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Maternal central obesity and birth size: a Mendelian randomization analysis

Ting-Ting Geng¹ and Tao Huang^{2*}

Abstract

Background: Observational studies have illustrated that maternal central obesity is associated with birth size, including of birth weight, birth length and head circumference, but the causal nature of these associations remains unclear. Our study aimed to test the causal effect of maternal central obesity on birth size and puberty height growth using a Mendelian randomization (MR) analysis.

Methods: We performed two-sample MR using summary-level genome-wide public data. Thirty-five single nucleotide polymorphisms (SNPs), 25 SNPs and 41 SNPs were selected as instrumental variables for waist-to-hip ratio adjusted for BMI, waist circumference adjusted for BMI and hip circumference adjusted for BMI, respectively to test the causal effects of maternal central obesity on birth size and puberty height using an inverse-variance-weighted approach.

Results: In this MR analysis, we found no evidence of a causal association between waist circumference or waist-to-hip ratio and the outcomes. However, we observed that one standard deviation (SD) increase in hip circumference (HIP) was associated with a 0.392 SD increase in birth length ($p = 1.1 \times 10^{-6}$) and a 0.168 SD increase in birth weight ($p = 7.1 \times 10^{-5}$), respectively at the Bonferroni-adjusted level of significance. In addition, higher genetically predicted maternal HIP was strongly associated with the puberty heights (0.835 SD, $p = 8.4 \times 10^{-10}$). However, HIP was not associated with head circumference ($p = 0.172$).

Conclusions: A genetic predisposition to higher maternal HIP was causally associated with larger offspring birth size independent of maternal BMI. However, we found no evidence of a causal association between maternal waist circumference, waist-to-hip ratio and birth size.

Keywords: Maternal central obesity, Birth size, Birth weight, Birth length, Puberty height, Mendelian randomization

Background

Overweight has become a world epidemic affecting women of childbearing age. Up to 50% of reproductive age women were overweight or obesity in Europe and the USA [1, 2]. Maternal overweight and obesity are associated with higher risks of many pregnancy complications and perinatal outcomes [3–6]. In addition, maternal overweight and obesity in pregnancy have been reported to be associated with early puberty development, such as earlier ages at menarche in daughters and earlier ages of voice break, acne and first nocturnal emission in sons [7, 8]. A previous Mendelian randomization study has illustrated

that increased maternal BMI was causally associated with higher offspring birth weight [9].

However, waist circumference (WC), waist-to-hip ratio (WHR) and hip circumference (HIP), as indicators of central obesity have been suggested as being superior to BMI, given the relationship with visceral adiposity and the natural pregnant process [10–14]. Observational studies have documented that maternal central obesity is associated with an increased risk of adverse birth outcomes [15–18]. Nevertheless, maternal socioeconomic status and unmeasured lifestyle, such as smoking status, physical activity and diet might confound the observed associations. In addition, the inter-correlation of obesity traits also makes it difficult to examine the causal associations. Identifying a potential causal effect of maternal central obesity independent of BMI on birth size could clarify the causal association between maternal central

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obesity traits and birth size. Hence evidenced-based recommendations could be provided for pregnant women.

Mendelian Randomization (MR) analysis has become widely used to assess the potential causal relationship between environmental risk factors and diseases. MR studies have often been likened to natural randomized trials, in which genotype plays the role of random treatment assignment, avoiding the possibility of confounding and reverse causation [19–22]. It has been successfully explained the causal relationship between maternal BMI and birth weight [9]. Therefore, we conducted an MR analysis to investigate the relations of maternal central obesity with birth size and puberty heights using summary level data.

Methods

Study design

An MR analysis is free of confounding and reverse causation compared with observational studies. There are three assumptions of MR analysis (Fig. 1). First, the genetic variants used as instrumental variables (IVs) must be associated with maternal central obesity; second, the genetic variants must not be associated with any confounders; third, the genetic variants must be conditionally independent of the birth size and puberty height given the maternal central obesity and confounders of the risk factor-outcome relationship. The second and third assumptions are known as independence from pleiotropy [23, 24].

Genetically predicted maternal central obesity

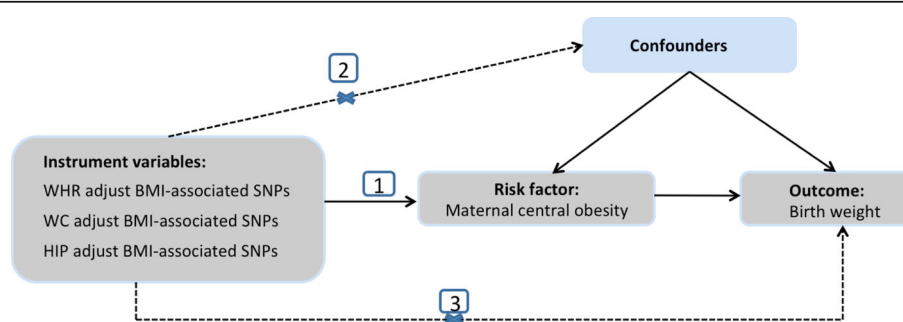
Genetically predicted maternal central obesity including of waist-to-hip ratio adjusted for BMI (WHRadjBMI), waist circumference adjusted for BMI (WCadjBMI) and hip circumference adjusted for BMI (HIPadjBMI) were based on single nucleotide polymorphisms (SNPs) of genome-wide

significant ($P < 5 \times 10^{-8}$) from the Genetic Investigation of Anthropometric Traits (GIANT) Consortium, which have been downloaded from http://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files.

GIANT consortium is an international collaboration that seeks to identify genetic loci that modulate human body size and shape, including height and measure of obesity. This genome-wide association meta-analysis (GWAS) included 224,459 individuals of European ancestry [25]. We assessed correlation (linkage disequilibrium) between SNPs using SNP Annotation and Proxy (SNAP) Search system (<https://www.broadinstitute.org/snap/snap>) for the same reference catalogue and population [26]. Highly correlated SNPs ($r^2 > 0.05$) were discarded based on larger P value. We used 35 SNPs from GIANT consortium as an IV for WHRadjBMI, 25 SNPs for WCadjBMI and 41 SNPs for HIPadjBMI. Full details of the selected SNPs are provided in Additional file 1: Tables S1a, S1b and S1c. Any SNP for exposures not available for an outcome was replaced with a highly correlated proxy SNP ($r^2 > 0.8$).

Genetically predicted birth size and puberty height

Genetic associations with birth weight [27], birth length [28], head circumference [29] and puberty growth [30] have been contributed by the Early Growth Genetics (EGG) Consortium from <http://egg-consortium.org>. The EGG Consortium represents a collaborative effort to combine data from multiple GWAS in order to identify additional human genome loci that have an impact on a variety of traits related to early growth. EGG birth weight data were imputed up to the reference panels from the 1000 Genomes Project (Phase 1 v 3) or combined 1000G and UK10K Project. Birth weight was z-score transformed in



Three assumptions of MR:

1. Genetic variants must be associated with maternal central obesity
2. Genetic variants must not be associated with confounders.
3. Genetic variants must influence birth size or puberty height only through maternal central obesity, not through other pathways

Fig. 1 Schematic representation of a Mendelian randomization analysis

males and females separately. The birth weight dataset was generated by a European-ancestry GWAS meta-analysis ($n = 153,781$ individuals); the birth length, head circumference and puberty height growth datasets were generated by performing a meta-analysis of 22 European population-based studies ($n = 28,459$ individuals), a meta-analysis of 7 population-based European studies ($n = 10,678$ individuals) and a meta-analysis of 9 European cohort studies ($n = 18,737$), respectively.

Statistical analysis

The study design of the present MR was to explore the causal effect of maternal central obesity upon offspring birth size (Fig. 2). SNPs were matched by assigning to the same effect allele firstly. The estimates of the causal effect of maternal central obesity on birth size were analysed using the inverse variance weighted (IVW). Provided that the genetic variants are uncorrelated, the IVW estimate is equivalent to a two-stage least squares analysis used with individual-level data. In IVW, the ratio estimates from each IV are combined in an inverse-variance weighted estimator [21, 24]. From the analyses we reported the mean difference for birth weight, birth length, head circumference and puberty height with 95% confidence interval (CI).

Sensitivity analysis

Mendelian randomization analyses are becoming more powerful and efficient to perform based on summary public data. However, when using multiple genetic variants from different gene regions as IVs in an MR study, it is almost impossible that all the SNPs could meet the MR assumptions as mentioned previously [31]. Even if only one of the multiple genetic variants is an invalid instrumental variable, the casual effect will be overestimated [20]. In our study, we performed a series of sensitivity analyses to ensure the robust casual inferences.

If the causal association depends only on a single genetic variant and the estimate is heterogeneous with other

variants' estimates, then the results may be driven by a pleiotropic effect rather than the biology causal effect. We repeated the analyses excluding SNPs (26 SNPs left) that could influence WHRadjBMI and high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), adiponectin adjusted for BMI, fasting insulin adjusted for BMI, T2D, and height manually [25].

We also conducted sensitivity analyses to assess whether the estimates were robust to methodological choices. Weighted median method and MR-Egger regression were performed as complementary methods to ensure the robustness of the results. Weighted median estimate defines that each instrumental variable estimate appears with probability proportional to the inverse of its variance [32], which is consistent under the assumption that genetic variants, more than 50% of the weight in the analysis are valid instruments [21, 33].

MR-Egger regression based on Egger regression to examine publication bias in the meta-analysis was also used to test directional pleiotropy effects given no assumptions about the genetic variants but under an assumption that pleiotropic effects of genetic variants are independent of instrument strength. Using the MR-Egger regression method, the effect of IV on the exposure is plotted against its effect on the outcome, and an intercept distinct from the origin provides evidence for pleiotropic effects. The slope of the MR-Egger regression can provide pleiotropic-corrected causal estimates. If the intercept is zero, it suggests that there is no violation of the exclusion restriction criteria (i.e., no horizontal pleiotropy). It provides an estimate of the average pleiotropic effect across all of the genetic variants, because it reflects the effect of the joint instruments on outcome, when there is zero effect of the genetic variants of the risk factor [34–36].

Informed consent was obtained from all participants of contributing studies. Contributing studies received ethical approval from their respective institutional review boards.

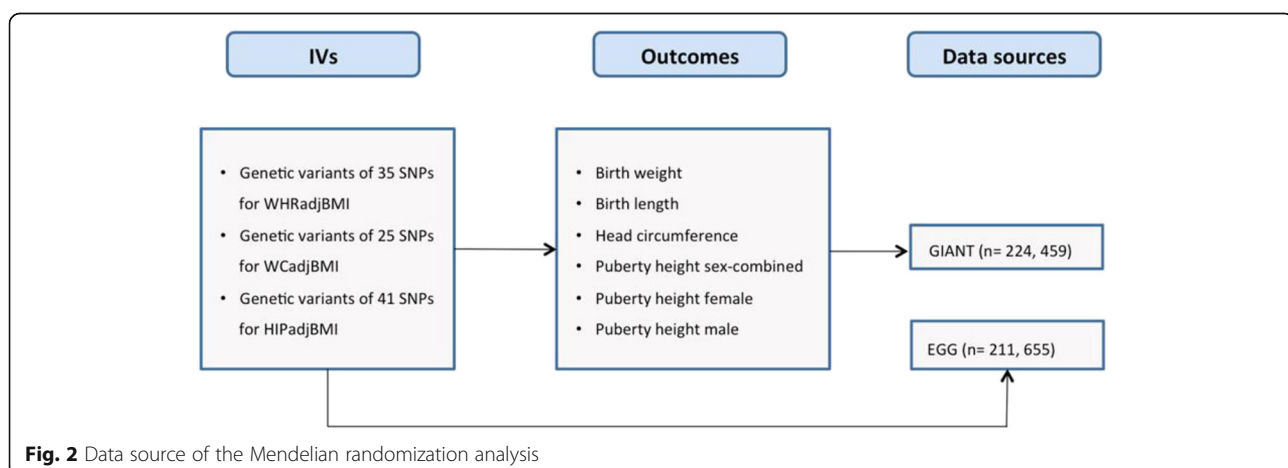


Fig. 2 Data source of the Mendelian randomization analysis

The statistical analyses were conducted using R version 3.2.4 (R Project for Statistical Computing). All statistical tests were 2-sided. The thresholds of statistical significance for WHRadjBMI, WCadjBMI and HIPadjBMI as exposures were $P < 0.00142$ (0.05/35 SNPs = 0.00142), $P < 0.002$ (0.05/25 SNPs = 0.002) and $P < 0.00125$ (0.05/41 SNPs = 0.00122), using Bonferroni test.

Results

Selected SNPs and instrumental variable validation

Based on the results of meta-analyses of GWAS, 35 SNPs, 25 SNPs and 41 SNPs reaching genome-wide significance for waist-to-hip ratio adjust for BMI, waist circumference adjust for BMI and hip circumference adjust for BMI were selected [25]. The characteristics of the selected SNPs for WHRadjBMI, WCadjBMI and HIPadjBMI selected are presented in Additional file 1: Tables S1a, S1b and S1c. None of the SNPs was found to be in LD with each other at an $r^2 > 0.05$.

Causal effects of WHRadjBMI, WCadjBMI on birth size and puberty height

We used the inverse-variance weighted method as the primary approach to examine the causal effect in the present MR study. Tables 1 and 2 show that genetically predicted WHRadjBMI and WCadjBMI were not associated with birth weight (beta, -0.021, 95% CI: -0.095 to 0.053; beta, 0.114, 95% CI: -0.028 to 0.255), birth length (beta, -0.01, 95% CI: -0.154 to 0.135; beta, 0.279, 95% CI: 0.095 to 0.464), head circumference (beta, -0.01, 95% CI: -0.154 to 0.135; beta, -0.02, 95% CI: -0.199 to 0.159) or puberty height (beta, -0.01, 95% CI: -0.26 to 0.05; beta, 0.354, 95% CI: -0.022 to 0.627). The results of the weighted median based method were consistent, illustrating non-causal effects of maternal WC on birth size or puberty height. The intercept term estimated from MR-Egger regression was centred at the origin with a confidence interval including the null showed that no evidence of directional horizontal pleiotropy effects.

Causal effects of HIPadjBMI on birth size and puberty height

Table 3 shows that estimates for the causal effect of one SD increase in HIPadjBMI were consistently in the direction of 0.168 SD increase in birth weight (beta, 0.168, 95%CI: 0.093 to 0.242, $p = 1.1 \times 10^{-6}$) and 0.392 SD increase in birth length (beta, 0.392, 95%CI: 0.258 to 0.526, $p = 7.1 \times 10^{-5}$), respectively. We also found that one SD increase in HIPadjBMI was causally associated with a 0.835 SD increase in sex-combined puberty height (beta, 0.835, 95%CI: 0.631 to 1.038, $p = 8.4 \times 10^{-10}$), a 0.747 SD increase in puberty height among females at 10 years old (beta, 0.747, 95%CI: 0.452 to 1.041, $p = 1.4 \times 10^{-5}$) and a 0.828 SD increase in puberty height

among males at 14 years old (beta, 0.828, 95%CI: 0.557 to 1.1, $p = 5.6 \times 10^{-7}$). However, HIPadjBMI was not associated with head circumference (beta, 0.141, 95%CI: -0.057 to 0.339). The results of the weighted median based method were consistent and even more significant than IVW method. The intercept term estimated from MR-Egger regression was centred at the origin with a confidence interval including the null showed that no evidence of pleiotropy effects.

Sensitivity analyses of MR

We used the weighted median based method and MR-Egger method to estimate the causal effects of WHRadjBMI, WCadjBMI and HIPadjBMI on birth weight, birth length, head circumference and puberty height. The results consistently supported the robustness of our findings. The results of the causal effects of WHRadjBMI and outcomes were consistent with or without the 9 SNPs which had potentially pleiotropic effects.

Discussion

In the present study, we used MR analyses to test the causal effect of maternal central obesity on offspring birth size and puberty height growth. We found that genetic predisposition to higher hip circumference independent of maternal BMI was associated with increased level of birth weight, birth length and puberty height. We observed one SD increase in HIPadjBMI (cm) was associated with 0.168 SD increase in birth weight, 0.392 SD increase in birth length and 0.835 SD increase in sex-combined puberty height. However, HIPadjBMI was not causally associated with head circumference. There was no evidence of causal effects of maternal WHRadjBMI and WCadjBMI on the birth size.

Observational studies have shown that maternal overweight and obesity were associated with many maternal and neonatal complications [37]. However, unmeasured or unknown confounding variables in the observational studies might have affected these associations. Socioeconomic factors and related behaviors such as smoking are critical confounders of observational associations between maternal central obesity and offspring birth size, since they are associated with both variables. In addition, the causal effects of maternal central obesity on birth size could also be confounded by maternal BMI. Therefore, the causality of these observations remains unclear. The IVs used in this MR were genetic variants associated with maternal central obesity adjusted for BMI, which could avoid the socioeconomic, behavior factors and BMI confounding, since genotypes are determined at conception.

The findings from this study were inconsistent with the results from the observational studies that showed women with increased WHR or WC were more likely to give birth to macrosomia [16, 38]. Li et al. reported that

Table 1 Mendelian randomization analyses of maternal waist-to-hip ratio and birth size and puberty height

Outcomes	Consortium	Maternal WHtRadjBMI (value of 1 SD with units, GIANT)									
		Main analysis					Sensitivity analysis				
		IWW		Weighted-median			MR-Egger		P-value		
		β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value	Intercept (95%CI)	P-value	P-value	
Birth length(SD), cm											
Birth length	EGG	-0.01 (-0.154 to 0.135)	0.896	-0.03 (-0.169 to 0.109)	0.675	-0.029 (-0.583 to 0.524)	0.918	0.001 (-0.002 to 0.021)	0.943		
Birth weight(SD), kg											
Birth weight	EGG	-0.021 (-0.095 to 0.053)	0.579	-0.015 (-0.073 to 0.043)	0.622	0.142 (-0.136 to 0.419)	0.317	-0.006 (-0.017 to 0.004)	0.232		
Head circumference (HC)(SD), cm											
HC	EGG	-0.01 (-0.154 to 0.135)	0.896	-0.03 (-0.169 to 0.109)	0.675	-0.029 (-0.583 to 0.524)	0.918	0.001 (-0.002 to 0.021)	0.943		
Puberty height single height measurement(SD), cm											
10F & 12 M	EGG	-0.10 (-0.26 to 0.05)	0.207	-0.05 (-0.24 to 0.14)	0.604	-0.23 (-0.86 to 0.39)	0.466	0.005 (-0.018 to 0.028)	0.678		
10F	EGG	-0.064 (-0.267 to 0.137)	0.537	-0.09 (-0.352 to 0.172)	0.499	-0.078 (-0.843 to 0.687)	0.841	0.001 (-0.028 to 0.029)	0.97		
12 M	EGG	-0.062 (-0.252 to 0.128)	0.529	-0.058 (-0.317 to 0.201)	0.662	0.128 (-0.62 to 0.876)	0.738	-0.007 (-0.035 to 0.02)	0.607		

The threshold of significance was at the Bonferroni-adjusted level $P < 0.0026$ ($0.05/35 = 0.00142$)

10F Height SDS for females at age 10, 12 M Height SDS for males at age 12, 10F&12 M Height SDS for females at age 10 and males at age 12 combined

Table 2 Mendelian randomization analyses of maternal waist circumference and birth size and puberty height

Outcomes	Consortium	Maternal WCadjBMI (value of 1 SD with units, GIANIT)		Sensitivity analysis				P-value	Intercept (95% CI)	P-value	P-value
		Main analysis		Weighted-median		MR-Egger					
		β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value				
Birth length(SD), cm											
Birth length	EGG	0.279 (0.095 to 0.464)	0.007	0.251 (0.057 to 0.446)	0.011	0.484 (-0.361 to 1.328)	0.262	-0.007 (-0.036 to 0.022)	0.627		
Birth weight(SD), kg											
Birth weight	EGG	0.114 (-0.028 to 0.255)	0.129	0.001 (-0.074 to 0.077)	0.977	0.1 (-0.524 to 0.723)	0.753	0.001 (-0.022 to 0.023)	0.964		
Head circumference (HC)(SD),cm											
HC	EGG	-0.02 (-0.199 to 0.159)	0.821	0.039 (-0.21 to 0.288)	0.76	-0.304 (-1.092 to 0.484)	0.45	0.01 (-0.016 to -0.036)	0.452		
Puberty height single height measurement(SD), cm											
10F & 12 M	EGG	0.345 (0.059 to 0.632)	0.027	0.358 (0.088 to 0.627)	0.009	0.359 (-1.138 to 1.856)	0.638	0 (-0.051 to 0.05)	0.985		
10F	EGG	0.379 (0.103 to 0.655)	0.013	0.305 (-0.018 to 0.628)	0.064	-0.132 (-1.371 to 1.108)	0.835	0.018(-0.025 to 0.061)	0.407		
12 M	EGG	0.303 (-0.022 to 0.627)	0.081	0.194(-0.171 to 0.558)	0.297	0.948 (-0.727 to 2.623)	0.267	-0.022 (-0.078 to 0.034)	0.441		

The threshold of significance was at the Bonferroni-adjusted level $P < 0.0026$ (0.05/25 = 0.002)
 10F Height SDS for females at age 10, 12 M Height SDS for males at age 12, 10F&12 M Height SDS for females at age 10 and males at age 12 combined

Table 3 Mendelian randomization analyses of maternal hip circumference and birth size and puberty height

Outcomes	Consortium	Maternal HIPadjBMI (value of 1 SD with units, GIANIT)		Sensitivity analysis		MR-Egger β (95% CI)	P-value	Intercept (95% CI)	P-value	
		Main analysis β (95% CI)	P-value	Weighted-median β (95% CI)	P-value					
Birth length(SD), cm										
Birth length	EGG	0.392(0.258 to 0.526)	1.12 × 10 ⁻⁰⁶	0.433 (0.291 to 0.574)	2.2 × 10 ⁻⁰⁹	0.798 (0.247 to 1.349)	0.005	-0.015 (-0.036 to 0.005)	0.136	
Birth weight(SD), kg										
Birth weight	EGG	0.168 (0.093 to 0.242)	7.1 × 10 ⁻⁰⁵	0.175 (0.108 to 0.241)	2.5 × 10 ⁻⁰⁷	0.153 (-0.157 to 0.464)	0.332	0.001 (-0.011 to 0.012)	0.972	
Head circumference (HC)(SD), cm										
HC	EGG	0.141 (-0.057 to 0.339)	0.172	0.111 (-0.106 to 0.328)	0.315	-0.149 (-0.989 to 0.691)	0.728	0.011 (-0.02 to 0.042)	0.487	
Puberty height single height measurement(SD), cm										
10F & 12 M	EGG	0.835 (0.631 to 1.038)	8.36 × 10 ⁻¹⁰	0.77 (0.556 to 0.985)	2.2 × 10 ⁻¹²	0.963 (0.086 to 1.841)	0.031	-0.005 (-0.037 to 0.027)	0.768	
10F	EGG	0.747 (0.452 to 1.041)	1.37 × 10 ⁻⁰⁵	0.8 (0.506 to 1.094)	7.7 × 10 ⁻⁰⁸	0.509 (-0.758 to 1.775)	0.431	0.009 (-0.038 to 0.056)	0.705	
12 M	EGG	0.828 (0.557 to 1.1)	5.63 × 10 ⁻⁰⁷	0.834 (0.549 to 1.12)	1.0 × 10 ⁻⁰⁸	0.953 (-0.218 to 2.125)	0.111	-0.005 (-0.048 to 0.038)	0.83	

The threshold of significance was at the Bonferroni-adjusted level $P < 0.0026$ (0.05/40 = 0.00125)
 10F Height SDS for females at age 10, 12 M Height SDS for males at age 12, 10F&12 M Height SDS for females at age 10 and males at age 12 combined

WC was positively associated with risk of macrosomia (OR, 1.58; 95%CI, 1.07–2.32) [16]. Salem et al. showed that the risk of macrosomia was 1.7 times higher in fourth quartiles WHR [38]. Piperata et al. illustrated women who had normal birth weight infants showed substantial positive association with HIP [39], which corroborates with our findings.

The pathophysiological mechanisms underlying the causation relationship between HIP and birth size is not fully understood. The potential mechanism could be explained below. Larger HIP potentially reflects increased gluteofemoral muscle mass. As muscle mass increases with weight even in the overweight and obese women, HIP increases with WC as well. The side effects of larger WC might be counteracted by the increased muscle mass to some extent [40]. In addition, maternal lean body mass has been illustrated to be one of the major determinants of birth weight [41, 42]. Whereas WC and WHR are predictors of abdominal adiposity, which were reported to be substantially associated with macrosomia [38]. Maternal visceral obesity was found to impair the anabolic response and the activity of SNAT, which is associated with fetal growth, such as skeletal growth or lean mass growth and final birth size [43, 44]. In addition, maternal larger WC or WHR is associated with a higher risk of gestational weight gain, which has been reported to increase the risk of high birth weight, macrosomia and large-for-gestational-age infants [45]. WC and WHR seem to be more sensitive to the low birth weight (< 2.5 kg) or macrosomia (> 4 kg). The mean birth weight included in the cohort studies in EGG consortia that used in our MR were ranged from 3.0 kg to 3.7 kg, which was the normal birth weight according to the birth weight cut off (2.5 kg–4 kg) [27]. Therefore, in our MR study, HIP, rather than WC or WHR was causally associated with birth weight.

Strength and limitations

Our large two sample MR study using public data provided more precise estimates with greater statistical power because of the large sample size. The consistency significant causal effects estimates from different approaches showed no evidence of a violation of the MR assumption and suggested robustness of our findings. Additionally, we used three genetic IVs as indicators of central obesity (WHRadjBMI, WCadjBMI and HIPadjBMI) to test the associations of maternal central obesity independent of maternal BMI and offspring birth size and puberty height. However, there are several limitations of our study. Firstly, we used two-sample MR to explore the causal effect of maternal exposure on later offspring outcomes. Though in theory two-sample MR could be used to explain this issue; in general it is impossible to assess many questions related to intrauterine effects on offspring outcomes. Therefore,

individual participant data of maternal genetic variants on offspring outcomes are warranted replicating the results. Second, the causal relationship between maternal hip circumference and offspring birth size could be violated via the offspring's genetic variants [46]. This issue would be more serious in the situation when the maternal exposure and offspring outcomes are the same characteristic or very similar. Our study aimed to investigate the causal effect of maternal central obesity and offspring birth weight; it is plausible that there would be some overlap between the maternal genetic IVs and offspring genetic IVs. Due to our summary data MR study design, it is impossible to adjust offspring IVs in our study. Further MR is warranted in the use of individual data. Third, we used genetic variants that have been shown to be robustly related to the exposure in GWAS conducted in non-pregnant women. The critical question here is whether genetic variants identified in non-pregnant women are valid IVs for pregnancy exposures. However, it has been illustrated that for some genetic variants, associations with exposures measured in pregnancy are similar to those in GWAS of non-pregnant women [9, 47]. Fourth, MR studies are often investigating the causal effect of the life cumulative exposure on outcomes. In this study, we addressed the specific question in the specific time period, intra-uterine period. The causal effects on birth size could be biased by the pre or post pregnancy maternal central obesity [48]. In addition, we assumed that the association between maternal central obesity and birth size was linear. If the relationship was non-linear, it is necessary for the association of the IV with the exposure in the population to remain constant at different levels of the exposure [31]. However, deviations from the assumption would result in reduced statistical power in risk analyses, rather than generating spurious associations. Finally, our study was restricted to individuals of European ancestry; the association of genetic HIP adjusted for BMI with birth weight may differ by ethnicity or genetic ancestry. Our results may not be generalized to non-European populations.

Conclusions

In this MR study, a genetic predisposition to higher maternal hip circumference was potentially causally associated with higher offspring birth weight, birth height and puberty height.

Additional file

Additional file 1: Table S1a. WHRadjBMI loci achieving genome-wide significance ($P < 5 \times 10^{-8}$) in European women-specific meta-analyses. **Table S1b.** WCadjBMI loci achieving genome-wide significance ($P < 5 \times 10^{-8}$) in European women-specific meta-analyses. **Table S1c.** HIPadjBMI loci achieving genome-wide significance ($P < 5 \times 10^{-8}$) in European women-specific meta-analyses. (XLSX 22 kb)

Abbreviations

EGG: Early Growth Genetics; GIANT: Genetic Investigation of Anthropometric Traits; GWAS: Genome-wide association meta-analysis; HDL-C: High-density lipoprotein cholesterol; HIP: Hip circumference; HIPadjBMI: Hip circumference adjusted for BMI; IV: Instrumental variable; IVW: Inverse-variance weighted; LDL-C: Low-density lipoprotein cholesterol; MR: Mendelian randomization; SD: Standard deviation; SNAP: SNP Annotation and Proxy; SNPs: Single nucleotide polymorphisms; T2DM: Type 2 diabetes mellitus; TG: Triglycerides; WC: Waist circumference; WCadjBMI: Waist circumference adjusted for BMI; WHR: Waist-to-hip ratio; WHRadjBMI: Waist-to-hip ratio adjusted for BMI

Acknowledgements

We are grateful for the valuable suggestion from reviewers of the manuscript.

Availability of data and materials

All data analyzed during this study are included in the reference.

Authors' contributions

TG and TH contributed to study concept and design, acquisition of data, interpretation of the data, drafting of the manuscript, and critical revision of the manuscript. TH is the guarantor of this work and, as such, has full access to all the data in the study and takes responsibility for the work. Both authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 1 May 2018 Accepted: 18 July 2018

Published online: 31 July 2018

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