stratified by sex was also performed to test for heterogeneity between males and females. Egger-MR and weighted median MR were conducted as two methods of sensitivity analysis to test whether the results of instrumental variables were robust. The statistical analyses were performed using Stata/SE 12.0 (StataCorp, College Station, Texas) unless otherwise specified. A two-tailed P value < 0.05 was considered nominally significant. Bonferroni correction was used to adjust for multiple testing (i.e., two tests for the analysis of glucose deterioration and ten tests for the analyses of glycemic traits). As such, associations of $P < 0.025$ for glucose deterioration and $P < 0.005$ for glycemic traits were considered significant. Combined effects from different studies were calculated by Comprehensive Meta-Analysis (version 2.2.057; Biostat, Englewood, New Jersey) with a fixed- or random-effect model after testing for heterogeneity. The extent of heterogeneity was examined by the Cochran Q statistic and the I^2 statistic.

Power calculation

We estimated the study power for each SNP with BMI and WHR by Quanto (http://biostats.usc.edu/Quanto.html, version 1.2.4, University of Southern California, Los Angeles, California). With the current sample size, the statistical power was 81% to detect the effect size of 0.147 kg/m^2 for BMI with a minor allele frequency of 0.49 (as of rs6265 in *BDNF*) and was 61% to detect the effect size of 0.004 for WHR with a minor allele frequency of 0.41 (as of rs984222 in *TBX15*) given a two-sided type I error rate of 0.05 (Supporting Information Table S1).

Results

Observational analysis of the association of BMI and WHR with risk of glucose deterioration

Over a mean follow-up time of 9.51 years (SD = 2.16), 300 of 2,547 subjects experienced type 2 diabetes and 454 subjects experienced prediabetes in the SHDS cohort. The overall incidence of type 2 diabetes during 15,086 person years of follow up was 19.9 per

TABLE 1 Characteristics of the subjects at baseline and at follow-up

		SHDS cohort	SHDS II cohort	FADE cohort
N		2,547	1,569	2,360
Sex, male (%)	Baseline	1,029 (40.4%)	548 (34.9%)	1,040 (45.6%)
Age (y)	Baseline	54.2 ± 14.7	50 ± 12	51.1 ± 6.8
BMI (kg/m^2)	Baseline	23.9 ± 3.5	23.6 ± 3.3	23.9 ± 3.2
	Follow-up	23.8 ± 3.5	23.8 ± 3.3	24.4 ± 3.1
Waist (cm)	Baseline	80 (73-87)	78 (71-85)	81.5 (74.5-88)
	Follow-up	82 (75-89.5)	82 (75-88)	82.5 (76-89.5)
WHR	Baseline	0.9 (0.8-0.9)	0.8 (0.8-0.9)	0.9 (0.8-0.9)
	Follow-up	0.9 (0.8-0.9)	0.9 (0.8-0.9)	0.9 (0.8-0.9)
Body fat percentage (%)	Baseline	29.1 (23.7-35.5)	28.1 (23.3-32.9)	28.1 (23.7-32.9)
	Follow-up	28.2 (23.1-34.4)	29.6 (23.6-34.9)	29.1 (24.6-34.3)
FPG (mmol/L)	Baseline	4.9 (4.6-5.3)	5 (4.6-5.4)	5.2 (4.8-5.6)
	Follow-up	5.5 (5.1-6)	5.3 (4.9-5.7)	5.2 (4.9-5.5)
Fasting plasma insulin (mU/L)	Baseline	7 (4.6-10)	6.1 (4.3-8.2)	9.5 (7.3-12.6)
	Follow-up	14.4 (8.3-20.8)	4.9 (3.9-6.8)	7.7 (5.4-10.5)
HbA_{1c} (%)	Baseline	5.4 (5.1-5.7)	5.5 (5.3-5.8)	5.6 (5.3-5.9)
	Follow-up	5.7 (5.4-6)	5.5 (5.2-5.8)	5.5 (5.3-5.8)
Stumvoll first-phase insulin secretion	Baseline	1,162.2 (965.6-1,370)	972.9 (784.7-1,157)	1,096.3 (879.8-1,324.2)
	Follow-up	1,206.7 (830.9-1,607.9)	831.1 (617-1,021.3)	1,030.5 (823.5-1,279.7)
Stumvoll second-phase insulin secretion	Baseline	301 (257.6-353.4)	252.7 (214.7-291.8)	293 (245.3-340.8)
	Follow-up	335.1 (252.4-433)	235.5 (190.6-280)	277.3 (235-338.1)
HOMA-B	Baseline	99.5 (67.5-144.8)	80 (55.4-119.5)	118.6 (85.1-163.6)
	Follow-up	140.4 (71.3-206.4)	58.2 (42.3-84.8)	91.5 (63.7-130.9)
HOMA-IR	Baseline	1.5 (1-2.3)	1.3 (0.9-1.8)	2.2 (1.6-3)
	Follow-up	3.6 (2-5.3)	1.2 (0.9-1.7)	1.8 (1.2-2.5)
Gutt index	Baseline	88.3 (71-111.2)	102.7 (82-134.5)	86.8 (70.3-109.8)
	Follow-up	62.7 (47.6-85.1)	93.6 (70-123.8)	81.2 (63.6-103.4)

Data are shown as mean ± SD, median (interquartile range), or *N* (%)

1,000 person years. The mean follow-up time of the combined analysis of the SHDS II and FADE cohorts was 3.68 years (SD = 0.7). In total, 241 of 3,929 subjects experienced type 2 diabetes and 509 subjects experienced prediabetes. The incidence of type 2 diabetes during 15,409 person years of follow-up was 15.6 per 1,000 person years. We found that the levels of fasting plasma insulin, HbA_{1c}, Stumvoll first- and second-phase insulin secretion, and HOMA-B were elevated relative to those at baseline in the SHDS cohort, whereas these indices were reduced during follow-up in the SHDS II cohort and FADE cohort (Table 1). In general, the observational analysis showed that baseline BMI and WHR could predict the incidence of glucose deterioration and the alteration of glycemic-related traits in the 9-year cohort as well as in the combined 3-year cohort (Supporting Information Table S2). For example, the ORs for each additional SD increase in BMI were 1.386 (95% CI = 1.266-1.517, $P < 0.0001$) in the combined 3-year cohort and 1.170 (95% CI = 1.072-1.277, $P = 0.0005$) in the 9-year cohort with adjustment for age and sex.

MR analysis of the association of BMI and WHR with glucose deterioration

As expected, a 1-point-higher BMI-GRS was positively associated with BMI at baseline in the combined 3-year cohort ($\beta = 0.035$, $P = 3.4 \times 10^{-15}$) and 9-year cohort ($\beta = 0.025$, $P = 4.44 \times 10^{-6}$) after adjustment for age and sex; and a 1-point-higher WHR-GRS was positively associated with WHR at baseline in the combined 3-year cohort ($\beta = 0.024$, $P = 0.004$) and 9-year cohort ($\beta = 0.027$, $P = 0.005$) after adjustment for age, sex, and BMI (Figure 2). The range of WHR-GRS among males and females was comparable (Supporting Information Figure S1). Using the MR approach, a 1-SD genetically higher WHR (equivalent to 0.077) instrumented by WHR-GRS was nominally associated with an 81.4% higher risk of glucose deterioration in the 9-year cohort after adjustment for age, sex, and BMI (95% CI = 1.031-3.183, $P = 0.038$), and the effect direction for glucose deterioration in the combined 3-year cohort per 1-SD greater WHR (equivalent to 0.074) was consistent with that derived from the 9-year cohort, although this result was not statistically significant (OR = 1.441 [0.716-2.903], $P = 0.306$). The combined analysis of three cohorts by a meta-analysis revealed that a 1-SD genetically instrumented higher WHR was associated with a 65.7% higher risk of glucose deterioration (95% CI = 1.069-2.569, $P = 0.024$). The Cochran Q test showed no heterogeneity in the instrumental variable estimates from the 9-year cohort and the combined 3-year cohort ($I^2 = 0$, $P = 0.800$). The MR estimate was consistent with that derived from the observational analysis (OR = 1.657 vs. 1.17; $I^2 = 57.18$, P for heterogeneity = 0.126). However,

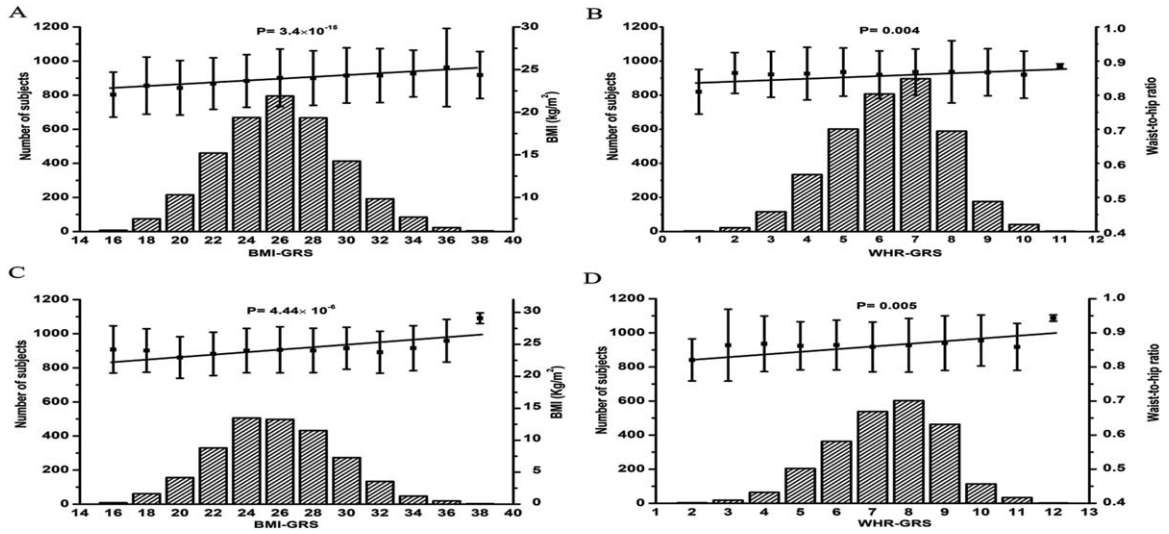

Figure 2 BMI-GRS distribution and its association with BMI (**A**) in the combined 3-year cohort and (**C**) in the 9-year cohort. WHR-GRS distribution and its association with WHR (**B**) in the combined 3-year cohort and (**D**) in the 9-year cohort. Histograms represent the number of subjects, and mean (± SD) BMI and WHR are plotted with the trend lines across the BMI-GRS or WHR-GRS.

the causal analysis for BMI and glucose deterioration risk did not show any significant results in the 9-year cohort (OR = 0.972 [0.789-1.195], $P = 0.787$) or in the combined 3-year cohort (OR = 0.906 [0.804-1.021], $P = 0.105$) (Table 2).

We repeated the analyses in the subgroup stratified by sex. No substantial difference was observed between males and females (P for heterogeneity > 0.05) (Supporting Information Table S3). For example, the ORs of glucose deterioration per 1-SD greater WHR were 1.42 in males (95% CI = 0.649-3.106, $P = 0.380$) and 1.357 in females (95% CI = 0.874-2.109, $P = 0.174$) in a meta-analysis of the three cohorts.

MR analysis of BMI and WHR with glycemic-related traits

Furthermore, both genetic instruments were also used to assess the causal relationship of BMI and WHR with glycemic-related traits, namely, Stumvoll first-phase insulin secretion, Stumvoll second-phase insulin secretion, HOMA-B, HOMA-IR, and Gutt index. Genetically instrumented BMI was positively associated with Stumvoll first-phase insulin secretion ($\beta = 0.101$, 95% CI = 0.037 to 0.164, $P = 0.002$), Stumvoll second-phase insulin secretion ($\beta = 0.074$, 95% CI = 0.021 to 0.127, $P = 0.006$), and HOMA-B ($\beta = 0.124$, 95% CI = 0.048 to 0.199, $P = 0.001$) in the combined 3-year cohort after adjustment for age and sex. In the 9-year cohort, we did not find any significant results for BMI and glycemic-related traits. Therefore, the combined analysis by meta approach revealed causality between BMI and insulin secretion indices, including HOMA-B ($\beta = 0.117$, 95% CI = 0.045 to 0.189, $P = 0.001$), Stumvoll first-phase insulin secretion ($\beta = 0.101$, 95% CI = 0.042 to 0.161, $P = 0.001$), and Stumvoll second-phase insulin secretion traits ($\beta = 0.073$, 95% CI = 0.025 to 0.121, $P = 0.003$). In contrast, we did not observe significant associations of WHR with insulin secretion and insulin resistant traits at follow-up, but we found 1-SD genetically instrumented higher WHR was nominally inversely associated with the Gutt index at baseline ($\beta = -0.105$, 95% CI= −0.2 to −0.01, $P = 0.030$) with adjustment for age, sex, and BMI in the combined three cohorts (Table 2).

To account for the difference in the glycemic status at baseline, we additionally adjusted for baseline values of corresponding outcomes to test for each outcome variable. No substantial difference in effect sizes between the models with or without adjustment of the baseline values of the outcome variable was observed (P for heterogeneity > 0.05). In the combined 3-year cohort, the signals of HOMA-B ($\beta = 0.160$, 95% CI = 0.068-0.252, $P = 0.001$) remained significant after adjusting for baseline values of corresponding outcomes. The combined analysis by the meta approach revealed causality between BMI and HOMA-B ($\beta = 0.143$, 95% CI = 0.059-0.227, $P = 0.001$) and nominal association with Stumvoll second-phase insulin secretion traits ($\beta = 0.074$, 95% CI = 0.011-0.138, $P = 0.022$) (Table 2).

Sensitivity analysis

We performed MR-Egger and weighted-median MR analyses to test the robustness of the results. The MR-Egger analysis revealed the absence of unmeasured pleiotropy in the instruments for glucose deterioration risk and glycemic traits (intercept $P > 0.05$), with the exception of HOMA-IR and HOMA-B (intercept $P = 0.045$ and 0.043, respectively). The causal ORs for the association of WHR with glucose deterioration risk were 9.934 in the MR-Egger analysis (95% CI = 0.932 to 105.864, $P = 0.057$) and 6.214 in the weighted-median MR analysis (95% CI = 0.496 to 7.123, $P = 0.155$), which were directionally consistent with the conventional MR, although the CIs were wider and included the null. We also derived the causal estimate of WHR on the Gutt index in the MR-Egger analysis ($\beta = -0.379$, 95% CI = −0.704 to −0.055, $P = 0.022$) and the causal estimate of BMI on HOMA-B in the weighted-median MR analysis ($\beta = 0.128$, 95% CI = 0.023 to 0.233, $P = 0.017$) (Table 3).

TABLE 2 Association of overall obesity and abdominal obesity with glucose deterioration and glycemic traits in conventional MR

		9-year cohort		Combined 3-year cohort		Meta-analysis of three cohorts			
Outcome		Estimate (95% CI) per 1-SD higher BMI or WHR	*P*	Estimate (95% CI) per 1-SD higher BMI or WHR	*P*	Estimate (95% CI) per 1-SD higher BMI or WHR	*P*	*P* for heterogeneity	I^2
BMI									
Glucose deterioration[a]	Model 1	0.972 (0.789 to 1.195)	0.787	0.906 (0.804 to 1.021)	0.105	0.922 (0.831 to 1.022)	0.123	0.567	0
Stumvoll first-phase insulin secretion	Model 1	0.107 (−0.116 to 0.33)	0.347	0.101 (0.037 to 0.164)	**0.002**[b]	0.101 (0.042 to 0.161)	**0.001**[b]	0.977	0
Stumvoll second-phase insulin secretion	Model 1	0.065 (−0.067 to 0.196)	0.334	0.074 (0.021 to 0.127)	**0.006**	0.073 (0.025 to 0.121)	**0.003**[b]	0.939	0
Gutt index	Model 1	−0.015 (−0.123 to 0.093)	0.788	−0.034 (−0.086 to 0.018)	0.195	−0.033 (−0.08 to 0.014)	0.172	0.918	0
HOMA-IR	Model 1	0.118 (−0.085 to 0.322)	0.255	0.077 (0.001 to 0.153)	**0.048**	0.082 (0.011 to 0.153)	**0.024**	0.747	0
HOMA-B	Model 1	0.062 (−0.14 to 0.265)	0.548	0.124 (0.048 to 0.199)	**0.001**[b]	0.117 (0.045 to 0.189)	**0.001**[b]	0.605	0
Stumvoll first-phase phase insulin secretion	Model 2	0.104 (−0.086 to 0.294)	0.282	0.05 (−0.029 to 0.129)	0.213	0.056 (−0.018 to 0.13)	0.136	0.637	0
Stumvoll second-phase insulin secretion	Model 2	0.069 (−0.049 to 0.187)	0.252	0.077 (0.003 to 0.15)	**0.040**	0.074 (0.011 to 0.138)	**0.022**	0.875	0
Gutt index	Model 2	−0.028 (−0.13 to 0.073)	0.581	−0.039 (−0.102 to 0.023)	0.215	−0.033 (−0.087 to 0.021)	0.234	0.706	0
HOMA-IR	Model 2	0.111 (−0.081 to 0.302)	0.257	0.052 (−0.036 to 0.141)	0.249	0.062 (−0.019 to 0.143)	0.131	0.560	0
HOMA-B	Model 2	0.066 (−0.14 to 0.271)	0.533	0.16 (0.068 to 0.252)	**0.001**[b]	0.143 (0.059 to 0.227)	**0.001**[b]	0.387	0
WHR									
Glucose deterioration[a]	Model 3	1.814 (1.031 to 3.183)	**0.038**	1.441 (0.714 to 2.903)	0.306	1.657 (1.067 to 2.569)	**0.024**[b]	0.800	0
Stumvoll first-phase insulin secretion	Model 3	0.107 (−0.596 to 0.81)	0.765	0.169 (−0.393 to 0.73)	0.556	0.145 (−0.294 to 0.583)	0.517	0.893	0
Stumvoll second-phase insulin secretion	Model 3	−0.01 (−0.436 to 0.415)	0.962	0.35 (−0.326 to 1.025)	0.311	0.092 (−0.268 to 0.452)	0.616	0.377	0

TABLE 2. (continued).

Outcome		9-year cohort Estimate (95% CI) per 1-SD higher BMI or WHR	*P*	Combined 3-year cohort Estimate (95% CI) per 1-SD higher BMI or WHR	*P*	Meta-analysis of three cohorts Estimate (95% CI) per 1-SD higher BMI or WHR	*P*	*P* for heterogeneity	I^2
Gutt index	Model 3	0 (−0.313 to 0.312)	0.998	−0.343 (−0.987 to 0.301)	0.297	−0.065 (−0.346 to 0.216)	0.650	0.348	0
HOMA-IR	Model 3	−0.251 (−0.916 to 0.414)	0.459	0.712 (−8.642,10.065)	0.881	−0.246 (−0.909 to 0.417)	0.467	0.840	0
HOMA-B	Model 3	−0.325 (−1.07 to 0.42)	0.392	0.356 (−0.363 to 1.075)	0.332	0.027 (−0.49 to 0.545)	0.917	0.197	39.821
Stumvoll first-phase insulin secretion	Model 4	0.111 (−0.59 to 0.812)	0.756	0.01 (−0.231 to 0.251)	0.933	0.021 (−0.207 to 0.249)	0.859	0.790	0
Stumvoll second-phase insulin secretion	Model 4	−0.014 (−0.441 to 0.413)	0.948	0.085 (−0.138 to 0.308)	0.456	0.064 (−0.134 to 0.262)	0.528	0.687	0
Gutt index	Model 4	0.038 (−0.291 to 0.366)	0.822	−0.132 (−0.356 to 0.092)	0.248	−0.078 (−0.263 to 0.106)	0.406	0.402	0
HOMA-IR	Model 4	−0.275 (−0.912 to 0.363)	0.399	0.317 (−0.717 to 1.351)	0.548	−0.112 (−0.654 to 0.43)	0.686	0.339	0
HOMA-B	Model 4	−0.33 (−1.076 to 0.415)	0.385	0.134 (−0.185 to 0.453)	0.411	0.062 (−0.232 to 0.356)	0.679	0.262	20.589

Model 1 adjusts for age and sex; model 2 adjusts for age, sex, and baseline value of outcome variables; model 3 adjusts for age, sex, and BMI; model 4 adjusts for age, sex, BMI, and baseline value of outcome variables. Bold numbers indicate $P < 0.05$.

[a]Effect estimate (95% CI) is OR (95% CI) per 1-SD higher BMI or WHR; otherwise, it is β (95% CI) per 1-SD higher BMI or WHR.

[b]Associations remained significant after Bonferroni correction for multiple tests, and Bonferroni corrected cutoff *P* value is 0.025 for glucose deterioration (0.05/2) and is 0.005 for glycemic traits (0.05/10).

TABLE 3 Association of overall obesity and abdominal obesity with glucose deterioration and glycemic traits in sensitivity analyses

		MR-Egger			Weighted median MR	
Outcome		Estimate (95% CI) per 1-SD higher BMI or WHR	*P*	Intercept *P*	Estimate (95% CI) per 1-SD higher BMI or WHR	*P*
BMI						
Glucose deterioration[a]	Model 1	0.889 (0.433 to 1.823)	0.749	0.712	0.871 (0.458 to 1.653)	0.673
Stumvoll first-phase insulin secretion	Model 2	0.065 (−0.025 to 0.155)	0.156	0.956	0.063 (−0.02 to 0.147)	0.138
Stumvoll second-phase insulin secretion	Model 2	0.063 (−0.018 to 0.144)	0.129	0.655	0.02 (−0.057 to 0.097)	0.611
HOMA-IR	Model 2	0.01 (−0.088 to 0.108)	0.837	0.602	0.011 (−0.077 to 0.099)	0.804
HOMA-B	Model 2	0.1 (−0.01 to 0.21)	0.074	0.412	0.128 (0.023 to 0.233)	**0.017**
Gutt index	Model 2	−0.073 (−0.152 to 0.007)	0.074	0.212	−0.038 (−0.11 to 0.034)	0.301
WHR						
Glucose deterioration[a]	Model 3	9.934 (0.923 to 105.864)	0.057	0.351	6.214 (0.496 to 77.123)	0.155
Stumvoll first-phase insulin secretion	Model 4	−0.158 (−0.48 to 0.165)	0.339	0.336	−0.105 (−0.394 to 0.184)	0.478
Stumvoll second-phase insulin secretion	Model 4	0.026 (−0.284 to 0.335)	0.871	0.753	0.039 (−0.223 to 0.302)	0.769
HOMA-IR	Model 4	0.553 (0.009 to 1.097)	**0.046**	**0.045**	0.213 (−0.205 to 0.632)	0.318
HOMA-B	Model 4	0.552 (0.044 to 1.061)	**0.033**	**0.043**	0.017 (−0.5 to 0.534)	0.949
Gutt index	Model 4	−0.379 (−0.704 to −0.055)	**0.022**	0.108	−0.172 (−0.463 to 0.119)	0.248

Model 1 adjusts for age and sex; model 2 adjusts for age, sex, and baseline value of outcome variables; model 3 adjusts for age, sex, and BMI; model 4 adjusts for age, sex, BMI, and baseline value of outcome variables. Bold numbers indicate $P < 0.05$.
[a]Effect estimate (95% CI) is OR (95% CI) per 1-SD higher BMI or WHR; otherwise, it is β (95% CI) per 1-SD higher BMI or WHR.

Discussion

Our study evaluated the potential causal effect of BMI and WHR on glucose deterioration risk using the MR method based on 30 BMI variants and 6 WHR variants in three dependent prospective cohorts from Chinese Han populations. We provided evidence that abdominal obesity causally increased the risk of glucose deterioration independent of BMI, which may be driven by impaired insulin sensitivity. In contrast, overall obesity had causal relevance for insulin secretion. These results highlight the different mechanisms by which overall obesity and abdominal obesity contributed to individual risk of type 2 diabetes.

Our findings are supported by numerous lines of evidence from observational and MR studies. Previous cross-sectional and longitudinal studies demonstrated that both a genetic predisposition to a higher WHR adjusted for BMI and a genetic predisposition to a higher BMI were associated with an increased risk of type 2 diabetes in European and East Asian populations (21-25). Because of the benefits of MR, the analysis by Emdin et al. revealed that a 1-SD increase in WHR (0.068) was causally associated with a higher risk of type 2 diabetes (OR = 1.77, 95% CI = 1.57-2.00) based on 48 WHR loci as a genetic instrument (10). A more recent MR study by Dale et al. using 97 BMI loci and 49 WHR loci revealed an OR of 1.82 (95% CI = 1.38-2.42) for a 4.6 kg/m^2 increase in BMI and an OR of 1.98 (95% CI = 1.41-2.78) for a 0.08-unit increase in WHR (11). These analyses were restricted to individuals of European ancestry. We identified that abdominal obesity had a potential causal effect on glucose deterioration in Chinese populations, whereas we did not replicate the causal association between BMI and glucose deterioration. The reasons for the negative results for the association of BMI with type 2 diabetes are unclear and warrant further investigation.

Although elucidating the burden of diabetes imposed by obesity has been a hot topic, the different mechanisms of abdominal obesity and overall obesity contributing to individual risk of diabetes have been poorly investigated because of the high correlation between them. In the current study, we enhanced the understanding of dynamic changes

in insulin secretion and insulin sensitivity followed by obesity by using the MR approach, strongly indicating the increased insulin secretion as a compensatory response to obesity-driven insulin resistance in overall obesity but impaired insulin sensitivity in abdominal obesity. This is supported by those studies that indicated that the predisposition to WHR was associated with insulin sensitivity (quantified by the Matsuda index) as well as an increased risk of diabetes (26). Numerous biology studies also provided evidence that abdominal obesity is always accompanied by ectopic fat storage, which could lead to an excess lipid delivery to nonadipose tissue accelerating insulin resistance and hyperglycemia (27,28). If further research validates our findings, identification and management of subjects with overall obesity and abdominal obesity could become important guides to reduce individual risk of type 2 diabetes.

Several limitations should be noted. First, the change of insulin secretion during follow-up differs between the 9-year cohort and the combined 3-year cohort (i.e., insulin secretion-related traits were increased in the SHDS cohort but decreased in the SDHS II and FADE cohorts from baseline to follow-up), which may be explained by the difference in follow-up periods, to some extent. This is possibly accounted for by the fact that the results from the 9-year cohort were not replicated in the combined 3-year cohort, even though we did not test the heterogeneity between these cohorts with the comparable sample sizes and characteristics of subjects at baseline. Second, we did not conduct sex-specific instruments of WHR for type 2 diabetes because of the limited numbers of subjects. But we found that the WHR-GRS performed similarly in males and females. Thus, future research that explores sex-specific instruments in larger data sets may prove more conclusive. Additionally, further investigations to test the generalizability of our GRS in other populations are warranted.

Conclusion

In summary, our results indicated that abdominal obesity, beyond the simple measurement of BMI, could contribute to the risk of glucose deterioration in Chinese Han populations, which may be mediated by aggravating insulin resistance, compared to the underlying causal relationship between insulin secretion and overall obesity.O

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