Childhood BMI and Adult Type 2 Diabetes, Coronary Artery Diseases, Chronic Kidney Disease, and Cardiometabolic Traits: A Mendelian Randomization Analysis

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OBJECTIVE

To test the causal effect of childhood BMI on adult cardiometabolic diseases using a Mendelian randomization analysis.

RESEARCH DESIGN AND METHODS

We used 15 single nucleotide polymorphisms as instrumental variables for childhood BMI to test the causal effect of childhood BMI on cardiometabolic diseases using summary-level data from consortia.

RESULTS

We found that a 1-SD increase in childhood BMI (kg/m^2) was associated with an 83% increase in risk of type 2 diabetes (odds ratio [OR] 1.83 [95% CI 1.46, 2.30]; $P = 2.5 \times 10^{-7}$) and a 28% increase in risk of coronary artery disease (CAD) (OR 1.28 [95% CI 1.17, 1.39]; $P = 2.1 \times 10^{-8}$) at the Bonferroni-adjusted level of significance ($P < 0.017$) in adults. In addition, a 1-SD increase in childhood BMI was associated with a 0.587-SD increase in adulthood BMI (kg/m^2), a 0.062-SD increase in hip circumference (cm), a 0.602-SD increase in waist circumference (cm), a 0.111 pmol/L increase in log fasting insulin, a 0.068 increase in log-transformed HOMA of ß-cell function (%), a 0.126 increase in log-transformed HOMA of insulin resistance (%), and a 0.109-SD increase in triglyceride (mg/dL) but a 0.138-SD decrease in HDL (mg/dL) in adults at the Bonferroni-adjusted level of significance ($P < 0.0026$).

CONCLUSIONS

A genetic predisposition to higher childhood BMI was associated with increased risk of type 2 diabetes and CAD in adult life. These results provide evidence supportive of a causal association between childhood BMI and these outcomes.

Obesity has become a worldwide epidemic. The prevalence rates of obesity in adults have dramatically increased in the past several decades (1). It is particularly worrisome that the rate of increase in childhood obesity has been nearly double that in adults (2). Even more disconcerting is that obese children are more likely to develop cardiometabolic diseases in adult life than obese adults (3).

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Compelling observational studies have documented that higher BMI during childhood is associated with an increased risk of cardiometabolic morbidities such as coronary artery disease (CAD), type 2 diabetes, hypertension, and dyslipidemia in adult life (4–6), as well as the adult levels of insulin, lipids, and systolic blood pressure (7). However, both socioeconomic status and unmeasured lifestyle factors might confound these observational associations. Therefore, the causality of these observations remains unclear. Identifying a potentially causal effect of childhood obesity on later life disease development could help guide prevention efforts.

Mendelian randomization (MR) analysis has become widely used to assess the potential causal relations of environmental risk factors and diseases (8,9). This MR method is analogous to a randomized controlled trial (RCT) where randomization to genotype takes place at conception and is less likely to be affected by confounding and reverse causation (8). Recently, MR analyses have demonstrated that both adult general and central obesity have causal effects on CAD, type 2 diabetes, and cardiometabolic traits in midlife (10,11). However, little is known about the causal effect of childhood obesity on these outcomes in adults. Therefore, in this study, we performed an MR analysis to examine the causal effect of childhood BMI on cardiometabolic diseases and related quantitative traits using summary-level data.

RESEARCH DESIGN AND METHODS

Study Design

Observational studies are prone to reverse causation, confounding, and biases. Therefore, observational findings are unreliable for substantiating causal relationships. MR analysis can be used for unbiased detection of causal effects. The genetic variants used in an MR analysis must satisfy three assumptions (12) (Fig. 1): *1*) the genetic variants used as instrumental variable (IV) must be associated with childhood BMI, *2*) the genetic variant must not be associated with any confounders, and *3*) the genetic variant must be conditionally independent of the cardiometabolic diseases and related traits given the childhood BMI and confounders. The second and third assumptions are known as independence from pleiotropy (12).

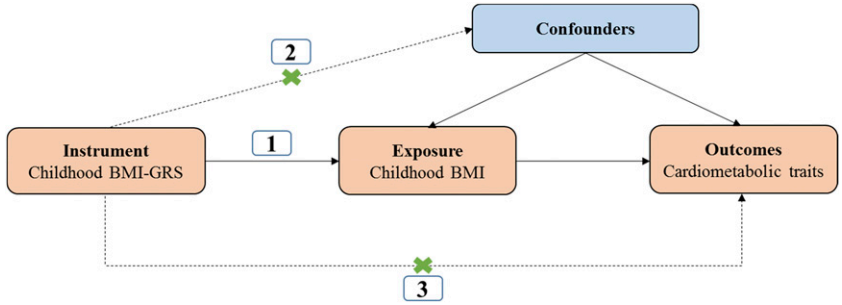

Figure 1—Schematic representation of an MR analysis. MR can be used to test the hypothesis that exposure (childhood BMI) causes outcomes (cardiometabolic diseases and related traits). Three assumptions of MR are as follows: *1*) genetic variants must be associated with childhood BMI, *2*) genetic variants must not be associated with confounders, and *3*) genetic variants must influence cardiometabolic diseases and related traits only through childhood BMI, not through other pathways. GRS, genetic risk score.

The study design of the present MR analysis consisted of two components (Fig. 2). First, we explored the causal effect of childhood BMI upon adult type 2 diabetes, CAD, and chronic kidney disease (CKD) as primary outcomes. Second, we tested the causal effect of childhood BMI on adult levels of cardiometabolic traits such as anthropometrics, glycemic traits, and lipids.

Single Nucleotide Polymorphism Selection and Validation of IV

We used 15 single nucleotide polymorphisms (SNPs; $P < 5 \times 10^{-8}$) identified from previous genome-wide association studies (GWAS) by the Early Growth Genetics (EGG) consortium as an IV for childhood BMI. This GWAS included 35,668 children from 20 studies in the discovery phase and 11,873 children from 13 studies in the replication phase (13). All children included in this GWAS were of European ethnic origin and 53% of the children were Caucasian. The specific study population is described in the Supplementary Data. Sex- and age-adjusted SD scores were created for childhood BMI at the latest time point (oldest age, if multiple measurements existed); the mean age was between 36.4 ± 0.7 and 120.0 ± 0.5 months. In the case of twin pairs, only one twin was included, either randomly or based on genotyping or imputation quality (13). The GWAS study combined these 15 genome-wide significant SNPs into a genetic risk score that summed the number of BMI-increasing alleles weighted based on their β. The genetic risk score was strongly associated with childhood BMI ($P = 3.12 \times 10^{-10}$). This score explained 2.0% of the variance in childhood BMI (13), thus validating assumption 1 (Fig. 1).

Data Sources

For disease outcomes, summary-level data were extracted from the Diabetes Genetics Replication and Meta-analysis (DIAGRAM) consortium (n = 149,821) (14) for type 2 diabetes (Supplementary Table 1), the CKDGen consortium (n = 133,413) (15) for CKD (Supplementary Table 2), and the Coronary Artery Disease Genome-wide Replication and Meta-analysis (CARDIoGRAM) plus the Coronary Artery Disease (C4D) Genetics (CARDIoGRAMplusC4D) consortium (60,801 CAD case subjects and 123,504 control subjects) (16) for CAD (Supplementary Table 3 and Supplementary Data). Case subjects with type 2 diabetes were diagnosed according to the 1999 World Health Organization criteria of fasting plasma glucose concentration ≥7.0 mmol/L or 2-h plasma glucose concentration ≥11.1 mmol/L, by report of diabetes medication use, or based on medical record review (17). CKD was classified in people with eGFRcrea (estimated glomerular filtration rate calculated based on serum creatinine) <60 mL/min/1.73 m^2 (15), and CAD case subjects were determined with a broad definition including myocardial infarction, acute coronary syndrome, chronic stable angina, or coronary artery stenosis >50% (16).

For cardiometabolic traits, summary-level data were extracted from the Meta-analyses of Glucose and Insulin-Related Traits Consortium (MAGIC) (17,18) for glycemic traits such as fasting glucose, log-transformed fasting insulin, 2-h glucose, log-transformed HOMA of ß-cell function (log HOMA-B), log-transformed HOMA of insulin resistance (log HOMA-IR), log-transformed proinsulin, and hemoglobin A_{1c} (HbA_{1c}) (Supplementary Table 1); the

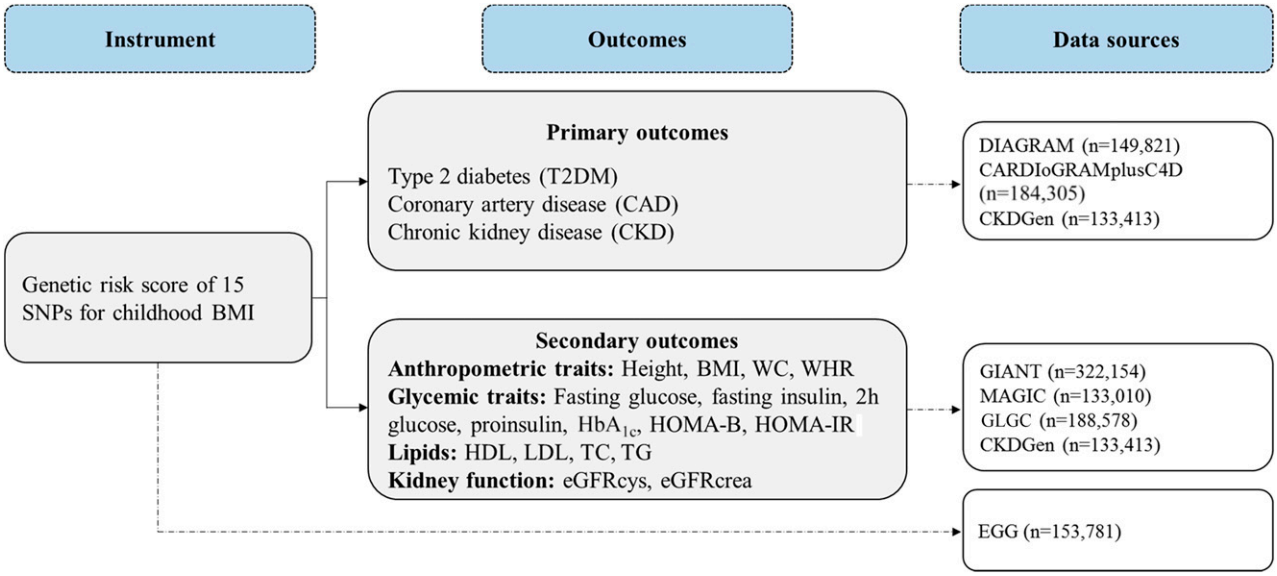

Figure 2—Study design. HOMA is used for assessing β-cell function (HOMA-B) and insulin resistance (HOMA-IR). eGFR was calculated based on serum creatinine (eGFRcrea) and cystatin C (eGFRcys, an additional complementary biomarker of renal function). CKD was defined as eGFRcrea $<$60 mL/min/1.73 m^2. Estimates of 15 SNPs for childhood BMI were extracted from the EGG consortium (13). Summary-level data were from DIAGRAM (n = 149,821) for type 2 diabetes (14), MAGIC (n = 133,010) for glycemic traits (17,18), CKDGen (n = 133,413) for CKD and kidney function (15), CARDIoGRAMplusC4D (60,801 CAD case subjects and 123,504 control subjects) for CAD (16), GLGC (n = 188,578) for lipids (19), and GIANT for BMI (n = 322,154) (20), WCadjBMI and WHRadjBMI (n = 224,459) (21), and height (n = 253,288) (22). TC, total cholesterol; WC, waist circumference; WHR, waist-to-hip ratio.

Global Lipids Genetics Consortium (GLGC) (n = 188,578) for lipids (19) (Supplementary Table 3); the CKDGen consortium (n = 133,413) for kidney function (15) (Supplementary Table 2); and the Genetic Investigation of Anthropometric Traits (GIANT) consortium (Supplementary Table 4) for BMI (n = 322,154) (20), waist circumference–adjusted BMI (WCadjBMI) and waist-to-hip ratio–adjusted BMI (WHRadjBMI) (n = 224,459) (21), and height (n = 253,288) (22) (Supplementary Data). Informed consent was obtained from all participants of contributing studies. Contributing studies received ethical approval from their respective institutional review boards.

Statistical Analysis

Linkage Disequilibrium Assessment

Based on MR assumption 2, the IV is not associated with any confounders. In this study, to verify that the SNPs selected met this assumption, we assessed correlation linkage disequilibrium (LD) between the 15 childhood BMI SNPs and sentinel SNPs associated with all outcomes using the SNP Annotation and Proxy (SNAP) search system (http://www.broadinstitute.org/mpg/snap/ldsearchpw.php) for the same reference catalog and population (23). When the correlation coefficient between SNPs was high ($r^2 \geq 0.05$), we discarded the SNP with the larger P value. The selected SNPs must not be in LD because if a selected SNP is highly correlated with other risk loci, this may result in confounding (8).

Pleiotropy Assessment

MR analysis assumes that the selected SNPs do not exert pleiotropic effects on cardiometabolic diseases by operating through other biological pathways (independent of childhood BMI). In this study, we used MR-Egger regression to assess the presence of pleiotropy (12). In brief, this approach is based on Egger regression, which has been used to examine publication bias in meta-analysis. Using the MR-Egger method, the SNP's effect upon the childhood BMI is plotted against its effect upon cardiometabolic diseases, and an intercept distinct from the origin provides evidence for pleiotropic effects.

MR Analysis

For the summary-level data from EGG, DIAGRAM, CKDGen, CARDIoGRAM, GIANT, and MAGIC, we conducted the MR analyses using the summarized data of associations (β-coefficients and SEs) of each genetic variant with the childhood BMI and cardiometabolic diseases and traits. The estimates of the causal effect of childhood BMI on cardiometabolic diseases and quantitative traits were analyzed using the inverse variance–weighted (IVW) method, weighted median method, and MR-Egger for multiple genetic variants. It was recommended to use all the methods when there are multiple genetic variants to assess the robustness of causal findings to different sets of assumptions. In the present MR analyses, MR-Egger and weighted median methods were considered as sensitivity analyses for MR investigations with multiple genetic variants (24–26). The detailed information on these methods is as follows.

IVW Method. The IVW method was used to provide a combined estimate of the causal estimate from each SNP. The IVW method, which uses weighted linear regression, is equivalent to two-stage least squares or allele score analysis using individual-level data and is hence considered here as conventional MR. If the variants are correlated, the method is implemented using generalized weighted linear regression. The causal estimate is obtained by regression of the associations with the outcome on the associations with the risk factor, with the intercept set to zero and weights being the inverse variances of the associations with the outcome (24).

Median-Based Method. The median-based methods have greater robustness to individual genetics with strongly outlying

causal estimates compared with IVW and MR-Egger methods, which give a consistent estimate of the causal effect when at least 50% of the genetic variants are valid IVs. The simple median estimate is the same as the weighted median estimate when all the weights are equal. SEs for both the simple and weighted median methods are calculated through bootstrapping (26).

MR-Egger Method. The MR-Egger regression test was used to evaluate the directional pleiotropy and investigate the null causal hypothesis under the InSIDE (Instrument Strength Independent of Direct Effect) assumption (12). The slope of the MR-Egger regression can provide pleiotropy-corrected causal estimates. However, an important condition of MR-Egger regression is that the IV–childhood BMI association must be independent of the SNP's direct effects upon the outcomes, which may not always be satisfied in cases where all pleiotropic effects can be attributed to a single confounder. Nonetheless, the MR-Egger method can provide unbiased estimates even if all the chosen SNPs are invalid (12).

Calculation of Absolute Risk Increases

To estimate the absolute risk increase (ARI) based on calculated odds ratios (ORs) estimated for cardiometabolic diseases, the U.S. population level estimate of the incidence of diabetes by the Centers for Disease Control and Prevention (7.8 per 1,000 person-years of follow-up) (27), the incidence of CAD by the American Heart Association (3.7 per 1,000 person-years of follow-up) (28), and the incidence of CKD (258 per 1,000 person-years) (29) were used. The ARI associated with cardiometabolic diseases was calculated using the formula ARI = (OR − 1) × AI, where AI is the absolute incidence in events per 1,000 person-years.

The effect size for each meta-analysis is reported in the main results as the effect of a 1-SD change in childhood BMI because this metric is more interpretable than an arbitrary difference. Analyses were performed using Stata version 13 (StataCorp) and R version 3.2.3 (R Project for Statistical Computing). The threshold of statistical significance for type 2 diabetes, CAD, and CKD as primary outcomes was $P < 0.017$ (0.05/3 = 0.017) to account for testing three associations. The threshold of significance for the analysis of cardiometabolic quantitative traits as secondary outcomes was $P < 0.0026$ (0.05/19 = 0.0026) to account for 19 tests.

RESULTS

Selected SNPs and IV Validation

The characteristics of the 15 selected SNPs are presented in Table 1. To examine assumptions 2 and 3, we tested whether any of the selected SNPs were influenced by LD and pleiotropy. None of the SNPs was found to be in LD with each other at an $r^2 > 0.05$. In addition, the intercept term estimated for type 2 diabetes from MR-Egger regression was centered at the origin with a CI including the null (−0.030 [95% CI −0.085, 0.025]; $P = 0.281$) (Supplementary Table 5), suggesting that the results were not influenced by pleiotropy. Similarly, the intercept term estimated was 0.007 (95% CI −0.011, 0.025; $P = 0.45$) for CAD and 0.006 (95% CI −0.030, 0.043; $P = 0.738$) for CKD. For cardiometabolic traits, intercepts (SE) from MR-Egger regression also showed that the observed results were not influenced by pleiotropy (Supplementary Table 5).

Causal Effect of Childhood BMI on Risk of Adult Type 2 Diabetes, CAD, and CKD

In the present MR study, we used the IVW method as the primary approach to examine the causal effect. We found that a 1-SD increase in childhood BMI (kg/m^2) was associated with a substantial increase in risk of type 2 diabetes, ranging from 47 to 83% (OR 1.47 [95% CI 1.18, 1.82] to 1.83 [95% CI 1.46, 2.30]; ARI per 1,000 person-years, 3.67 [95% CI 1.40, 6.40] to 4.37 [95% CI 2.03, 7.25]; $P = 4.0 \times 10^{-4}$; $P = 2.5 \times 10^{-7}$), and a 28% increase in risk of CAD (OR 1.28 [95% CI 1.17, 1.39]; ARI per 1,000 person-years, 1.04 [95% CI 0.63, 1.44]; $P = 2.1 \times 10^{-8}$) at the Bonferroni-adjusted level of significance ($P < 0.017$). However, childhood BMI was not associated with adult CKD (OR 1.14 [95% CI 0.99, 1.31]; ARI per 1,000 person-years, 36.12 [95% CI −2.58, 79.98]; $P = 0.076$). Furthermore, complementary MR approaches such as simple median–based method and weighted median–based method replicated the direction and magnitude of the effect for type 2 diabetes

Table 1—Characteristics of 15 included SNP loci with *P* values <5 × 10^{-8}

SNP	Chromosome	Position	Nearest gene	EA/OA	EAF	β	SE	*P* value
rs13130484	4	44870448	*GNPDA2*	T/C	0.44	0.067	0.007	1.58×10^{-23}
rs11676272	2	24995042	*ADCY3*	G/A	0.46	0.068	0.007	7.12×10^{-23}
rs4854349	2	637861	*TMEM18*	C/T	0.83	0.09	0.009	5.41×10^{-22}
rs543874	1	176156103	*SEC16B*	G/A	0.2	0.077	0.009	2.20×10^{-19}
rs7132908	12	48549415	*FAIM2*	A/G	0.39	0.066	0.008	1.57×10^{-18}
rs1421085	16	52358455	*FTO*	C/T	0.41	0.059	0.007	4.53×10^{-16}
rs12429545	13	53000207	*OLFM4*	A/G	0.13	0.076	0.01	2.08×10^{-14}
rs987237	6	50911009	*TFAP2B*	G/A	0.19	0.062	0.009	1.80×10^{-12}
rs12041852	1	74776088	*TNNI3K*	G/A	0.46	0.046	0.007	2.28×10^{-10}
rs6567160	18	55980115	*MC4R*	C/T	0.23	0.05	0.008	1.21×10^{-9}
rs13253111	8	28117893	*ELP3*	A/G	0.57	0.042	0.007	4.89×10^{-9}
rs8092503	18	50630485	*RAB27B*	G/A	0.27	0.045	0.008	8.17×10^{-9}
rs3829849	9	128430621	*LMX1B*	T/C	0.36	0.041	0.007	8.81×10^{-9}
rs13387838	2	206989692	*ADAM23*	A/G	0.04	0.139	0.025	2.84×10^{-8}
rs7550711	1	109884409	*GPR61*	T/C	0.04	0.105	0.019	4.52×10^{-8}

P values indicate genome-wide significance in the joint analysis. The data source was the EGG consortium. EA/OA, effect allele/other allele; EAF, effect allele frequency.

and CAD (Fig. 3), supporting the robustness of our results with no influence by pleiotropy (Supplementary Table 5).

Causal Effect of Childhood BMI on Cardiometabolic Quantitative Traits Among Adults

The IVW method showed that a 1-SD increase in childhood BMI was causally associated with a 0.587-SD increase in BMI (β 0.587 [95% CI 0.458, 0.716]; $P = 4.9 \times 10^{-18}$), a 0.062-SD increase in hip circumference–adjusted BMI (HIPadjBMI) (β 0.062 [95% CI 0.025, 0.099]; $P = 0.001$), a 0.602-SD increase in WCadjBMI (β 0.602 [95% CI 0.370, 0.834]; $P = 4.8 \times 10^{-7}$), a 0.111 pmol/L increase in log fasting insulin (β 0.111 [95% CI 0.065, 0.157]; $P = 2.7 \times 10^{-6}$), a 0.068 increase in log HOMA-B (β 0.068 [95% CI 0.026, 0.110]; $P = 0.001$), a 0.126 increase in log HOMA-IR (β 0.126 [95% CI 0.085, 0.168]; $P = 4.7 \times 10^{-9}$), and a 0.109-SD increase in triglyceride (TG) (β 0.109 [95% CI 0.058, 0.160]; $P = 3.0 \times 10^{-5}$), but a 0.138-SD decrease in HDL (β −0.138 [95% CI −0.207, −0.069]; $P = 9.3 \times 10^{-5}$) at the Bonferroni-adjusted level of significance ($P < 0.0026$) (Table 2). However, there was no significant causal association of childhood BMI with other cardiometabolic traits such as fasting glucose level, 2-h glucose, proinsulin, HbA_{1c}, LDL, and total cholesterol levels (Table 2). The intercept term estimated from MR-Egger regression was centered at the origin with a CI including the null, showing that the observed results were not influenced by pleiotropy (Table 2).

Sensitivity Analyses of MR

In sensitivity analyses, we used four different methods, including the IVW method, simple median–based method, weighted median–based method, and MR-Egger method, to estimate the causal effect of childhood BMI on risk of cardiometabolic diseases and quantitative trait levels using summary-level data. The results showed consistent significant causal effects (Fig. 3 and Table 2), supporting the robustness of our findings.

CONCLUSIONS

To the best of our knowledge, this is the first MR to examine the causal relationship between childhood BMI and cardiometabolic diseases in adult life. Our results showed that a 1-SD increase in childhood BMI (kg/m^2) was associated with a 47–83% increase in risk of type 2 diabetes and a 28% increase in risk of CAD in adult life, as well as increased adult levels of BMI, HIPadjBMI, WCadjBMI, log fasting insulin, HOMA-IR, and TG, but a decreased adult level of HDL. The well-powered MR analysis suggested a causal effect of higher childhood BMI on increased risk of type 2 diabetes, CAD, and related traits.

The findings of our study corroborate results from the observational studies. Observational studies have shown that higher childhood BMI is related to higher risk of cardiometabolic diseases (2,4–7). For example, the meta-analysis of observational studies documented that high childhood BMI was associated with an increased incidence of diabetes (30), CAD (2,6), hypertension (31), and mortality (32,33) in midlife. In addition, the increases in weight and BMI during childhood were significantly related to the adult levels of insulin, lipids, and systolic blood pressure (7), emphasizing the adverse effects of elevated childhood BMI levels. These data suggest that weight gain in excess of normal growth during childhood might be a determinant of adult cardiometabolic risk. However, another study did not provide evidence to support this view (34). Long-term epidemiological studies of the effects of childhood obesity are challenging, but several prospective studies have assessed the impact of childhood BMI on adult cardiometabolic disease over long periods of time (31–33,35). However, childhood BMI was not associated with adult CKD, which is inconsistent with the observational studies. The observational associations are possibly explained by reverse causation bias or confounding from the socioeconomic status and other unmeasured lifestyle factors (diet and smoking are associated with both obesity and risk of CKD). In addition, BMI is a complex phenotype. SNPs associated with certain subphenotypes of BMI could potentially play critical roles in CKD, which requires further investigation with specific SNPs to refined adiposity phenotypes.

In the current study, we used MR analysis to address potential confounders. The MR approach, a natural RCT (8), has been widely used to assess potential causality. The genetic variants used in the present MR analysis were independent of potential confounders and validated as a robust and reliable IV for childhood BMI. We found a significantly higher risk of type 2 diabetes and CAD per 1-SD increase in childhood BMI. Therefore, our findings lend a genetic support to previous evidence of observational associations between childhood BMI and risk of type 2 diabetes and CAD in adulthood. Interestingly, the range of estimates for type 2 diabetes is less consistent than other diseases. It should be acknowledged that any causal effect of risk factors on the health outcomes is likely to depend on several aspects, such as magnitude, duration, and pathways; therefore

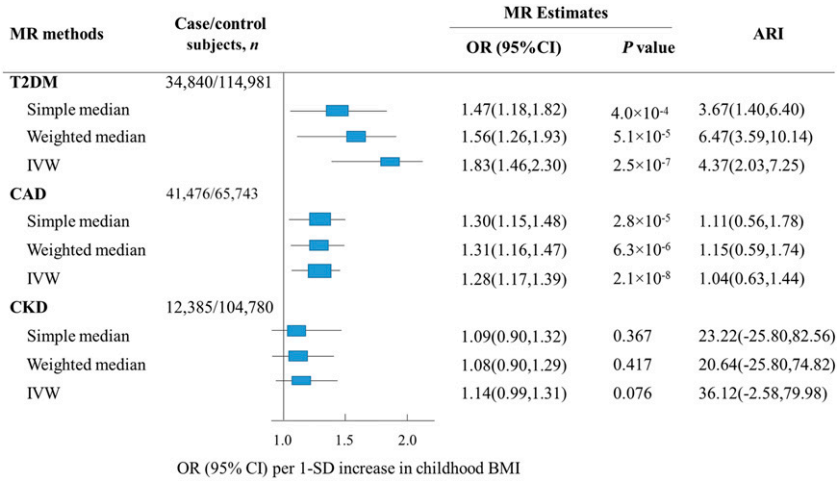

Figure 3—MR of childhood BMI and risk of type 2 diabetes, CAD, and CKD. CKD was defined as eGFRcrea <60 mL/min/1.73 m^2. We used the SD value from childhood BMI GWAS of the EGG consortium (13). Results are standardized to a 1-SD increase in childhood BMI due to the genetic risk score. The ARI associated with cardiometabolic diseases was then calculated using the formula ARI = (OR − 1) × AI where AI is absolute incidence. T2DM, type 2 diabetes.

Table 2—MR analyses of childhood BMI and cardiometabolic quantitative traits

			MR estimates, units per 1-SD increase in childhood BMI							
			Simple median–based method		Weighted median–based method		IVW method		MR-Egger regression	
Cardiometabolic traits	SNPs, *n*	Participants, *n*	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value	Intercept (95% CI)	*P* value
Anthropometric traits (SD) (GIANT)										
Height (m)	15	253,229	0.059 (0.006, 0.112)	0.028	0.055 (0.005, 0.104)	0.028	0.003 (−0.097, 0.104)	0.957	0.005 (−0.020, 0.029)	0.711
BMI (kg/m^2)	15	322,154	0.444 (0.354, 0.534)	**8.1×10^{-21}**	0.575 (0.489, 0.660)	**1.4×10^{-36}**	0.587 (0.458, 0.716)	**4.9×10^{-18}**	−0.002 (−0.034, 0.030)	0.901
HIPadjBMI (cm)	15	225,424	0.091 (0.041, 0.142)	**4.1×10^{-4}**	0.071 (0.024, 0.119)	**0.0032**	0.062 (0.025, 0.099)	**0.001**	0.003 (−0.006, 0.012)	0.556
WHRadjBMI	15	214,508	−0.037 (−0.082, 0.008)	0.105	−0.039 (−0.082, 0.003)	0.070	−0.038 (−0.069, −0.007)	0.016	0.004 (−0.004, 0.011)	0.334
WCadjBMI (cm)	15	104,574	0.384 (0.167, 0.602)	**5.3×10^{-4}**	0.445 (0.230, 0.660)	**5.3×10^{-5}**	0.602 (0.370, 0.834)	**4.8×10^{-7}**	−0.032 (−0.088, 0.024)	0.269
Glycemic traits (clinical unit) (MAGIC)										
Fasting glucose (mg/dL)	15	133,010	0.051 (−0.002, 0.104)	0.058	0.074 (0.024, 0.125)	0.0039	0.054 (0.012, 0.096)	0.011	−0.005 (−0.014, 0.005)	0.345
Log fasting insulin (pmol/L)	15	108,557	0.094 (0.038, 0.150)	**9.8×10^{-4}**	0.099 (0.046, 0.153)	**2.9×10^{-4}**	0.111 (0.065, 0.157)	**2.7×10^{-6}**	−0.001 (−0.012, 0.009)	0.797
HbA_{1c} (%)	15	46,368	0.022 (−0.027, 0.071)	0.383	0.057 (0.012, 0.102)	0.013	0.025 (−0.017, 0.068)	0.249	−0.003 (−0.013, 0.006)	0.495
Log HOMA-B	15	94,839	0.076 (0.027, 0.125)	**0.0023**	0.078 (0.032, 0.124)	**8.7×10^{-4}**	0.068 (0.026, 0.110)	**0.001**	−0.002 (−0.012, 0.007)	0.668
Log HOMA-IR	15	94,636	0.104 (0.046, 0.163)	**4.9×10^{-4}**	0.109 (0.053, 0.165)	**1.4×10^{-4}**	0.126 (0.085, 0.168)	**4.7×10^{-9}**	−0.003 (−0.012, 0.007)	0.603
Log proinsulin (pmol/L)	15	27,079	0.046 (−0.051, 0.142)	0.353	0.074 (−0.011, 0.160)	0.088	0.021 (−0.048, 0.090)	0.560	−0.005 (−0.022, 0.012)	0.582
2-h glucose (mg/dL)	15	42,854	0.086 (−0.175, 0.347)	0.527	0.088 (−0.163, 0.340)	0.501	0.020 (−0.169, 0.208)	0.845	−0.012 (−0.050, 0.026)	0.547
Lipids (SD) (GLGC)										
HDL (mg/dL)	15	187,130	−0.130 (−0.185, −0.076)	**3.5×10^{-6}**	−0.129 (−0.185, −0.074)	**6.1×10^{-6}**	−0.138 (−0.207, −0.069)	**9.3×10^{-5}**	0.002 (−0.014, 0.019)	0.801
LDL (mg/dL)	15	173,055	0.005 (−0.056, 0.065)	0.880	−0.008 (−0.068, 0.051)	0.803	−0.003 (−0.077, 0.071)	0.942	0.012 (−0.004, 0.029)	0.144
TC (mg/dL)	15	187,323	−0.044 (−0.103, 0.014)	0.139	−0.066 (−0.122, −0.011)	0.019	−0.033 (−0.108, 0.042)	0.393	0.007 (−0.010, 0.025)	0.415
TG (mg/dL)	15	177,828	0.094 (0.043, 0.144)	**2.6×10^{-4}**	0.101 (0.047, 0.154)	**2.2×10^{-4}**	0.109 (0.058, 0.160)	**3.0×10^{-5}**	−0.002 (−0.014, 0.010)	0.716
Kidney function (clinical unit) (CKDGen)										
eGFRcrea-DM (mL/min)	15	11,529	0.039 (−0.008, 0.086)	0.105	0.042 (−0.002, 0.086)	0.061	0.034 (0.001, 0.067)	0.058	−0.002 (−0.010, 0.006)	0.564
eGFRcrea (mL/min)	15	133,413	0.006 (−0.007, 0.018)	0.36	0.005 (−0.007, 0.017)	0.416	0.004 (−0.008, 0.016)	0.554	−0.001 (−0.004, 0.002)	0.558
eGFRcys (mL/min)	15	33,152	−0.024 (−0.048, 0.000)	0.053	−0.019 (−0.044, 0.006)	0.127	−0.027 (−0.052, −0.002)	0.055	−0.003 (−0.009, 0.003)	0.355

Results were standardized to a 1-SD decrease in childhood BMI due to genetic variants. For childhood BMI, the pooled results were from the EGG consortium (13). MAGIC and CKDGen did not report estimates of variants in units of SDs (15,17). Two-hour glucose refers to blood glucose levels measured 2 h after consumption of dissolved glucose. The threshold of significance was at the Bonferroni-adjusted level $P < 0.0026$ (0.05/19 = 0.0026). eGFRcrea-DM, eGFRcrea results among patients with diabetes; eGFRcys, eGFR calculated based on cystatin C (an additional, complementary biomarker of renal function); TC, total cholesterol.

it will not precisely correspond to the estimate from an MR analysis.

Previous MR has successfully unveiled the causal association between BMI and cardiometabolic diseases and traits (36). Holmes et al. (36) combined 14 BMI-associated SNPs to maximize the power and found that decrease of BMI was associated with reduced blood pressure, fasting glucose, and insulin resistance. However, our study selected SNPs associated with childhood obesity rather than adult adiposity to test for effects specific to early-life BMI on cardiometabolic diseases in adults. Recent MR analyses similarly demonstrated that both general and central adiposity in adults have causal effects on CAD, type 2 diabetes, and cardiometabolic traits in midlife (10,11). However, the MR analysis for central obesity observed that 33.7% of myocardial infarctions were attributed to increased waist-to-hip ratio compared with 10.8% of infarctions attributed to overweight and obesity (11), suggesting that abdominal adiposity, independent of elevated BMI, is a major driver of the global coronary heart disease burden (11). Unfortunately, we cannot assess the causal effect of childhood central obesity on cardiometabolic diseases here because genetic data for childhood central obesity are not available. Therefore, future causal estimates of childhood adiposity on adult health should include measures of central adiposity.

Our MR results demonstrated that childhood BMI is itself the causal exposure, implying the public health impact of childhood BMI modification. Fortunately, there have been previous efforts directed toward the development of therapies that modify childhood BMI. A meta-analysis of 85 RCTs of school-based lifestyle prevention interventions reported a 0.054 kg/m^2 decrease in BMI (37). In addition, two meta-analyses of >60 RCTs of lifestyle interventions for children with obesity reported that the reduction in BMI SD score ranged from −0.29 to −0.63, with better results in children younger than 12 years (38), which underscores the benefits of an early intervention in childhood obesity. Based on our MR results, such a decrease in childhood BMI could translate into a reduction in adult type 2 diabetes and CAD risks of up to 27% and 9%, respectively. Therefore, our findings highlight the potential importance of childhood prevention in curbing adult cardiometabolic diseases. In addition, ongoing research to understand the mechanistic links between the genetic loci that influence childhood BMI may lead to novel therapeutic strategies to modify childhood BMI and subsequently reduce the risk of cardiometabolic diseases in adults.

The MR analysis used in this study satisfied three assumptions. Assumption 1 requires a strong link between the genetic variants used as an IV and childhood BMI. The genetic risk score constructed based on the 15 identified genome-wide significant SNPs was strongly associated with childhood BMI ($P = 3.12 \times 10^{-10}$). This score explained 2.0% of the variance in childhood BMI (13), thus validating assumption 1. For assumption 2, MR assumes that the IV was not associated with potential confounders. We measured LD between all selected SNPs, and none of the SNPs was found to be in LD with each other at an $r^2 > 0.05$. However, we cannot exclude the possibility that our results might be affected by unmeasured confounders. For assumption 3, MR assumes that the IV affects cardiometabolic diseases only through childhood BMI, but not through other pathways. The MR-Egger regression showed that the estimated intercept term was centered at the origin with a CI including the null, suggesting that our results were not being influenced by pleiotropy (12).

Our current study has several other strengths. First, the large sample size allowed us to assess the consistency of associations across different methods and to gain sufficient power for reliable estimation of causal effects. Second, the consistent significant causal effects estimated from different MR approaches suggest robustness of our findings. However, this study has several limitations. First, we assumed that the associations between childhood BMI and all outcomes are linear. Indeed, an observational study has shown a nonlinear association (39). Therefore, further investigation is warranted on the use of nonlinear MR approaches. Second, although the MR-Egger method demonstrated that our results were not affected by pleiotropy, it is possible that our findings reflect a shared genetic basis between childhood BMI and cardiometabolic diseases rather than a causal relationship. Third, genetic variants influencing childhood BMI may also influence adult BMI; therefore, it is difficult to specify when these effects happen. Fourth, there would be some overlap between the genetic variants related to childhood BMI versus adult BMI. Although adult BMI is not strictly a confounder, 12 of the 15 SNPs for childhood BMI are also reported signals for adulthood. Further investigations on the timing of the exposure are warranted. Finally, we cannot directly assess whether population stratification and other potential confounders may be influencing our results; residual and unmeasured confounding might remain. Therefore, the results cannot be easily generalized.

Conclusion

In summary, a genetic predisposition to higher childhood BMI was associated with increased risk of type 2 diabetes, CAD, and cardiometabolic traits in adult life. These results provide evidence supportive of causal associations, implying a substantial public health impact of childhood BMI modification. However, the findings need further replications in other MR studies with larger sample sizes or large-scale, prospective, observational studies.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. T.G. and T.H. designed the study and planned analyses, conducted the data collection and statistical analysis, and drafted the manuscript. C.E.S. and C.L. contributed to the quality control of the study. All authors reviewed and approved the drafts of the manuscript. T.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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