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Childhood obesity leads to adult type 2 diabetes and coronary artery diseases

A 2-sample mendelian randomization study

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Abstract

Observational studies have reported that childhood obesity is positively associated with risks of type 2 diabetes (T2D) and coronary artery disease (CAD) in adults; however, whether this association is causal is still unclear. In the present study, we conducted the 2-sample Mendelian randomization (MR) studies to investigate whether childhood obesity is causally associated with T2D and CAD in adults.

Seven single-nucleotide polymorphisms (SNPs) that significantly associated with childhood obesity were used as instrumental variables. The 2-sample MR analyses were performed with the summary-level data of large-sample genome-wide association studies to evaluate the causal effects of childhood obesity on adult T2D and CAD and the levels of cardiometabolic traits.

The 2-sample MR analyses suggested that each 1-unit increase in the log-odds of having childhood obesity was causally associated with an increased risk of adult T2D (odds ratio [OR] = 1.16, 95% confidential interval [CI] = 1.06–1.28; $P = 1.0 \times 10^{-3}$) and CAD (OR = 1.07, 95% CI = 1.02–1.12; $P = 4.0 \times 10^{-3}$) based on the inverse-variance weighted method. The MR analyses also suggested that childhood obesity was positively associated with the levels of adult body mass index, waist circumference, hip circumference, waist and hip ratio, log-transformed fasting glucose, log-transformed homeostatic model assessment (HOMA) of insulin resistance (%), and triglycerides. The childhood obesity was negatively associated with the adult high-density lipoprotein cholesterol level; however, there was no evidence of a causal association between childhood obesity and the levels of fasting glucose, 2-hour glucose, HbA1c (%), log-transformed HOMA of ß-cell function (%), low-density lipoprotein cholesterol, or total cholesterol in adults.

In conclusion, a genetic predisposition to childhood obesity was associated with an increased risk of adult T2D and CAD, providing causal relations between childhood obesity and the risks of T2D and CAD in adults; however, the results need to be validated with larger-scale intervention studies.

Abbreviations: 95% CI = 95% confidential interval, BMI = body mass index, CAD = coronary artery disease, CARDIoGRAM = Coronary Artery Disease Genome-wide Replication and Meta-analysis, GWAS = genome-wide association study, HC = hip circumference, HDL-c = high-density lipoprotein cholesterol, HOMA-IR = homeostatic model assessment of insulin resistance, IV = instrumental variable, IVW = inverse variance weighted, LDL-c = low-density lipoprotein cholesterol, MR = Mendelian randomization, OR = odds ratio, RCT = randomized controlled trials, SD = standard deviation, SNP = single nucleotide polymorphism, T2D = type 2 diabetes, TC = total cholesterol, TG = triglycerides, WC = waist circumference, WHR = waist and hip ratio.

Keywords: childhood obesity, coronary artery disease, Mendelian randomization, type 2 diabetes

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1. Introduction

It has been estimated that 4% to 23% of children worldwide are overweight or obesity.[1] The prevalence of childhood obesity has been increasing dramatically during the past 4 decades, both in developed and developing countries.[1] Childhood obesity leads to short- and long-term problems of physical, social, and emotional health. Children with obesity are more prone to suffer from asthma, sleep apnea, bone and joint problems, and the heart diseases.[2–5] Furthermore, they are more likely to suffer from social isolation, depression, and lower self-esteem.[6,7] Childhood obesity has also been associated with long-term problems, such as an increased risks for various types of chronic cardiometabolic diseases including type 2 diabetes (T2D),[8] coronary artery disease (CAD),[9] ischemic stroke[10] and several types of cancer in adults;[11–15] however, socioeconomic status and unmeasured lifestyle factors may confound these observational associations. As observational studies are prone to bias, the causal associations between childhood obesity and cardiometabolic diseases need to be evaluated with more well-designed studies.

Mendelian randomization (MR) analysis is a genetic epidemiological method in assessing the potential causal relationships between modifiable exposure factors and risk of diseases. This method reduces the confounding factors as the genetic variants are assumed to be randomly allocated at the meiosis and thus not related to lifestyle or the habitable factors.[16] Furthermore, MR analyses also reduce the reverse causation as genetic randomization precedes the disease onset. Thus, MR analyses are recognized as analogous to randomized controlled trials (RCTs) and have been widely used to evaluate the causal relationship between modifiable factors and onset of diseases.[17] Several previous studies have reported that general and central obesity in adults is associated with increased risks of T2D and CAD in midlife,[18–22] and a recent study suggested that childhood body mass index (BMI) was causally associated with adult T2D and CAD;[23] however, the influence of the childhood obesity on these outcomes needs to be evaluated with more studies. Herein, we evaluated the causal association between the childhood obesity and the adult T2D and CAD using the 2-sample MR analysis based on the summary-level data from genome-wide association studies (GWASs) in the present study.

2. Material and methods

2.1. Study design

We performed 2-sample MR studies based on the publicly available summary-level data from GWASs to determine the causal relationship between childhood obesity and 2 most common metabolic diseases including T2D and CAD in adults (primary outcomes; Fig. 1). Furthermore, we evaluated the causality of childhood obesity and anthropometrics as well as glycemic and lipid risk factors for T2D and CAD (secondary outcomes; Fig. 1). The genetic instrumental variables (IVs) applied in the 2-sample MR studies should satisfy the following 3 assumptions:

(1) the genetic variants should be associated with childhood obesity,
(2) the genetic variants must not be associated with any confounders,
(3) the genetic variants are not directly associated with the outcome, nor is there any other alternative pathway by which the variants are associated with the outcome rather than through the exposure.

2.2. Instrumental variables selection and validation

For assumption 1, we first included 7 single nucleotide polymorphisms (SNPs) that reached genome-wide significance at the $P < 5 \times 10^{-8}$ level in the discovery stage of the GWAS with (5530 cases and 8318 controls) of childhood obesity by Bradfield et al.[24] Two more SNPs (rs9299 and rs9568856) that reached the $P < 5 \times 10^{-8}$ level in the joint study of the discovery and replication stage (2818 cases and 4083 controls) were also included as IVs.[24] The range of the age at which the body mass index (BMI) was measured was 0.1 to 18.9 years old for participants in discovery and replication stage. For assumption 2 that the variants were not associated with any confounders, we

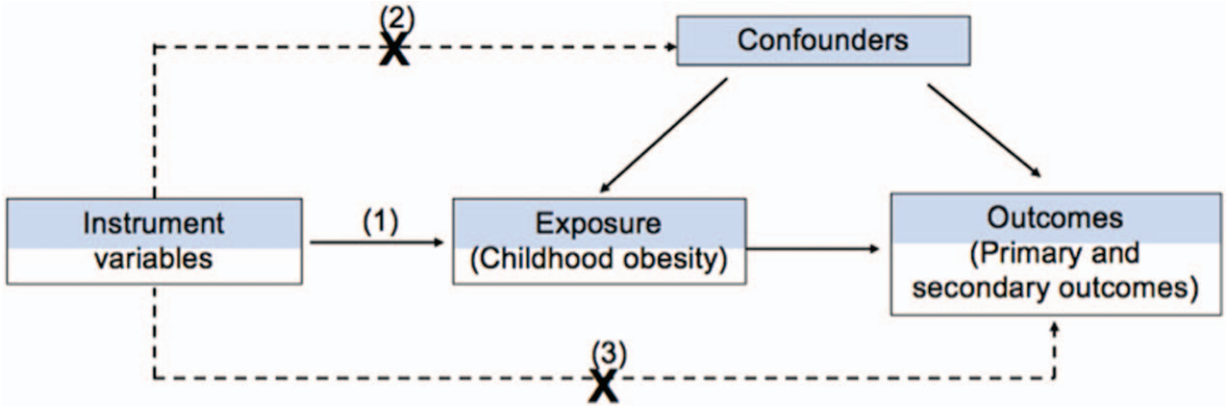

Figure 1. Study design and the assumptions for the 2 sample Mendelian randomization. Three assumptions including: (1) the genetic variants should be robustly associated with the exposure; (2) the genetic variants should not be associated with the confounders of the exposure-outcome association; (3) the genetic variants must influence the outcomes through the exposure only and not through any other indirect pathways. The dash lines represent pathways that violate the assumptions. The primary outcomes of the study were adult T2D and CAD, while the secondary outcomes were BMI, WC, HC, WHR, fasting glucose, 2-hour glucose, fasting insulin, HbA1c, log-transformed HOMA-B, log-transformed HOMA-IR, HDL-c, LDL-c, TC and TG levels. BMI = body mass index, CAD = coronary artery disease, HC = hip circumference, T2D = type 2 diabetes, WC = waist circumference, WHR = waist and hip ratio.

assessed the linkage disequilibrium (LD) between the loci using the clump functions implemented in the TwoSampleMR package of R (www.r-project.org) based on European ancestry. The correlation coefficient between the SNPs was lower ($r^2 < 0.01$), suggesting that these SNPs were suitable as IVs for MR studies. To further minimize the risk of pleiotropy of the SNPs, we performed MR analyses using 2 different models. The IV2 model included all 9 SNPs from the GWAS of childhood obesity. In the IV1 model, we excluded 2 SNPs (rs9941349 and rs663129) that were significantly associated with adult T2D (rs9941349) and CAD (rs9941349 and rs663129) at the genome-wide significance level ($P < 5 \times 10^{-8}$).[25,26] We decided to use IV1 as the main model as it balanced the statistical power and the risk of pleiotropy in the MR studies. In total, the 9 and 7 variants explained 2.38% and 1.69% variance of childhood obesity, respectively (Table 1).

2.3. Data sources

Summary-level data (β-coefficients and standard errors) for the 9 SNPs associated with childhood obesity and the primary and secondary outcomes were obtained from the public GWAS (Supplementary Table 1, http://links.lww.com/MD/D176) that had been assembled in the PhenoScanner database (http://www.phenoscanner.medschl.cam.ac.uk/phenoscanner).[27] Summary-level data were extracted from the Diabetes Genetics Replication and Meta-analysis (DIAGRAM) consortium (26,488 cases and 83,964 controls with the mean age ranged from 44.0 to 71.7 years old for individual participants cohorts) for T2D,[25] the Coronary Artery Disease Genome-wide Replication and Meta-analysis (CARDIoGRAM) plus the Coronary Artery Disease (C4D) Genetics (CARDIoGRAMplusC4D) consortium for CAD (60,801 cases and 12,354 controls with the age >18 years old).[26] The diagnosis of T2D was based on the 1999 World Health Organization criteria of fasting plasma glucose concentration >7.0 mmol/L or 2-hour plasma glucose concentration >11.1 mmol/L, by self-report of diabetes medication use, or by medical record review.[25] The CAD was defined using a broad definition that included myocardial infarction (about 70% of the total number of cases), acute coronary syndrome, chronic stable angina or coronary artery stenosis >50% in the pooled samples of CARDIoGRAMplusC4D.[26]

For cardiometabolic traits, summary-level data were obtained from the meta-analysis of Glucose and Insulin-Related Traits Consortium (MAGIC) for fasting glucose (n = 46,186),[28] 2-hour glucose (n = 15,234),[29] log-transformed HOMA of beta-cell function (log HOMA-B, n = 46,186),[28] log-transformed HOMA of insulin resistance (log HOMA-IR, n = 46,186),[28] log-transformed fasting insulin (n = 46,186),[28] and hemoglobin A1c (HbA1c, n = 46,368);[30] the Global Lipids Genetics Consortium (GLGC) for high-density lipoprotein cholesterol (HDL-c, n = 92,820 to 18,7071 for individual SNP), low-density lipoprotein cholesterol (LDL-c, n = 81,164 to 172,994 for individual SNP), total cholesterol (TC, n = 85,759 to 187,259 for individual SNP) and triglycerides (TG, n = 82,176 to 177,769 for individual SNP);[31] the Genetic Investigation of Anthropometric Traits (GIANT) consortium for BMI (n = 233,978 to 322,102 for individual SNP),[32] hip circumference (HC, n = 144,085 to 212,997 for individual SNP),[33] waist circumference (WC, n = 152,832 to 232,059 for individual SNP)[33] and waist-to-hip ratio (WHR, n = 144,575 to 212,167 for individual SNP).[33] Detailed information regarding the association between the SNPs and the T2D, CAD and the cardiometabolic traits were provided as Table S1, http://links.lww.com/MD/D176.

2.4. Statistical methods

We performed the 2-sample MR studies with 4 different models to evaluate the causal effects of childhood obesity on adult T2D, CAD, and the cardiometabolic traits:

(1) the conventional inverse-variance weighted (IVW) model;
(2) the robust penalized IVW model;
(3) the weighted median-based model, which provides a consistent estimate of the causal effect when at least 50% of the genetic variants are valid IVs; and
(4) the MR-Egger regression model, which was widely used to evaluate the directional pleiotropy of the IVs and the slope of the MR-Egger regression provided pleiotropy corrected causal estimates.[34]

The MR-Egger regression model evaluated the null causal hypothesis under the Instrument Strength Independent of Direct Effect (InSIDE) assumption, and this method could provide unbiased estimates even if all the chosen SNPs are invalid.[35]

We performed the leave-1-out sensitivity method to evaluate whether the causal estimates were influenced by individual locus under the conventional IVW model, and the heterogeneity between the causal estimates by the SNPs was also deter-

Table 1

Characteristics of 9 SNP loci included in the mendelian randomization analysis.

SNP	Position	Nearest gene	β	SE	EA†	OA	EAF	*P* value	% variance explained	IV1 (n = 7)	IV2 (n = 9)
rs9941349*	chr16:53825488	FTO	0.1978	0.0267	t	c	0.442	1.16×10^{-13}	0.395		√
rs4854344	chr2:638144	TMEM18	0.2445	0.0351	t	g	0.804	3.22×10^{-12}	0.349	√	√
rs6752378	chr2:25150116	POMC	0.1695	0.0262	a	c	0.458	1.05×10^{-10}	0.301	√	√
rs663129	chr18:57838401	MC4R	0.1989	0.0311	a	g	0.245	1.27×10^{-10}	0.295		√
rs7138803	chr12:50247468	FAIM2	0.1672	0.0271	a	g	0.369	6.50×10^{-10}	0.274	√	√
rs9568856	chr13:54064981	OLFM4	0.1947	0.0323	a	g	0.158	1.82×10^{-8}	0.169	√	√
rs1040070	chr1:74977870	TNNI3K	0.1497	0.0269	g	c	0.463	2.78×10^{-8}	0.223	√	√
rs9299*	chr17:46669430	HOXB5	0.1345	0.0227	t	c	0.652	3.54×10^{-8}	0.169	√	√
rs10913469	chr1:177913519	SEC16B	0.1767	0.0329	c	t	0.208	7.99×10^{-8}	0.208	√	√

Chr = chromosome, EA = effect allele, EAF = effect allele frequency, IV = instrumental variable, OA = other allele, SNP = single nucleotide polymorphism.

* β and SE for each SNP loci were obtained from the discovery stage of genome-wide association study on childhood obesity (5530 cases and 8318 controls), while the estimates for rs9941349 and rs9299 were obtained from the combined analysis of discovery and replication stage (8341 cases and 12,401 controls).[24]

† Allele associated with increased risk of childhood obesity.

mined.[36] The MR analyses were conducted with the TwoSampleMR and MendelianRandomization packages of R software (www.r-project.org).[37,38] All statistical tests were 2 sided and considered statistically significant at the $P < .05$ level.

3. Results

3.1. Causal effects of childhood obesity on risks of adult T2D and CAD

In the main MR analyses based on the IV1 model with 7 valid SNPs that were significantly associated with childhood obesity (Table 1 and Table S1, http://links.lww.com/MD/D176), we found that childhood obesity was associated with a 16% increased risk of adult T2D under the IVW model (odds ratio [OR] = 1.16, 95% confidence interval [CI] = 1.06–1.28; $P = .001$; Fig. 2) for each unit increase in the log-odds of having childhood obesity. Similar results were obtained under the penalized robust IVW and the weighted median methods (Fig. 2). With the MR-Egger regression method, the intercept term was −0.076 with the 95% CI of −0.161 to 0.008 ($P = .080$), suggesting that the causal estimate may not be influenced by pleiotropy. There was a modest heterogeneity between the causal estimate by different SNPs under the IVW model (*P-heterogeneity* = .051), Under the IV2 model with 9 SNPs that were significantly associated with the children obesity (Table 1 and Table S1, http://links.lww.com/MD/D176), we found that childhood obesity was also associated with increased risk of adult T2D; however, the MR-Egger regression suggested that the IVs violated the pleiotropy assumption ($P = .028$; Table S2, http://links.lww.com/MD/D176). The pleiotropy-adjusted coefficients also supported the causal association between childhood obesity and T2D in adult ($\beta = 0.909$, se = 0.308; $P = .003$).

Based on the IV1 model with 7 valid SNPs that were associated with children obesity, the MR analysis suggested that a 7% increased risk of adult CAD (OR = 1.07, 95% CI = 1.02–1.12; $P = .004$; Fig. 2) was caused by each unit increase in the log-odds of having childhood obesity. The penalized robust IVW and weighted-median models provided similar results (Fig. 2), and the MR-Egger regression method suggested that the causal estimate for childhood obesity on CAD was not influenced by pleiotropy (intercept term = −0.042, se = 0.023; $P = .062$; Table 2). No significant heterogeneity between the causal estimate was noted between the SNPs under the IVW model (*P-heterogeneity* = .468), and none of the SNPs significantly influenced the causal estimate, as suggested by the leave-1-out sensitivity analyses. The MR-Egger regression did not identify a violation of pleiotropy assumption under IV2 model (intercept = -0.042, se = 0.023; $P = .062$), and the pleiotropy-adjusted coefficient also suggested a causal association between childhood obesity and adult CAD ($\beta = 0.306$, se = 0.131; $P = .019$). In addition, the MR analyses based on the IV2 model with 9 SNPs also suggested childhood

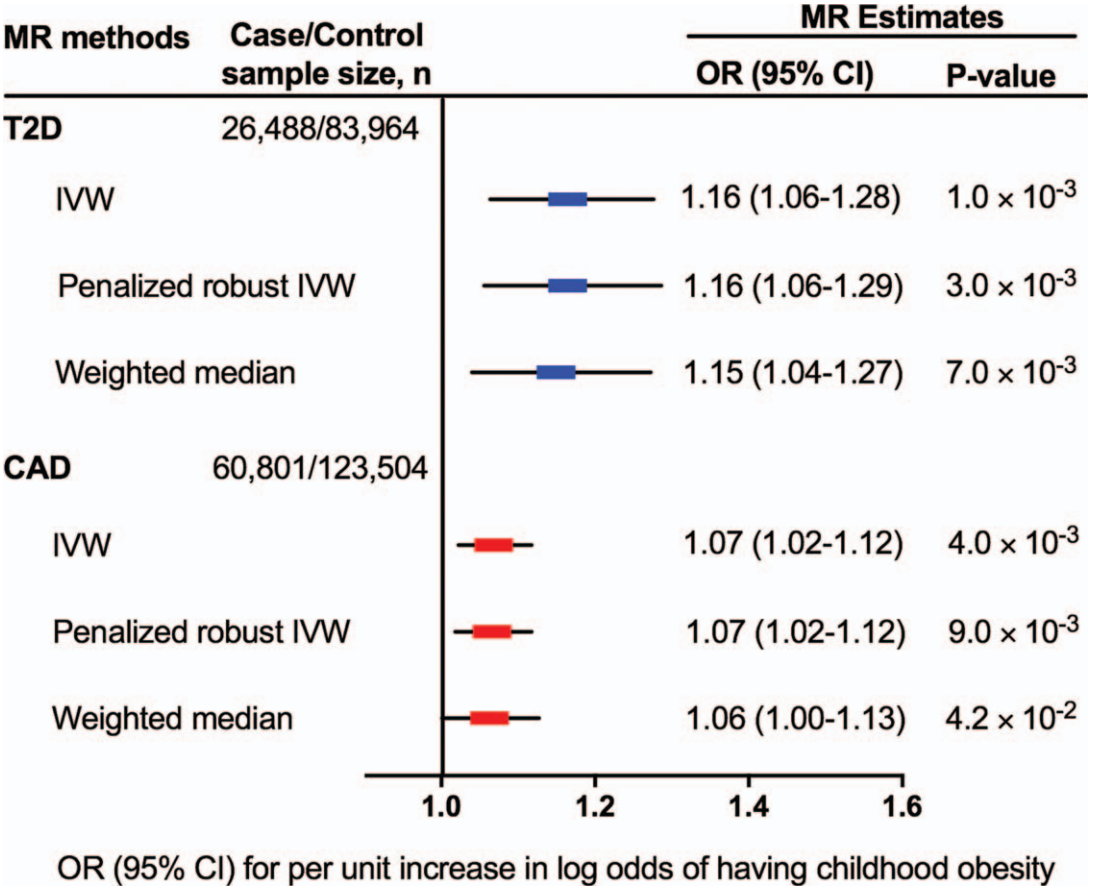

Figure 2. MR analysis results of childhood obesity and the risk of T2D and CAD using the conventional inverse variance weighted (IVW), penalized robust IVW and the weighted median methods under the IV1 model. Results are standardized to a unit increase in the log-odds of having childhood obesity. CAD = coronary artery disease, T2D = type 2 diabetes.

Table 2

The 2-sample MR analyses of childhood obesity and the cardiometabolic traits levels based on IV1 model.

			MR estimates, per unit increase in log odds of having childhood obesity							MR-Egger regression	
			IVW			Penalized robust IVW		Weighted median			
Outcomes*	SNPs, n	Participants, n	beta (se)	*P* value	*P* heterogeneity	beta (se)	*P* value	beta (se)	*P* value	Intercept (se)	*P* value
Anthropometric traits (SD, GIANT)											
BMI (kg/m^2)	7	322,102	0.192 (0.018)	<.001	<.001	0.167 (0.011)	<.001	0.184 (0.021)	<.001	−0.034 (0.013)	.007
HC (cm)	7	212,997	0.168 (0.023)	<.001	< .001	0.153 (0.001)	<.001	0.160 (0.021)	<.001	−0.040 (0.017)	.020
WC (cm)	7	232,059	0.155 (0.021)	<.001	< .001	0.145 (0.018)	<.001	0.159 (0.021)	<.001	−0.037 (0.016)	.027
WHR	7	212,159	0.066 (0.012)	<.001	.112	0.071 (0.012)	<.001	0.079 (0.014)	<.001	−0.016 (0.01)	.132
Glycemic traits (clinical units, MAGIC)											
Fasting glucose (mmol/L)	7	46,186	0.012 (0.010)	.223	.294	0.012 (0.01)	.218	0.014 (0.012)	.260	−0.003 (0.011)	.777
2-hour glucose (mmol/L)	7	15,234	−0.044 (0.047)	.349	.639	−0.044 (0.040)	.281	−0.033 (0.061)	.586	−0.087 (0.045)	.054
HbA_{1c} (%)	7	46,368	0.011 (0.009)	.192	.665	0.012 (0.01)		0.016 (0.011)	.160	−0.01 (0.008)	.242
Log fasting insulin (pmol/L)	7	46,186	0.025 (0.010)	.011	.671	0.025 (0.008)	.002	0.033 (0.013)	.008	−0.015 (0.009)	.114
Log HOMA-B (%)	7	46,186	0.017 (0.009)	.071	.277	0.017 (0.009)	.068	0.013 (0.011)	.262	−0.15 (0.008)	.067
Log HOMA-IR (%)	7	46,186	0.025 (0.010)	.012	.709	0.026 (0.008)	.002	0.032 (0.013)	.014	−0.015 (0.010)	.126
Lipids (SD, GLGC)											
HDL-c (mg/dL)	7	187,071	−0.047 (0.009)	<.001	.526	-0.046 (0.008)	<.001	-0.045 (0.013)	<.001	0.008 (0.009)	.352
LDL-c (mg/dL)	7	172,999	−0.001 (0.017)	.939	.010	−0.003 (0.022)	.884	−0.015 (0.015)	.319	0.023 (0.015)	.130
TC (mg/dL)	7	187,238	−0.005 (0.014)	.727	.046	−0.011 (0.013)	.381	−0.016 (0.013)	.247	0.011 (0.014)	.456
TG (mg/dL)	7	177,769	0.036 (0.009)	<.001	.419	0.036 (0.008)	<.001	0.038 (0.012)	.002	0.002 (0.010)	.875

BMI = body mass index, GIANT = Genetic Investigation of Anthropometric Traits, GLGC = Global Lipids Genetics Consortium, HC = hip circumference, HDL-c = high-density lipoprotein cholesterol, HOMA-B = homeostatic model assessment of beta-cell, HOMA-IR = homeostatic model assessment of insulin resistance, IVW = inverse variance weighted, LDL-c = low-density lipoprotein cholesterol, MAGIC = meta-analysis of Glucose and Insulin-Related Traits Consortium, MR = Mendelian Randomization, SD = standard deviation, SNP = single nucleotide polymorphism, TC = total cholesterol, TG = triglycerides, WC = waist circumference, WHR = waist and hip ratio.

* For anthropometric traits, the summary-level data were obtained from the GIANT consortium (in SD), glycemic traits from the MAGIC consortium (in clinical units) and lipids from GLGC consortium (in SD).

obesity was associated with increased risk of adult CAD (Table S2, http://links.lww.com/MD/D176).

3.2. Causal effect of childhood obesity on adult cardiometabolic traits

By using the IV1 model (Table 1 and Table S1, http://links.lww.com/MD/D176), we found that per-unit increase in the log-odds of having childhood obesity was causally associated with a 0.192-standard deviation (SD) increase in BMI ($\beta = 0.192$, se = 0.018; $P = 6.64 \times 10^{-26}$), a 0.168-SD increase in HC, a 0.155-SD increase in WC, and a 0.066-SD increase in WHR under the conventional IVW model (Table 2). Significant heterogeneity for the causal estimates between individual SNPs was noticed for BMI, WC, and HC but not for WHR (Table 2). Similar results were noticed with the IV2 model with 9 SNPs as the IVs (Table 1 and Table S1, http://links.lww.com/MD/D176) in assessing the causal estimates between childhood obesity and adult BMI, HC, WC, and WHR. The MR-Egger regression suggested that both the IV1 and IV2 model violated the pleiotropy assumption for BMI, HC, and WC but not WHR (Table 2 and Table S2, http://links.lww.com/MD/D176); however, the pleiotropy-adjusted coefficients also suggested that there were significant causal effects of childhood obesity on the anthropometric traits.

For the glycemic traits, we found that each 1-unit increase in the log-odds of having childhood obesity was causally associated with an increase of 0.025 pmol/L of log-transformed fasting insulin ($P = .011$) and .025 of log-transformed HOMA-IR ($P = .012$) in adults based on the conventional IVW method with the IV1 model (Table 1 and Table S1, http://links.lww.com/MD/D176). There was no evidence for the causal effects of childhood obesity on fasting glucose, 2-hour glucose, HbA1c, or the log-transformed homeostatic model assessment of beta-cell (HOMA-B) level in adults. No significant heterogeneity was noticed for the causal estimates between individual SNPs for these traits (Table 2). The MR-Egger regression suggested that the causal associations for glycemic traits were not influenced by the pleiotropy effects. Similar results were noticed with the MR analyses based on the IV2 model with 9 SNPs (Table S2, http://links.lww.com/MD/D176).

For the lipid traits, each unit increase in the log-odds of having childhood obesity was causally associated with a 0.047-SD reduction in HDL-c and a 0.036-SD increase in TG in adults with IV1 model (Table 1 and Table S1, http://links.lww.com/MD/D176). There was no evidence for the causal effects of childhood obesity on the LDL-c or TC level in adults (Table 2). No significant heterogeneity for the causal estimates between individual SNPs was noticed for the conventional IVW method regarding HDL-c or TC (*P-heterogeneity* >.05); however, significant heterogeneity for the causal estimates between individual SNPs was noted for LDL-c and TC (*P-heterogeneity* = .010 and .046, respectively). For all traits, the intercept term estimated in the MR-Egger regression was centered at the origin with a 95% CI including the null, suggesting that the observed results were not influenced by the pleiotropy. Similar results were obtained for the MR analyses based on the IV2 model with 9 SNPs (Table S2, http://links.lww.com/MD/D176).

3.3. Sensitivity analyses of MR studies

We performed the leave-1-out sensitivity analyses with the IV1 model using the conventional IVW method to evaluate the causal effects of childhood obesity on the risks of adult T2D and CAD (Figure S1, http://links.lww.com/MD/D176), anthropometric traits (Figure S2, http://links.lww.com/MD/D176), glycemic traits (Figure S3, http://links.lww.com/MD/D176), and lipids (Figure S4, http://links.lww.com/MD/D176) using the summary-level data from GWASs. We did not identify any heterogeneous SNPs that largely influence the causal estimates for childhood obesity on T2D, CAD, and cardiometabolic traits in adults.

4. Discussion

The present study evaluated the childhood obesity and adults T2D, CAD and the cardiometabolic traits using the MR method, a natural RCT, which has been widely used to evaluate the causal relationship between the exposures and outcomes. With 7 SNPs that were significantly associated with childhood obesity as the main IVs in the 2-sample MR analyses, we found a genetic predisposition of children with obesity was significantly associated with an increase of T2D and CAD in adult life, as well as increased adult levels of BMI, WC, HC, WHR, log fasting insulin, HOMA-IR, and TG. The 2-sample MR analyses also suggested that childhood obesity may cause a decrease in HDL-c level in adult. In contrast, no causal association between childhood obesity and the levels of fasting glucose, 2-hour glucose, HbA1c, log-transformed HOMA of ß-cell function, low-density lipoprotein cholesterol, or total cholesterol in adult was noticed.

Many prospective cohort studies have reported that childhood overweight was associated with increased risk of adult T2D and CAD.[20–22] Furthermore, the childhood obesity was associated with the adult level of insulin, lipids and the systolic blood pressure, which may underly the effects of childhood obesity on the cardiometabolic diseases.[39] A recent study published by Bjerregaard et al reported that children with persistent of overweight at 7 years old to puberty or early adults, or those only with overweight at 13 years old or at early adulthood were significantly associated with the increased risk of T2D in adult; however, children with overweight at 7 years but had had remission of the obesity before the age of 13 years, the risk of the adults T2D was reduced.[22] Juonala et al reported that overweight or obese children who were also obese as adults had increased risks of T2D, hypertension, dyslipidemia, and carotid-artery atherosclerosis; however, the risk of the cardiovascular disease was similar between those overweight or obese children who became nonobese by adulthood and those who were never obese.[40] The current MR analyses confirmed the observational studies that childhood obesity is associated with increased risk of cardiometabolic diseases and the related metabolic traits. Recently, Geng et al performed an MR analysis to test the causal effects of childhood BMI on adult cardiometabolic diseases.[23] With 15 SNPs that significantly associated with childhood BMI as the IVs, they found that a 1-SD increase of children BMI was associated with an 83% increase in risk of T2D and a 28% increase risk of CAD in adults.[23] These results provided strong evidence about the causal effects of childhood obesity and the risks of CAD and T2D and that early intervention methods should be performed for the obesity children to reduce the risk of adults T2D and CAD.

In the MR analyses, we found that the childhood obesity was significantly associated with higher adults of BMI, WC, HC, and WHR. This may be because that the childhood obesity and adult obesity may share the same genetic susceptibility factors. For the 7 SNPs that used as the IVs, 5 were significantly associated with the adults BMI at the GWAS level, 5 with adults HC, and 3 with WC (Table S1, http://links.lww.com/MD/D176), which may underlie the pleiotropy effects of the SNPs for adults BMI, HC, and WC as suggested by the MR-Egger regression analyses. In addition, we noticed that the childhood obesity was causally associated with the increased adult WHR, which is a simple measure of central obesity that is associated with T2D, glucose intolerance, insulin resistance, high blood pressure, atherosclerosis and so on. A recent MR study performed by Wang et al reported that higher WHR was causally associated with increased risk of glucose deterioration in adults through modulating the insulin sensitivity, while the overall obesity may modulate the insulin secretion.[41] Interestingly, we found that children obesity was causally associated increased log-transformed fasting insulin and the log-transformed HOMA-IR level; however, the childhood obesity was not associated with the fasting glucose, 2-hour glucose, and HbA1c level. Similarly, the MR analysis performed by Geng et al also reported that higher childhood BMI was causally associated with the increase of adulthood BMI, HC, WC, fasting insulin, and HOMA-IR using the 15 childhood BMI associated SNPs as the IVs.[23] These results suggesting that children obesity led to the impaired insulin sensitivity in adults and an increase of insulin secretion may act as a compensatory response to the insulin sensitivity, and the childhood obesity may not influence the adult T2D through directly modulating the glucose level.

For lipid traits, our MR analyses suggested that childhood obesity leads to an increased level of triglycerides and a reduction of HDL-c level in adults; however, there was no evidence support the causal relationship between the childhood obesity and the LDL-c or TC levels in adults. Different MR methods yield similar results and the MR-Egger regression analysis suggested that the causal association was not caused by the pleiotropy of the IVs. The results were in consistent with a previous system review and meta-analysis that has summarized the observational studies regarding the childhood obesity and the adult cardiovascular disease risk factors.[19] They found childhood obesity is significantly and positively associated with adult triglycerides but negatively associated with the adult HDL-c level; however, no significant association was noticed for TC, LDL-c and non-high density lipoprotein cholesterol (non-HDL-c).[19] Several studies have suggested that the non-HDL-c is superior to LDL-c in predicting the cardiovascular effects, as LDL-c is usually not measured directly and it is derived by means of an equation that incorporates total cholesterol, HDL-c and triglycerides levels.[42,43] At ultra-low levels achieved with aggressive treatment, the calculated LDL-c level could be artifactually depressed. In addition, the LDL-c may not fully present the atherogenic lipoproteins.[44] These may underly the null association noticed here; however, the results need to be validated in MR analysis with different design and larger sample in future.

The MR analysis performed here satisfied the 3 assumptions. The genetic variants used as the IVs in MR analysis was significantly associated with the childhood obesity in the GWAS and had been validated by other independent studies, and these genetic factors explained about 1.69% the childhood obesity among the population, which validating the assumption 1. To confirm the assumption 2 in MR analysis, we evaluated the linkage disequilibrium between the SNPs and none of the SNPs was found to be in LD with $r^2 > 0.01$; however, we could not exclude there were other potential confounders that may influence the results. For assumption 3, we performed the MR-Egger analysis to evaluate whether the causal relationship was caused by the pleiotropy. For T2D and CAD, the interception term of the regression was centered at origin with a 95% CI including the null with the main IV2 model, suggesting that the causal effects noticed here were not caused by the pleiotropy. In the IV1 model with the 9 SNPs including 2 SNPs have been found to be associated with the T2D or CAD, we noticed a significant pleiotropy for the SNPs, suggesting that IV2 model was suitable for MR analysis in assessing the causal relationship for childhood

obesity and T2D and CAD. For the lipids and glycemic traits, the MR-Egger method also suggested that there was no evidence for pleiotropy effects for SNPs I IV2. Interestingly, for both IV1 and IV2 model, we noticed that there was evidence for the pleiotropy effects in assessing the childhood obesity on the adult BMI, WC and HC. It has been suggested that there the childhood BMI was positively associated with the adult BMI, WC, and HC, and these anthropometric traits may share these genetic susceptibility factors. The childhood BMI and adult BMI, WC and HC may share the genetic susceptibility factors rather than a causal relationship, which need to be addressed with more studies in future.

Exception for the pleiotropy effects on adults BMI, WC, and HC in the MR analysis, there was several other limitations should be acknowledged. First, the genetic variants applied in the MR analysis are usually weak instruments, the null causal association for the childhood obesity on cardiometabolic traits including fasting glucose, TC and LDL-c may be due to the lower statistical power of the present study. Second, although the MR-Egger regression analysis suggested that pleiotropy may not contributed to main results of the MR analyses, other confounders such as the population stratification and the timing for exposure may influence the results. Third, the generalized of the results should be validated in other ethnics as the present study largely depended on the summary level data form GWAS performed in populations of European ancestry.

5. Conclusions

In conclusion, the current MR analyses suggested that childhood obesity is causally associated with an increased risk of T2D, CAD, and cardiometabolic traits in adults. These results support the notion that early interventions should be performed in children with obesity to reduce the risks of cardiometabolic diseases, but this needs to be confirmed using other study designs, including prospective cohort studies and larger-scale community-based intervention studies.

Author contributions

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