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Assessing the causal relationship of birth weight and childhood obesity on osteoarthritis: a Mendelian randomization study

Zengfeng Xin[1,2,3,4], Lingxiao Xu[1,2,3,4] and Lingling Sun[1,2,3,4]

[1]Department of Orthopaedics, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; [2]Orthopedics Research Institute of Zhejiang University, Hangzhou, China; [3]Key Laboratory of Motor System Disease Research and Precision Therapy of Zhejiang Province, Hangzhou, China and [4]Clinical Research Center of Motor System Disease of Zhejiang Province, Hangzhou, China

Original Article

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Corresponding author:
L. Sun; Email: sunlingling@zju.edu.cn

Zengfeng Xin and Lingxiao Xu contributed equally to this work and co-first authors.

Abstract

Obesity is associated with osteoarthritis (OA), but few studies have used fetal origin to explore the association. Our study aims to disentangle the causality between birth weight, childhood obesity, and adult OA using Mendelian randomization (MR). We identified single nucleotide polymorphisms (SNPs) related to birth weight ($n = 298,142$) and childhood obesity ($n = 24,160$) from two genome-wide association studies contributed by the Early Growth Genetics Consortium. Summary statistics of OA and its phenotypes (knee, hip, spine, hand, thumb, and finger OA) from the Genetics of Osteoarthritis Consortium ($n = 826,690$) were used to estimate the effects of SNPs on OA. Multivariable MR (MVMR) was conducted to investigate the independent effects of exposures. It turned out that genetically predicted standard deviation increase in birth weight was not associated with OA. In contrast, there was a marginally positive effect of childhood obesity on total [odds ratio (OR) = 1.07, 95% confidence interval (CI) = 1.00, 1.15 using IVW], knee (OR = 1.13, 95% CI = 1.05, 1.22 using weighted median), hip (OR = 1.13, 95% CI = 1.04, 1.24 using IVW), and spine OA (OR = 1.12, 95% CI = 1.03, 1.22 using IVW), but not hand, thumb, or finger OA. MVMR indicated a potential adulthood body mass index-dependent causal pathway between childhood obesity and OA. In conclusion, no association of birth weight with OA was suggested. Childhood obesity, however, showed a causality with OA in weight-bearing joints, which seems to be a general association of obesity with OA.

Introduction

Obesity and osteoarthritis (OA) are two major public healthcare problems due to their high prevalence among adults worldwide.[1,2] There is evidence for a higher risk of developing OA among overweight adults than those with normal weight.[3–5] More recently, the effects of childhood obesity and even birth weight on developing OA in adulthood were also recognized,[6–10] suggesting the fetal origins hypothesis.[11,12] The hypothesis indicates that adverse intrauterine environment may influence fetal growth and development, consequently, resulting in a long-term influence on later health status. Such idea is helpful to broaden the potential mechanisms for many chronic diseases in humans. Many observational studies have reported an increased risk of OA in individuals with early abnormal weight, such as lower birth weight as well as childhood obesity.[6,10] However, no significant effect of intra-pair birth weight differences on OA was observed in a prospective cohort study of female twins.[13] A British birth cohort study found that the association between body mass index (BMI) and later knee OA was not detectable until age 15 in women and 20 in men.[14] Thus, the association between birth weight, childhood obesity, and OA is still ambiguous.

On the other hand, the above controversial evidence may be since observational studies are likely to be affected by uncontrollable factors and reverse causality. Mendelian randomization (MR) provides a way to determine if the observed correlation between a risk factor and an outcome is actually indicative of a causal relationship. It utilizes genetic variations as instrumental variables (IVs) and takes advantage of genetic variants randomly, independently, and uniformly distributed during meiosis.[15] Three assumptions of MR must be met in order to obtain impartial results: (a) genetic IVs should be closely associated with exposure; (b) genetic IVs are not affected by any confounding factors related to the chosen exposure and outcome; and (c) genetic IVs affect outcome only through exposure and not through any other biological pathways.[15] Since the determination of genotype occurs at conception and before the onset of medically relevant trait or disease, this method largely avoids unmeasured confounding and reverse causality.[16]

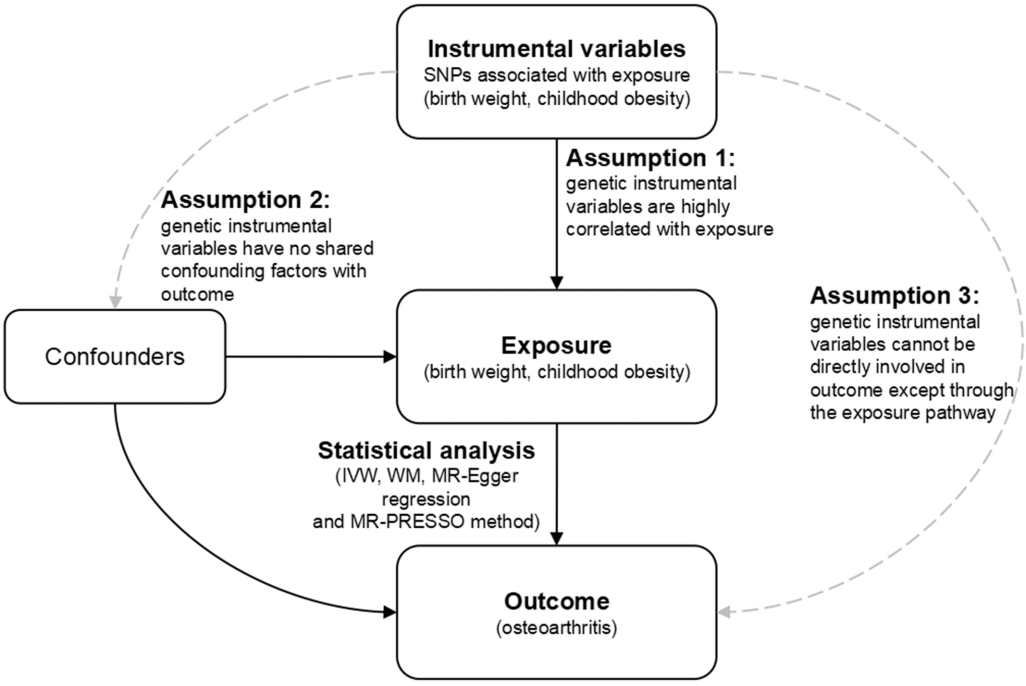

Figure 1. The design of two-sample MR study. The solid lines are significant; dashed lines should not exist based on MR assumptions. SNP: single nucleotide polymorphism; IVW, inverse-variance-weighted; WM, weighted median; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier.

The purpose of our study is to investigate the potential links between birth weight, childhood obesity, and the development of OA in adulthood using both univariable MR and multivariable MR (MVMR) methods. In addition, we sought to elucidate the origin of the association between birth weight and adult OA by examining the potential maternal and/or fetal effects on birth weight. A two-sample MR framework was used to disentangle the causality.

Material and methods

Study design

The design of two-sample MR study is overviewed in Figure 1. In the MR study, IVs are determined based on the following three core assumptions.[17] First, genetic IVs are highly correlated with exposure. Second, genetic IVs have no shared confounding factors with outcome (e.g., adulthood BMI, waist-to-hip ratio, and height). Finally, genetic IVs cannot be directly involved in outcome except through the exposure pathway. We further performed MR analysis using summary statistic datasets from large-scale genome-wide association studies (GWASs) of birth weight, childhood obesity, and OA.

Data sources

Summary association data of birth weight-related single nucleotide polymorphisms (SNPs) were publicly available from a recent GWAS of birth weight contributed by the Early Growth Genetics (EGG) Consortium.[18] The effects of each SNP on own ($n = 298{,}142$) and offspring ($n = 210{,}267$) birth weights were analyzed after adjusting for covariates (e.g., gestational age) in the GWAS. Besides, it used structural equation modeling to classify the genetic effects as maternal ($n = 264{,}498$) or fetal ($n = 179{,}360$) effects. Notably, the maternal effects adjusted for offspring genotype-specific effects and were therefore independent of offspring, representing the effects of intrauterine environment. The fetal effects were independent of maternal, representing the own inherited effect after adjustment of maternal genotype-specific effects. This partition approach thus facilitates the differentiation between the direct fetal effects and the indirect maternal effects of SNPs on birth weight, which is measured in grams as the weight of a newborn. We obtained SNPs associated with childhood obesity from another GWAS on EGG Consortium participants of European ancestry ($n = 24{,}160$).[19] EGG defined childhood obesity as having a BMI equal to or exceeding the 95th percentile for individuals aged 2–18 years old.

We extracted summary statistics of OA and its phenotypes from the Genetics of Osteoarthritis (GO) Consortium, including a total of 826,690 (177,517 cases and 649,173 controls) participants of mainly European ancestry.[20] The GWAS defined patients with OA who met criteria such as self-reported status, the hospital diagnosed, ICD10 codes, or radiography defined by the TREAT-OA consortium.

Detailed information on the study population can be found in Supplementary Table S1. As the present study involved only a secondary analysis of existing published data, ethical approval was not required.

SNP selection

We selected 209 SNPs associated with birth weight at genome-wide significance ($p < 6.6 \times 10^{-9}$), as reported by GWAS, to serve as IVs for our analysis. The association effect sizes for each SNP were divided into uncorrected, corrected fetal- and maternal-independent effect estimates. To assess the influence of inherited and environmental factors on the association between birth weight and OA, we conducted MR analyses of the three distinct effect sizes. We identified 19 SNPs that showed significant associations with childhood obesity ($p < 5 \times 10^{-8}$) in the GWAS analysis.

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We searched all of the obtained SNPs in the GWAS catalog (https://www.ebi.ac.uk/gwas) and removed those associated with confounding factors or outcome at high significance ($p < 1 \times 10^{-5}$). Thus, potential horizontal pleiotropy that violated assumptions 2 and 3 of the MR method was avoided. Meanwhile, we performed linkage disequilibrium (LD) tests for these SNPs. The parameters (kb = 10,000 and $r^2 = 0.001$) were set to select independent SNPs. Next, we matched the SNPs in the summary statistic datasets of SNP–outcome (OA) association estimates and removed SNPs that were not obtained in the OA GWAS. Furthermore, to guarantee the strength of IVs, R^2 and the *F*-statistics were calculated. Characteristics of instrument SNPs for birth weight and childhood obesity were summarized in Supplementary Table S2-S3.

MR analysis

To investigate the causal impact of genetically predicted exposure on outcome, we primarily employed the inverse-variance-weighted (IVW) method for our analysis.[21] In addition, we employed the weighted median (WM) method for additional MR analysis.[22] IVW estimates assume that all genetic variants are valid IVs, while WM estimates can provide consistent estimates of causality when up to 50% of the weight is attributed to valid IVs. Therefore, the WM estimator has lower type 1 error rates than the IVW method, especially when directional pleiotropy exists and InSIDE (instrument strength independent of direct effect) assumption is not satisfied.[23]

The MR-Egger regression and MR-PRESSO method were conducted as sensitivity analyses to guarantee the robustness of results. Among them, MR-Egger method may give a reliable estimate of causal effects, though no genetic variants are valid IVs.[24] And it could robustly detect the presence of pleiotropy. MR-PRESSO is a method that can be employed to identify and correct outliers in IVW linear regression.[25] Heterogeneity was detected by Cochran's Q test ($P < 0.05$ suggesting heterogeneity). Additionally, to investigate the impact of potential outlying and pleiotropic SNPs, we performed a "leave-one-out analysis" by systematically removing each SNP from the analysis in turn. We calculated statistical power for a type 1 error of 5% using an online tool (http://cnsgenomics.com/shiny/mRnd/). The power estimates for the MR were showed in Supplementary Table S4.

What's more, we performed a two-sample MVMR analysis to investigate the independent effects of correlated exposures. We extracted SNPs which were genome-wide significant in either the EGG GWAS of childhood obesity or the Genetic Investigation of ANthropometric Traits GWAS of adulthood BMI.[26] After LD test, 498 SNPs with r^2<0.001 were used in the analysis. Both the IVW and MR-Egger method were conducted to ascertain the independent effects in MVMR analysis.

All of the effect estimates of exposure on OA outcome were reported by odds ratios (OR). Notably, the OR of birth weight was in terms of per standard deviation (SD) increasing in birth weight, where the SD of birth weight was 539 g. Univariable MR analyses were performed using "TwoSampleMR" and "MR-PRESSO" packages with R software,[25,27] and MVMR analyses were performed using "MVMR" and "Mendelian Randomization" packages with R software.[27–29] *P* value was corrected by Bonferroni based upon the number of tests performed in all analyses. The statistical analyses had statistically significant evidence at *P*-values < 0.004 (0.05/14) and had marginal significance at *P*-values between 0.004 and 0.05.

Results

Causal effect of birth weight on OA and its phenotypes

We excluded 35 SNPs associated with confounding factors or outcome and 75 SNPs with LD through GWAS catalog search and LD test. Lastly, 99 SNPs were selected in the MR analysis. We find no evidence for the causal association of birth weight with OA and its phenotypes as shown in Table 1. Using the IVW method, genetically predicted 1-SD increase in birth weight was not found to be associated with total OA [1.01, 95% confidence interval (CI) = 0.94, 1.07, $P = 0.834$] or other site-specific OA. Other MR estimates provided consistent findings. Substantial heterogeneity was indicated by Cochran's Q test except for spine OA. The MR-Egger method did not find any evidence of directional pleiotropy.

The absence of a causality between birth weight and OA was likely due to the diverse effects of fetal and maternal genomes in the direction and size. Therefore, we further used genetic data on fetal- or maternal-independent effects of birth weight for validation. Finally, 104 and 97 LD-independent SNPs were taken as IVs for fetal and maternal effect of birth weight, respectively. Note that, after matching the SNPs of maternal effect in the spine and thumb OA GWAS, the number of final IVs used in the MR analysis was different (Supplementary Table S5). The IVW results did not show a causal impact of fetal effect of birth weight on total OA (OR = 1.01, 95% CI = 0.95, 1.08, $P = 0.728$) or other site-specific OA (Supplementary Table S6). In addition, the maternal effect of birth weight was not found to have causal effect on the risk of total OA (OR = 0.97, 95% CI = 0.90, 1.05, $P = 0.501$) or other site-specific OA using the IVW method (Supplementary Table S7). Other MR estimates provided consistent findings.

Causal effect of childhood obesity on OA and its phenotypes

For childhood obesity traits, 19 SNPs were taken as genetic variants, of which 9 SNPs were excluded due to association with confounders and 6 SNPs were ruled out due to LD. Lastly, a total of 4 SNPs were taken as IVs for childhood obesity. As shown in the Table 2, childhood obesity had marginally causal association with total OA (IVW OR = 1.07, 95% CI = 1.00, 1.15, $P = 0.036$). Childhood obesity was also marginally associated with hip OA (IVW OR = 1.13, 95% CI = 1.04, 1.24, $P = 0.005$) and spine OA (IVW OR = 1.12, 95% CI = 1.03, 1.22, $P = 0.008$) and was suggestively associated with knee OA (WM OR = 1.13, 95% CI = 1.05, 1.22, $P = 8E\text{-}04$). However, we discovered that childhood obesity had no causal effect on hand, thumb, and finger OA. Heterogeneity was only detected for total, knee, and thumb OA by Cochran's Q test. The MR-Egger method found no evidence of directional pleiotropy. The results of funnel plots and "leave-one-out analysis" demonstrated that no single SNP has a significant effect on the pooled results, verifying the stability of our results in Supplementary Fig. S1-S7.

Multivariable MR analyses

The MVMR analysis indicated that after controlling for adulthood BMI, the causal effect of childhood obesity on total (IVW OR = 0.99, 95% CI = 0.97, 1.02, $P = 0.612$) and knee (IVW OR = 1.00, 95% CI = 0.96, 1.03, $P = 0.859$) OA was not statistically significant (Table 3). The childhood obesity-hip OA (OR = 1.06, 95% CI = 1.01, 1.11, $P = 0.025$) and -spine OA (OR = 1.06, 95% CI = 1.00, 1.11, $P = 0.044$) associations were marginally significant using MR-Egger method, but attenuated completely using IVW

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Table 1. MR results of the causal association between birth weight and OA

Exposure	Outcome	N of SNPs	Method	OR (95%CI)	*P* value	Heterogeneity test Cochran's Q (P^a)	Pleiotropy test *P* Intercept
Birth weight	Total OA	99	IVW	1.01 (0.94, 1.07)	0.834	173.28 (<**0.001**)	
			WM	0.98 (0.91, 1.06)	0.618		
			MR-Egger	0.99 (0.86, 1.15)	0.925		0.838
			MR-PRESSO (Outlier-corrected)	1.00 (0.96, 1.04)	0.984		
Birth weight	Knee OA	99	IVW	1.04 (0.93, 1.15)	0.515	191.72 (<**0.001**)	
			WM	1.02 (0.89, 1.16)	0.795		
			MR Egger	0.97 (0.76, 1.24)	0.828		0.580
			MR-PRESSO (Outlier-corrected)	1.05 (0.96, 1.16)	0.299		
Birth weight	Hip OA	99	IVW	0.99 (0.87, 1.13)	0.850	179.73 (<**0.001**)	
			WM	1.03 (0.88, 1.20)	0.750		
			MR Egger	0.98 (0.73, 1.33)	0.911		0.973
			MR-PRESSO (Outlier-corrected)	0.97 (0.85, 1.10)	0.594		
Birth weight	Spine OA	99	IVW	1.06 (0.95, 1.18)	0.264	99.21 (0.447)	
			WM	1.09 (0.92, 1.29)	0.338		
			MR Egger	1.01 (0.79, 1.29)	0.947		0.638
			MR-PRESSO (Outlier-corrected)	–	–		
Birth weight	Hand OA	99	IVW	1.05 (0.90, 1.22)	0.539	129.90 (**0.017**)	
			WM	0.99 (0.81, 1.22)	0.961		
			MR Egger	0.77 (0.55, 1.10)	0.153		0.063
			MR-PRESSO (Outlier-corrected)	1.12 (0.97, 1.30)	0.127		
Birth weight	Thumb OA	99	IVW	1.13 (0.93, 1.38)	0.230	124.55 (**0.036**)	
			WM	0.90 (0.67, 1.20)	0.470		
			MR Egger	0.74 (0.46, 1.17)	0.200		0.050
			MR-PRESSO (Outlier-corrected)	–	–		
Birth weight	Finger OA	99	IVW	1.00 (0.80, 1.24)	0.977	134.71 (**0.008**)	
			WM	1.23 (0.91, 1.67)	0.177		
			MR Egger	0.87 (0.51, 1.48)	0.608		0.581
			MR-PRESSO (Outlier-corrected)	1.15 (0.94, 1.41)	0.189		

MR, Mendelian randomization; OA, osteoarthritis; SNPs, single nucleotide polymorphisms; OR, odds ratio; CI, confidence interval; IVW, inverse-variance-weighted; WM, weighted median; MR-PRESSO, MR-pleiotropy residual sum and outlier.
[a]Bolded *P* represents heterogeneity.

method. The results on hand, thumb, and finger OA were consistent in the adjusted model.

Discussion

To the best of our knowledge, this is the first two-sample MR analysis of the association between birth weight, childhood obesity, and OA risk in adulthood by using large genetic datasets. The MR results supported the association between childhood obesity and total, knee, hip, and spine OA, but not hand, thumb, and finger OA. It is worth noting that the causal effect of childhood obesity on OA was weakened after adjusting for adult BMI. Besides, we observed no evidence for the association between birth weight and OA. Indeed, when distinguish fetal- or maternal-independent effects of birth weight in additional analysis, we also observed a null association.

Previous observational results on the association between birth weight with total as well as site-specific OA remain inconclusive. Sultana *et al.* conducted a retrospective cohort study in 3,604 participants from Australian Diabetes, Obesity and Lifestyle Study and found that low birth weight was associated with a multivariable-adjusted HR of 2.04 for increased incidence of hip arthroplasty when compared to those with normal birth weight.[9] Several other cohort studies found that low birth weight was associated with the development of OA in men, but not in women.[13,30] On the contrary, the results from the Hertfordshire Cohort Study indicated that lower birth weight was not associated with increased risk of clinical knee, hip, and hand OA.[31] Indeed,

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Table 2. MR results of the causal association between childhood obesity and OA

Exposure	Outcome	N of SNPs	Method	OR (95%CI)	*P* value[a]	Heterogeneity test	Pleiotropy test
						Cochran's Q (*P*[b])	*P* Intercept
Childhood obesity	Total OA	4	IVW	1.07 (1.00, 1.15)	**0.036**	11.66 (**0.009**)	
			WM	1.08 (1.03, 1.44)	**7E-04**		
			MR-Egger	1.01 (0.76, 1.36)	0.936		0.725
			MR-PRESSO (Outlier-corrected)	–	–		
Childhood obesity	Knee OA	4	IVW	1.13 (0.98, 1.30)	0.083	20.51 (<**0.001**)	
			WM	1.13 (1.05, 1.22)	**8E-04**		
			MR Egger	1.11 (0.59, 2.09)	0.777		0.959
			MR-PRESSO (Outlier-corrected)	–	–		
Childhood obesity	Hip OA	4	IVW	1.13 (1.04, 1.24)	**0.005**	5.17 (0.160)	
			WM	1.18 (1.08, 1.30)	**2E-04**		
			MR Egger	1.29 (0.90, 1.85)	0.305		0.552
			MR-PRESSO (Outlier-corrected)	–	–		
Childhood obesity	Spine OA	4	IVW	1.12 (1.03, 1.22)	**0.008**	3.72 (0.294)	
			WM	1.14 (1.03, 1.25)	**0.009**		
			MR Egger	1.42 (1.07, 1.88)	0.136		0.232
			MR-PRESSO (Outlier-corrected)	–	–		
Childhood obesity	Hand OA	4	IVW	1.07 (0.97, 1.18)	0.190	3.56 (0.313)	
			WM	1.11 (0.99, 1.25)	0.079		
			MR Egger	0.98 (0.64, 1.51)	0.932		0.720
			MR-PRESSO (Outlier-corrected)	–	–		
Childhood obesity	Thumb OA	4	IVW	1.00 (0.81, 1.23)	0.989	8.60 (**0.035**)	
			WM	1.00 (0.85, 1.18)	0.981		
			MR Egger	0.80 (0.32, 1.97)	0.672		0.663
			MR-PRESSO (Outlier-corrected)	–	–		
Childhood obesity	Finger OA	4	IVW	1.07 (0.93, 1.23)	0.364	3.47 (0.325)	
			WM	1.09 (0.92, 1.28)	0.313		
			MR Egger	1.65 (1.01, 2.69)	0.181		0.210
			MR-PRESSO (Outlier-corrected)	–	–		

MR, Mendelian randomization; OA, osteoarthritis; SNPs, single nucleotide polymorphisms; OR, odds ratio; CI, confidence interval; IVW, inverse-variance-weighted; WM, weighted median; MR-PRESSO, MR-pleiotropy residual sum and outlier.
[a]Bolded *P* value represents statistical significance.
[b]Bolded *P* represents heterogeneity.

these studies may suggest the fetal origins hypothesis, which indicate the development of adult OA may due to early life factors, such as vitamin D receptor gene.[30] In our MR study, we found no evidence of a causal association between birth weight and OA using both the IVW and WM methods. MR Egger's result did not present any bias by directional pleiotropy. In contrast to previous MR study,[32] our study further distinguished fetal or maternal factors of effects on birth weight by taking advantage of the recent GWAS. By analyzing the fetal- or maternal-independent effects of birth weight, we found no association between birth weight and OA, suggesting that factors related to fetal development and intrauterine exposure are unlikely to confound the observed relationship.

Our findings of a positive relationship between childhood obesity and OA are consistent with the results of observational studies. Widhalm et al. found higher knee OA risk in morbidly obese children compared to controls.[33] A cohort study by Andrew *et al.* showed that increased BMI in childhood was associated with a higher risk of knee OA.[14] Other studies reported that obese children were at increased risk of many predisposing traits of OA, such as slipped capital femoral epiphysis, idiopathic genu valgum, and so on.[34,35] However, findings from a longitudinal study indicated that childhood obesity had no effect on the risk of hand OA.[36] The association between obesity and specific OA phenotype is well established. Higher force transmission on weight-bearing joints activates chondrocytes and advances cartilage degeneration.[37] Some

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Table 3. Multivariable MR associations of childhood obesity with OA adjusted for adulthood BMI

Outcome	Method	OR (95%CI)	*P* value[a]
Total OA	IVW adjusted for adulthood BMI	0.99 (0.97, 1.02)	0.612
	MR-Egger adjusted for adulthood BMI	0.99 (0.97, 1.02)	0.702
Knee OA	IVW adjusted for adulthood BMI	1.00 (0.96, 1.03)	0.859
	MR-Egger adjusted for adulthood BMI	1.00 (0.96, 1.04)	0.901
Hip OA	IVW adjusted for adulthood BMI	1.02 (0.98, 1.07)	0.313
	MR-Egger adjusted for adulthood BMI	1.06 (1.01, 1.11)	**0.025**
Spine OA	IVW adjusted for adulthood BMI	1.05 (1.00, 1.09)	0.063
	MR-Egger adjusted for adulthood BMI	1.06 (1.00, 1.11)	**0.044**
Hand OA	IVW adjusted for adulthood BMI	1.02 (0.97, 1.07)	0.542
	MR-Egger adjusted for adulthood BMI	1.04 (0.98, 1.09)	0.204
Thumb OA	IVW adjusted for adulthood BMI	1.03 (0.96, 1.09)	0.431
	MR-Egger adjusted for adulthood BMI	1.05 (0.98, 1.12)	0.195
Finger OA	IVW adjusted for adulthood BMI	0.98 (0.92, 1.05)	0.601
	MR-Egger adjusted for adulthood BMI	0.98 (0.90, 1.05)	0.512

MR, Mendelian randomization; OA, osteoarthritis; BMI, body mass index; OR, odds ratio; CI, confidence interval; IVW, inverse-variance-weighted.
[a]Bolded *P* value represents statistical significance.

adipokines secreted by adipose tissue and some joint cells have proinflammatory and prodegenerative effects on OA, including hand OA.[38,39] Previous MR study had found that increased BMI in childhood and adulthood was all associated with a higher risk of OA at weight-bearing joints.[40,41] Therefore, the present study performed a multivariable analysis to investigated the robustness of the relationship of childhood obesity with OA after adjusting for adulthood BMI. The causal effect of childhood obesity on hip and spine OA was attenuated and marginally significant and can be explained by a more general causal effect of adulthood obesity on OA. The findings of the study reveal that obesity contributes to OA at weight-bearing joints through a separate pathway different from that of fetal origins.

There are several limitations in our study. First, the number of SNPs for childhood obesity included in the study is relatively small. Thus, a GWAS with a greater number of SNP is required to replicate MR study to strengthen power of estimate causal effect. Second, the study only involves in participants of European descent, so it is unknown whether our findings can be transferable to non-European populations. Third, constrained by summary data, we are unable to stratify the causality between birth weight and childhood obesity and OA by sex or weight. Furthermore, we are unable to know whether the null results of the MR analysis are due to misclassification of OA participants at baseline. This limitation may lead to our underestimation of cases of hand OA. Finally, the sources of three samples have overlapping, so we mostly used powerful tools (i.e., the *F*-statistic > 10) to minimize its bias.[21]

It was worth noting that the study had some strengths. First, this is the first MR analysis to investigate the causal association between birth weight, childhood obesity and OA at the same time. The MR study further confirmed neither indirect maternal effects nor direct fetal effect have indirect long-term effects on the risk of OA. Besides, we included seven specific OA phenotypes obtained from the largest GWAS, enhancing the comprehensiveness of our analysis. By utilizing IVs extracted from the latest GWAS data for birth weight and childhood obesity, we ensure the relevance and accuracy of our findings. The large sample size employed in our study adds to the reliability and generalizability of our results. What's more, the statistical power for the causality between childhood obesity and total OA and OA at weight-bearing joints is highly enough, which improve the reliability of the results. Finally, we are more able to remove the bias due to adult BMI by using MVMR than using univariable MR.

Conclusion

Our study provided support for a suggestive association between genetically predicted childhood obesity and OA at weight-bearing joints. However, we did not find a significant association between childhood obesity and hand OA. Although evidence for the association between birth weight and OA is lacking, it is important to note that birth weight is considered a significant risk factor for the development of OA, mainly due to its impact on various other diseases.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S2040174424000114.

Data availability statement. All data included in this study is commercially available.

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Author contribution. Zengfeng Xin and Lingxiao Xu contributed equally to this work.

All authors participated in the study. LS and LX contributed to the conception or design of the work. ZX and LS contributed to the acquisition of data. ZX and LX contributed to the analysis and interpretation of data and the preparation of the manuscript. All authors read and approved the final manuscript.

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Competing interests. None.

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