IJC Heart & Vasculature 52 (2024) 101425

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature

Genetic associations of childhood and adult BMI on chronic heart failure and ischemic stroke: A Mendelian randomization

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ARTICLE INFO

Keywords:
Childhood BMI
Adult BMI
Chronic heart failure
Ischemic stroke
Mendelian randomization
Genome-wide association studies

ABSTRACT

Background: Obesity has been confirmed to be associated with cardiovascular disease, but previous studies have focused on adults, and whether childhood obesity is associated with cardiovascular disease in adulthood needs further research.
Objective: This Mendelian randomization (MR) study aimed to investigate the associations of childhood and adult body mass index (BMI) with the risk of chronic heart failure (CHF) and ischemic stroke (IS).
Methods: Independent genetic instruments, demonstrating a strong association with exposure at the genome-wide significance level ($P < 5 \times 10^{-8}$), were carefully selected from comprehensive genome-wide association studies conducted within relevant European populations. Summary-level data for CHF and IS were obtained from the EBI database and large consortia of European population. To enhance robustness and generalizability, the analysis was replicated in an East Asian population cohort.
Results: According to a MR analysis based on a European population, a higher adult BMI was associated with an increased risk of CHF [(odds ratio (*OR*) 1.594, 95% confidence interval (*CI*) 1.483–1.713)] and IS (*OR* 1.163, *95%CI* 1.096–1.233). In addition, higher childhood BMI level was associated with a higher risk of CHF (*OR* 1.323, 95%*CI* 1.153–1.524).and the effect was mainly driven by adult BMI. Replication analyses of adult BMI in East Asian populations showed consistent findings that adult BMI was associated with the risk of CHF (*OR* 2.167, *95%CI* 1.786–2.630) and IS (*OR* 1.259, *95%CI* 1.128–1.406).
Conclusions: Our study findings provide compelling evidence for the significant influence of adult BMI on the occurrence of CHF and IS. Furthermore, our observations suggest that the positive association between childhood BMI and the risk of CHF in adulthood can largely be attributed to individuals who maintain obesity into later life.

1. Introduction

Cardiovascular disease (CVD) includes stroke, heart failure, ischemic heart disease, and other diseases of the heart and blood vessels. CVD is the leading cause of human death and decreased quality of life [1]. Research has revealed an alarming trend in the increasing prevalence of CVD worldwide [2,3]. The number of individuals affected by CVD has risen significantly over the years, from 271 million cases in 1990 to a staggering 523 million cases in 2019 [4]. This upward trajectory highlights the urgent need for effective prevention and management strategies to mitigate the burden of CVD. A significant number of observational studies have consistently shown a robust link between obesity and an elevated risk of CVD [5–10]. Obesity is a major contributor to the rising incidence of CVD. However, observational studies are susceptible to confounding factors, which may easily lead to biased results.

Mendelian randomization (MR) analysis is a method used in epidemiology in recent years to infer causal relationships between exposures based on single nucleotide polymorphisms (SNPs) and disease outcomes, primarily through genetic variation [11]. In MR, using phenotypically associated genetic variations as instrumental variables (IVs) for exposure can enhance the strength of causal inference regarding the association between exposures and outcomes. Genetic separation adheres to the principle of random allele distribution from parents to offspring, reducing susceptibility to confounding factors. By utilizing genetic variations as IVs, researchers can mitigate the impact of confounders

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https://doi.org/10.1016/j.ijcha.2024.101425
Received 17 March 2024; Received in revised form 29 April 2024; Accepted 9 May 2024

and obtain stronger evidence for establishing causal relationships between exposures and outcomes [12].

In recent years, there has been an increasing number of published MR studies examining the relationship between obesity, primarily defined by body mass index (BMI) and CVD [13–15]. However, most of these studies have predominantly focused on adults, with limited research conducted on children. Furthermore, previous investigations have primarily concentrated on European populations, resulting in a paucity of studies on East Asian populations. To address these research gaps, our study aimed to be the first MR study investigating the association between children and adults BMI as exposures and ischemic stroke (IS) and chronic heart failure (CHF) as outcomes in European population. Additionally, the findings were validated in East Asian population.

2. Methods

As publicly published genome-wide association studies (GWAS) data were utilized in this study, which did not involve the use of raw data or human subjects directly, ethical approval was not necessary. The data utilized in this study were obtained from publicly available sources and complied with the relevant data sharing and usage guidelines.

2.1. Exposures and outcomes

Exposure data on childhood (aged 2–10 years) and adult BMI encompassed 39,620 and 681,275 individuals, from European population. The study outcomes focused on CHF and IS, involving 486,160 and 484,121 European individuals, respectively. To validate our findings in the East Asian population, we obtained a separate dataset comprising East Asian individuals. We applied the same SNP selection criteria. The exposure and outcome definitions, as well as the statistical models, were consistent with those used in the primary analysis to ensure comparability (Table1).

By replicating the analysis in this independent population, we aimed to confirm the robustness and generalizability of our findings across different ethnic groups.

2.2. Instrument identification and data harmonization

SNPs used as IVs must satisfy the following three assumptions: (1) The IVs should exhibit a strong association with the exposure of interest. (2) The IVs should not be associated with confounding factors related to both the exposures and the outcomes. (3) The IVs affect the outcome only through the pathway of exposure to outcome (Fig. 1).

To minimize the effect of linkage disequilibrium (LD), SNPs were screened by P value and elimination of linkage disequilibrium ($P < 5 \times 10^{-8}$, LD coefficient $r^2 = 0.001$, region width 10,000 kb). F value was calculated from the formula $F=\frac{R^2(N-2)}{1-R^2}$ [16], and selected IVs with $F > 10$ which are strongly correlated with exposures [17]. $R^2=\frac{2\times EAF\times(1-EAF)\times beta^2}{2\times EAF\times(1-EAF)\times beta^2+2\times EAF\times(1-EAF)\times N\times SE(beta)^2}$ [16], N represents the sample size of the dataset, *beta* represents the effect size of the SNPs on the exposures variable, *SE* denotes the standard error of *beta*, and *EAF* refers to the effect allele frequency. For multivariable MR, we first identified two separate sets of SNPs that were significantly associated with each of the two exposures based on prior GWAS. We then combined these two SNP sets into one unified set for further analysis. To account for potential LD among these SNPs, we performed LD clumping on the combined set. Additionally, when SNPs associated with one exposure were missing from the dataset related to the other exposure, we used proxy SNPs that were in strong LD (with an r^2 greater than 0.8) to represent the missing genetic variation [18].

Table 1
Information on outcome data.

	Sample size(n)	Population	Dataset
Exposure			
Adult BMI	681,275	European	ieu-b-40
Childhood BMI	39,620	European	ebi-a-GCST90002409
Adult BMI	163,835	East Asian	NA*
Outcome			
CHF	486,160	European	ebi-a-GCST90018806
IS	484,121	European	ebi-a-GCST90018864
CHF	178,726	East Asian	NA*
IS	174,686	East Asian	NA*

BMI: body mass index; CHF: chronic heart failure; IS: ischemic stroke.
* NA means that there no Dataset information that is not mentioned or available.

2.3. Mendelian randomization analysis

In this study, univariable MR analysis was utilized to assess the overall effect of genetically predicted childhood and adult BMI on each disease outcome. Subsequently, multivariable MR was employed to estimate the direct effect of childhood BMI, with adult BMI taken into account as an additional exposure in the model. To illustrate these analyses, directed acyclic graphs summarizing the relationships between the exposures and outcomes were included (Fig. 2). Additionally, we solely employed univariate MR to assess the overall effect of genetically predicted adult BMI on each disease outcome within East Asian populations. MR analysis was conducted using three methods: inverse variance-weighted (IVW), weighted median, and MR-Egger. The IVW analysis results were utilized as the primary criterion for evaluation. Heterogeneity and pleiotropy were assessed through Cochrane's Q and MR-Egger test, respectively. The stability of the MR results was examined using the leave-one-out method. The TwoSample MR package in R (version 4.3.1) was employed for the analysis, and a two-tailed P value < 0.05 was considered significant.

3. Results

3.1. The selection of instrumental variables

According to the screening criteria for IVs in this study (Supplementary 1), the MR-Egger regression intercept was $P > 0.05$ for childhood BMI and adult BMI (Table 2). The results of our analysis indicate the absence of horizontal pleiotropy between the exposures and outcomes.

3.2. Two-samples Mendelian randomization analysis

In comprehensive analysis, we utilized the IVW, weighted median, and MR-Egger methods to rigorously evaluate the putative causal associations between childhood BMI, adult BMI, and the risk of developing CHF and IS. According to MR analysis based on a European population, a higher genetically predicted adult BMI was associated with an increased risk of CHF [(odds ratio (*OR*)1.594, 95 % confidence interval (*CI*) 1.483–1.713)] and IS (*OR* 1.163,*95 %CI* 1.096–1.233), and higher childhood BMI level was associated with a higher risk of CHF (*OR* 1.323, 95 %*CI* 1.153–1.524) (Table 1, Fig. 3, Supplementary2 Fig. S1-2). Replication analyses of adult BMI in East Asian populations showed consistent findings that genetically predicted adult BMI was associated with the risk of CHF (*OR* 2.167, 95 %*CI* 1.786–2.630) and IS (*OR* 1.259, *95 %CI* 1.128–1.406) (Table 3, Fig. 4, Supplementary2 Fig. S3-4).

3.3. Univariable and multivariable mendelian randomization analyses

Univariable analyses provided strong evidence that childhood BMI was associated with risk of CHF (*OR* 1.594, 95 %*CI* 1.483–1.713). However, the direct effect (not mediated through adult BMI) of

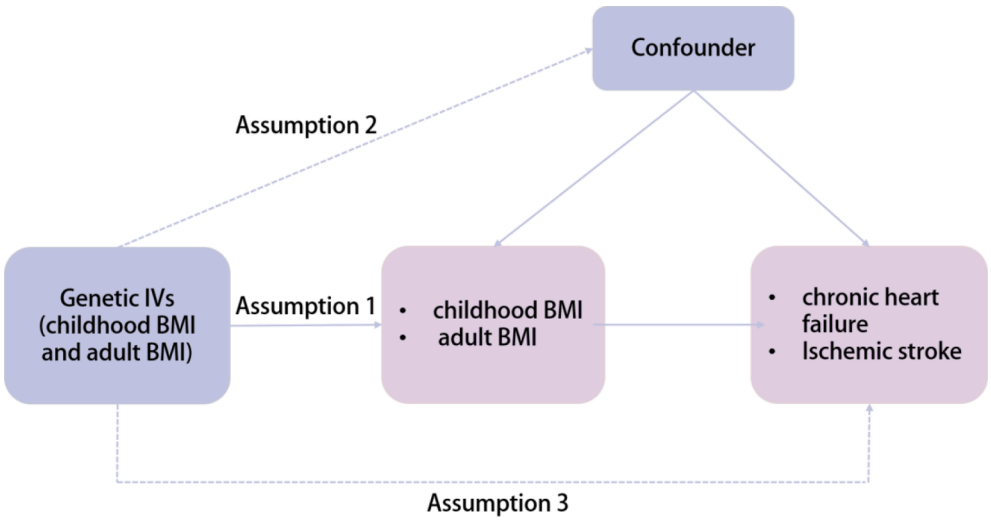

Fig. 1. Mendelian randomization (MR) design overview. Assumption 1 indicates that the used genetic variants as instrumental variables should be strongly associated with the exposure; assumption 2 indicates that the used genetic variants should not associated with confounders; and assumption 3 indicates the used genetic variants should affect the outcome merely via the exposure, not partly or entirely via other alternative pathways. IVs, instrumental variables; BMI, body mass index.

childhood BMI (*OR* 0.989, 95 % *CI* 0.897–1.090) was much smaller than the total effect, whereas strong evidence of a direct effect was identified for adult BMI (*OR* 1.600, 95 %*CI* 1.436–1.782) (Table 4).

3.4. Heterogeneity analysis

In the analysis of the European population, significant heterogeneity was observed in the causal analyses of adult BMI for CHF and IS, as well as in the causal analyses of children BMI for CHF ($P < 0.05$). However, no significant heterogeneity was found for other exposures and outcomes (Table 2).

3.5. Sensitivity analysis

In the sensitivity analysis, a leave-one-out test was conducted to assess the robustness of the MR results. By eliminating one SNPs at a time indicating that the MR results of this study were robust (Supplementary Fig. S1-4).

4. Discussion

Numerous observational studies have consistently demonstrated a significant association between adult BMI and the risk of cardiovascular disease [5,19]. In addition, MR studies have provided compelling evidence linking genetically predicted adult BMI to an increased risk of developing CVD [20,21]. However, despite the strong association between childhood BMI and adult BMI, there has been relatively limited research on childhood BMI. Additionally, the existing studies have primarily focused on conditions such as coronary artery disease [22,23], hypertension [24,25], and type 2 diabetes [25–27]. To best of our knowledge, no studies have examined the role of childhood BMI on risk of CHF and IS. Our findings can help fill this knowledge gap and inform the prevention and management of cardiovascular risks in the pediatric population.

Firstly, this study explored the relationship between adult BMI and the risk of CHF and IS. The findings of the study revealed a significant causal association between adult BMI and the increased risk of CHF and IS within the European population. Importantly, this association was further confirmed and validated among individuals of East Asian population. We analyzed the possible causes of obesity leading to CHF as follows: Excess adipose tissue accumulation results in hemodynamic alterations, such as increased blood volume, elevated cardiac output, and a decrease in systemic vascular resistance [28]. Obesity directly impacts the myocardium, leading to the accumulation of fat within the heart muscle and subsequent fibrosis [29]. Obesity contributes to an increase in circulating blood volume, which in turn elevates cardiac preload [30].

Possible causes of IS are as follows: Obesity has been strongly linked to an elevated incidence of coronary artery disease [31], a condition characterized by the narrowing or blockage of coronary arteries leading to myocardial ischemia [32]. Myocardial ischemia can contribute to abnormal heart rhythms and CHF, consequently increasing the risk of IS. Furthermore, obesity can also contribute to the development of metabolic disorders such as hypertension, diabetes, and hyperlipidemia, which independently increase the risk of IS [33].

Second, this study conducted a MR analysis with childhood BMI as the exposure and CHF and IS as the outcomes. Univariable MR analysis suggested that genetically predicted childhood BMI is associated with an increased risk of CHF. Furthermore, multivariable MR analyses using both childhood BMI and adult BMI as exposures were performed. The results showed that estimates of the direct effect of childhood BMI were significantly smaller, which suggests that the effect of childhood BMI on this outcome was mediated by adult BMI. The results suggests that the association between childhood BMI and CHF may be explained by individuals who remain overweight into adulthood. This finding supports the “tracking” hypothesis [34], which suggests that individuals who are overweight or obese during childhood have a higher likelihood of persisting in this state into adulthood. Consequently, they are at an increased risk of developing CVD throughout their lifespan.

Given the increasing prevalence of obesity worldwide [35,36]. The findings of this study carry significant implications for clinical practice and public health interventions. Healthcare providers should take into account the long-term consequences of obesity on cardiovascular health and proactively counsel patients on adopting lifestyle changes that promote and maintain a healthy weight. Public health policies should prioritize primordial prevention by implementing initiatives that promote healthy eating habits and physical activity among children to prevent the onset of obesity in early life. By having these aspects targeted, the burden of cardiovascular diseases can be reduced, and the overall health of the population can be improved.

However, the study has some limitations that should be considered. First, MR analysis relies on the assumption that genetic variants associated with BMI are randomly allocated during conception, which might not always be the case. Second, the study did not account for potential

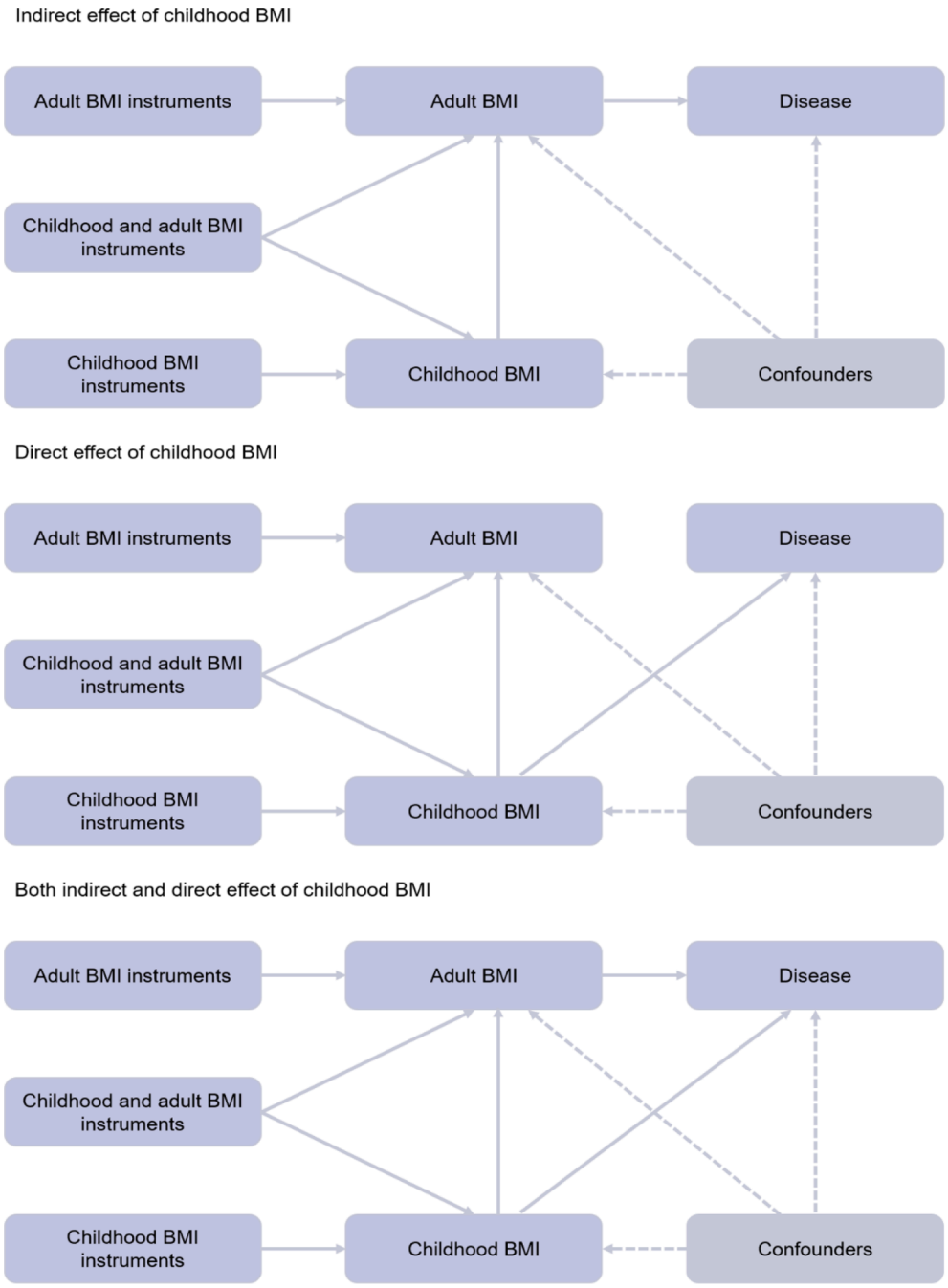

Fig. 2. Directed acyclic graphs depicting three possible scenarios that could explain a causal effect between childhood BMI and disease outcomes in adulthood. (Top) Childhood BMI has an indirect effect on disease risk only through adult BMI, (middle) Childhood BMI has a direct effect on disease risk independent of adult BMI, and (bottom) Childhood BMI exerts both direct and indirect effects on disease risk. BMI, body mass index.

confounding factors such as diet, physical activity, and smoking, which are known to influence both BMI and CVD risk. Future MR studies should incorporate a broader range of environmental and lifestyle factors to provide a more comprehensive understanding of the interplay between BMI and CVD.

5. Conclusions

The findings of this study lend support to the concept that adult BMI plays a substantial part in the development of CHF and IS. Furthermore, strong evidence has been provided through the utilization of multivariable MR, indicating that the link between childhood BMI and the chance of CHF is probably attributed to individuals who maintain a high BMI into adulthood. This study therefore yields insight into the pathway between early life BMI and disease outcomes.

6. Lay summary

This study used Mendelian randomization to investigate the association between body mass index (BMI) in childhood and adulthood with the risk of chronic heart failure (CHF) and ischemic stroke (IS). It found that a higher BMI in adulthood is strongly associated with an increased risk of both CHF and IS. Additionally, childhood obesity was linked to a higher risk of CHF in adulthood, primarily due to those who maintained obesity into later life. Replication analyses in East Asian populations supported these findings.

Table 2
MR results from exposures and outcomes in European population.

Exposure	Outcome	nSNP	Method	*OR,95 %CI*	*P*	Cochran's Q-derived *P* value	MR-Egger intercept-derived *P* value
Adult BMI	IS	486	IVW	1.163(1.096,1.233)	<0.001	0.021	0.302
			Weighted median	1.142(1.036,1.260)	<0.001		
			MR-Egger	1.080(0.929,1.257)	0.316		
	CHF	486	IVW	1.594(1.483,1.713)	<0.001	<0.001	0.373
			Weighted median	1.552(1.389,1.734)	<0.001		
			MR-Egger	1.724(1.430,2.078)	<0.001		
Childhood BMI	IS	16	IVW	1.057(0.552,1.103)	0.174	0.945	0.099
			Weighted median	1.061(0.952,1.184)	0.284		
			MR-Egger	0.780(0.975,1.145)	0.182		
	CHF	16	IVW	1.323(1.153,1.524)	<0.001	<0.001	0.139
			Weighted median	1.189(1.033,1.368)	0.016		
			MR-Egger	0.853(0.484,1.504)	0.592		

BMI: body mass index; CHF: chronic heart failure; IS: ischemic stroke; IVW: inverse variance-weighted.

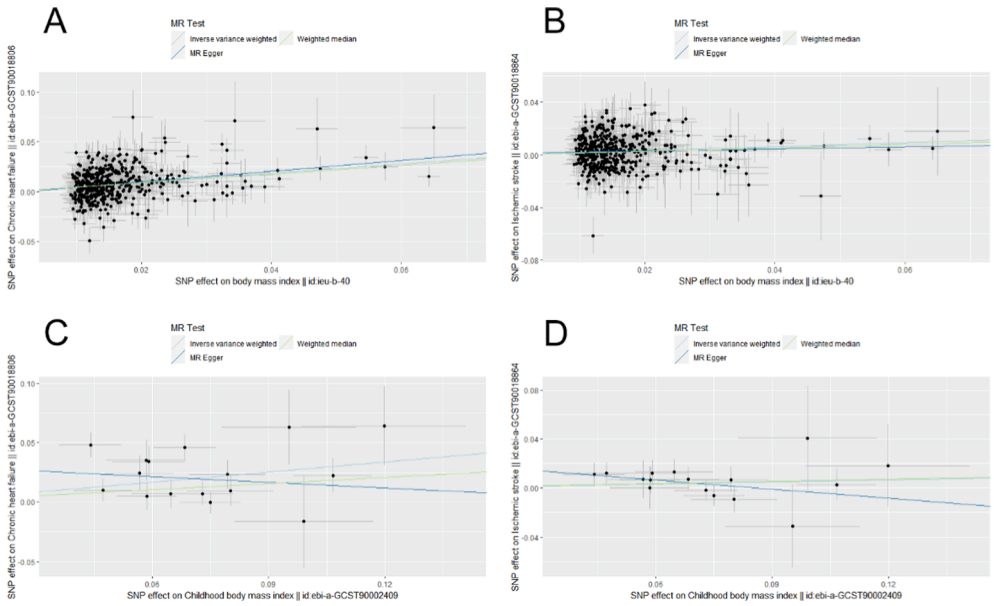

Fig. 3. Mendelian randomization results in European population: (A) The scatter plot illustrates the genetic correlations between adult BMI and chronic heart failure using different MR methods. (B) The scatter plot illustrates the genetic correlations between adult BMI and ischemic stroke using different MR methods. (C) The scatter plot illustrates the genetic correlations between childhood BMI and chronic heart failure using different MR methods. (D) The scatter plot illustrates the genetic correlations between childhood BMI and ischemic stroke using different MR methods.

Table 3
MR results from exposures and outcomes in East Asian population.

Exposure	Outcome	nSNP	Method	*OR, 95 %CI*	*P*	Cochran's Q-derived *P* value	MR-Egger intercept-derived *P* value
Adult BMI	IS	72	IVW	1.259(1.128,1.406)	<0.001	0.079	0.560
			Weighted median	1.219(1.043,1.424)	0.013		
			MR-Egger	1.065(0.783,1.446)	0.691		
	CHF	27	IVW	2.167(1.786,2.630)	<0.001	0.144	0.254
			Weighted median	2.152(1.623,2.853)	<0.001		
			MR-Egger	1.542(0.857,2.776)	0.161		

BMI: body mass index; CHF: chronic heart failure; IS: ischemic stroke; IVW: inverse variance-weighted.

Author Contributions

All authors contributed substantially to this study. J.G.J supervised and designed the study. G.L.L helped to design the study and wrote the article. H.M.Z and G.L.L generated and analyzed the data.

Key Findings: 1. Higher BMI in adulthood is strongly associated with increased risks of chronic heart failure and ischemic stroke. 2. Childhood obesity is also linked to a higher risk of chronic heart failure in adulthood, primarily among those who maintain obesity into later life. These findings highlight the importance of maintaining a healthy weight throughout life to reduce the risk of cardiovascular diseases.

Funding

All authors declare no funding for this contribution.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

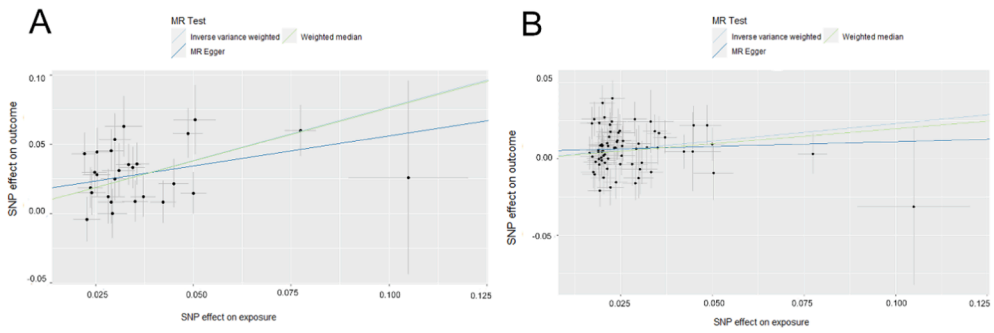

Fig. 4. Mendelian randomization results in East Asian population: (A) The scatter plot illustrates the genetic correlations between adult BMI and chronic heart failure using different MR methods. (B) The scatter plot illustrates the genetic correlations between adult BMI and ischemic stroke using different MR methods.

Table 4
Estimates from univariable and multivariable mendelian randomization analysis assessing effect of predicted childhood and adult BMI on CHF.

Outcomes and exposures	Univariable analysis		Multivariable analysis	
	OR, 95 %CI	*P*	*OR, 95 %CI*	*P*
Adult BMI	1.594 (1.483,1.713)	<0.001	1.600 (1.436,1.782)	<0.001
Childhood BMI	1.325 (1.153,1.524)	<0.001	0.989 (0.897,1.090)	0.824

BMI: body mass index, CHF: chronic heart failure.

the work reported in this paper.

Acknowledgements

We thank Professor W.J.Z, School of Public Health, Zhejiang Chinese medical University, for helping with statistics and data analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101425.

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