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Relationship between childhood obesity and cardiovascular and cerebrovascular diseases: a study based on the combination of multiple databases

Chunrong Chen[1,2], Bo Xie[2,3], Fulin Tao[4], Jiming Chen[2,5], Lili Ye[2,3], Lei Zhong[2,3], Shuangfeng Yan[2,6] and Wenkai Cheng[2,6*]

Abstract

Background The relationship between childhood obesity and cardiovascular and cerebrovascular diseases (CCVD) remains ambiguous. This study aims to explore the causal relationship between childhood obesity and CCVD utilizing the two-sample Mendelian randomization (MR) method. Furthermore, the study investigates the prognostic implications of obesity on CCVD, utilizing insights derived from the Global Burden of Disease (GBD) study 2021.

Methods This study utilized pooled data on childhood obesity from the genome-wide association study (GWAS) available in the IEU Open GWAS database, alongside data on 20 types of CCVD from the GWAS in the 2024 Finngen database for analysis. The inverse variance weighted (IVW) method was served as the primary analysis method, while MR-Egger regression, weighted median, simple mode and weighted mode were employed as supplementary analyses to explore the causal relationship between childhood obesity and CCVD in adulthood. Cochran's Q test, MR-Egger intercept test, and leave-one-out test were performed to access the robustness of the results. Simultaneously, summary data on childhood obesity from GWAS in the EGG database were utilized to replicate the analysis to verify the robustness of the results. Additionally, the latest data from the 2021 GBD study were employed to analyze the prognostic correlation between obesity and CCVD.

Results IVW analysis finds positive causal relationship between childhood obesity and risk of coronary atherosclerosis, cardiovascular diseases, hard cardiovascular diseases, ischemic heart disease, angina pectoris, unstable angina pectoris, myocardial infarction, heart failure, major coronary heart disease event, cardiac arrhythmias, atrial fibrillation and flutter, coronary revascularization (ANGIO or CABG), coronary angioplasty, coronary artery bypass grafting, stroke, and embolic stroke (all $P < 0.05$). These causal relationships remained significant after correcting for the false discovery rate (all $P < 0.05$). Steiger directional test confirmed that the direction of the effect of childhood obesity on CCVD was correct (all $P < 0.001$). No causal relationship was identified between childhood obesity and cardiac arrest, stroke (excluding SAH), subarachnoid haemorrhage, and intracerebral haemorrhage (all $P > 0.05$).

*Correspondence:
Wenkai Cheng
Cwk1139533301@163.com

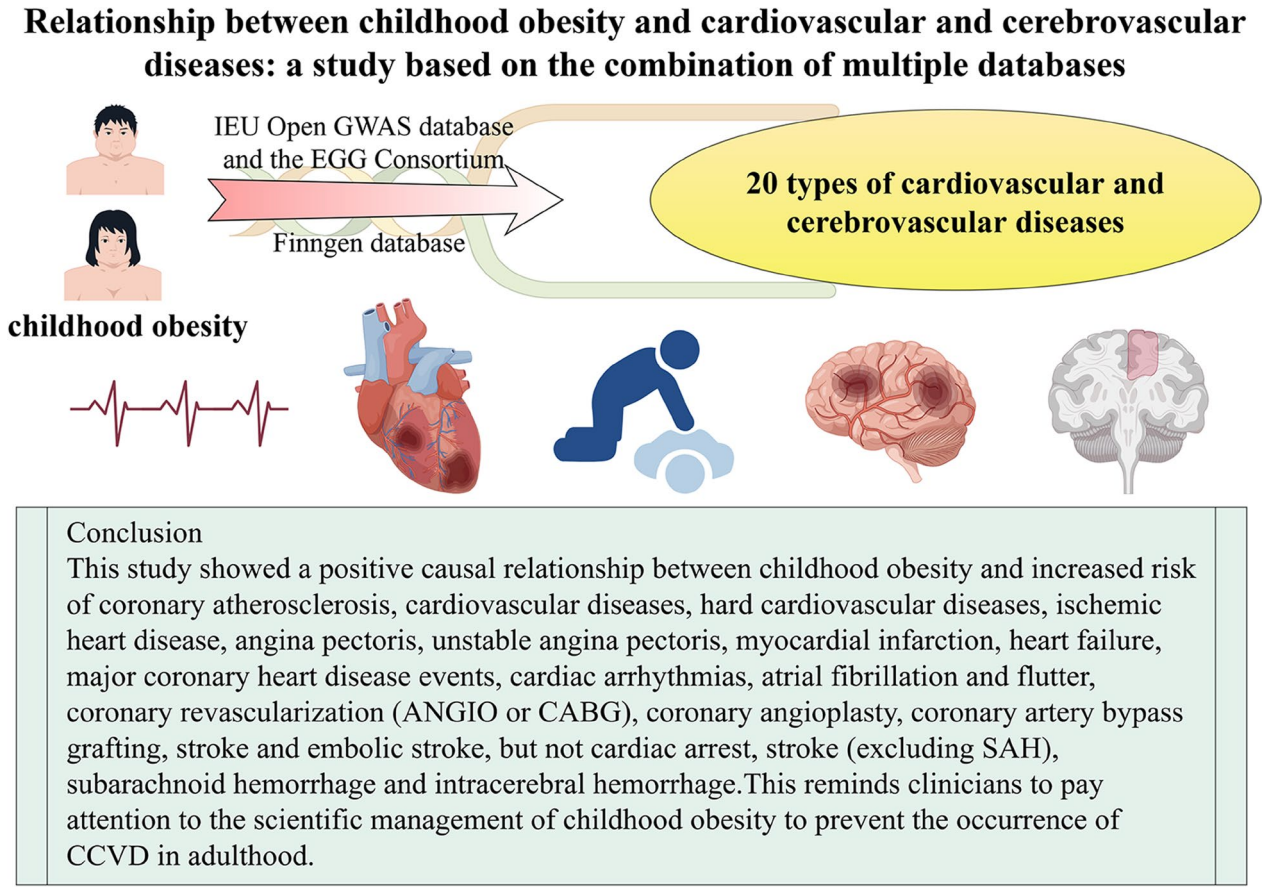
Full list of author information is available at the end of the article

MR-Egger intercept test and leave-one-out test suggested that the research results are robust. The replication analysis corroborated the consistent findings, thereby further confirming the robustness of the results. The findings of GBD study showed that obesity was an important risk factor for deaths and DALYs in patients with CCVD.

Conclusion This study revealed the positive causal relationship between childhood obesity and various CCVD. Obesity was identified as a risk factor for contributing to adverse prognostic outcomes in CCVD patients. This highlights the need for clinicians to prioritize evidence-based strategies in the management of childhood obesity to prevent the onset and adverse progression of CCVD in adulthood.

Keywords Childhood obesity, Cardiovascular and cerebrovascular disease, Mendelian randomization, Causality, GBD study

Graphical abstract



Introduction

Cardiovascular and cerebrovascular diseases (CCVD) are prevalent conditions and rank among the primary causes of mortality on a global scale. Over the past three decades, the number of individuals affected by cardiovascular disease has surged from 271 million in 1990 to 523 million in 2019, with mortality figures reaching as high as 18.6 million in 2019 [1]. In China, there were approximately to 2.87 million cases of stroke in 2019, yielding a crude mortality rate of 149 per 100,000, which accounted for 22.17% of all deaths [2]. CCVD are characterized by high morbidity, disability, mortality, and substantial economic burden, rendering them an urgent public health concern worldwide [3]. Hyperlipidemia, hyperglycemia, and hypertension are all risk factors for CCVD [4, 5]. Moreover, studies have shown that obesity directly leads to the occurrence of cardio-cerebrovascular risk factors, independent of type 2 diabetes, hyperlipidemia and other risk factors, and is related to the occurrence and death of CCVD [6, 7].

Obesity is a chronic metabolic disorder characterized by abnormal or excessive accumulation of fat in adipose tissue. Due to shifts in socioeconomic conditions, lifestyle and environmental factors, the prevalence of obese children worldwide has shown a significant upward trend. In 2016, approximately 120 million children were

classified as obese globally, a sharp increase from just 11 million in 1975, with the most notable rises occurring in East Asia and the Middle East ([8]).Obesity can increase the incidence and mortality risks of many non-communicable diseases ([9]), and has become a child health issue that should not be underestimated. Existing observational studies have established a link between childhood obesity and CCVD ([10, 11]).However, because the results of traditional observational studies may be affected by confounding factors such as socioeconomic status, unmeasured lifestyle, or reverse causal bias [12], it is difficult to accurately assess the relationship between childhood obesity and CCVD.

Mendelian randomization (MR) is a technique based on the summary data of genome-wide association studies (GWAS) that uses genetic variation, namely single nucleotide polymorphism (SNP), as instrumental variable (IV) to assess whether the observational association between exposure factors and outcomes is consistent with a causal effect [13]. MR Method is similar to randomized controlled trials. Genetic randomization occurs at conception, thereby minimizing the influence of confounding factors and reverse causality, thus providing more reliable causal evidence [14]. MR has gained traction as a valuable tool for inferring causal relationships in health sciences. Previous research has identified associations between childhood obesity and individual cardiovascular diseases through MR methods [15–17]. Nevertheless, there is a paucity of studies examining the causal relationship between childhood obesity and multiple CCVD, so we conducted a two-sample MR analysis and performed a replication analysis of genetic exposure factors to investigate the causal relationship between childhood obesity and CCVD. Moreover, MR analysis is limited to establishing causal relationships, and does not provide prognostic implications. Consequently, in order to comprehensively assess the global health impact of obesity on various CCVD, we undertook the Global Burden of Disease (GBD) study. This study aims to address the limitations inherent in prior observational studies, which were influenced by diverse regional, economic, and social factors, and to evaluate the impact of obesity on adverse outcomes (deaths and disability adjusted life years ([DALYs]) in patients with CCVD. This study is expected to serve as a complement and extension to previous studies, helping policymakers develop more precise prevention strategies.

Materials and methods

Study design

This study employed a two-sample MR analysis to assess the causal relationship between childhood obesity and CCVD. SNPs were utilized as IVs, with childhood obesity serving as the exposure factor and CCVD as the outcome variable. The MR approach is advantageous in mitigating the influence of unmeasured confounding variables, thereby providing a more accurate estimation of causal effects. The MR design is predicated upon three core assumptions [18]: the genetic variant used as an IV is strongly associated with the exposure; the genetic variant is independent of confounding factors; and the genetic variant influences the outcome exclusively through the exposure, without any alternative pathways or reverse causality. To ensure the robustness of the findings, sensitivity and replication analysis were conducted. The experimental design is detailed in Supplementary File 1 (Fig. 1). Furthermore, the GBD study was undertaken to further investigate the impact of obesity on the prognosis of CCVD. The study strictly adhered to the STROBE-MR guidelines [19]. All methods were carried out in compliance with the Helsinki Declaration.

MR study

Data sources

The GWAS data pertaining to childhood obesity were sourced from the IEU Open GWAS database (https://gwas.mrcieu.ac.uk/), which comprises 453,169 samples. The findings from the GWAS analysis of this database focusing on genetic factors and childhood obesity, were published in the British Medical Journal in 2020 [20]. Childhood obesity is defined as early life body size at age 10, as presented in Table 1.

The GWAS data for CCVD were sourced from the 2024 Finngen database (https://www.finngen.fi/en/access_results) [21]. In order to explore whether there is a causal relationship between childhood obesity and CCVD, we analyzed a wide range of cardiovascular diseases, including coronary atherosclerosis, cardiovascular diseases, hard cardiovascular diseases, ischemic heart disease, angina pectoris, unstable angina pectoris, myocardial infarction, heart failure, cardiac arrest, major coronary heart disease event, cardiac arrhythmias, atrial fibrillation and flutter, coronary revascularization (ANGIO or CABG), coronary angioplasty, coronary artery bypass grafting and cerebrovascular diseases, including stroke, stroke (excluding SAH), embolic stroke, subarachnoid haemorrhage, intracerebral haemorrhage. Among these, hard cardiovascular diseases mainly include unstable angina, acute myocardial infarction, subsequent myocardial infarction, certain current complications following acute myocardial infarction, other acute ischaemic heart diseases, chronic ischaemic heart disease, cardiac arrest, other sudden death, cause unknown, unattended death, intracerebral haemorrhage, cerebral infarction, stroke, not specified as haemorrhage or infarction, cerebral infarction due to cerebral venous thrombosis, nonpyogenic, etc. (https://r12.finngen.fi/pheno/I9_CVD_HARD). Major coronary heart disease event primarily include chronic ischaemic heart disease, acute myocardial infarction, certain

Table 1 Summary information of the exposure and outcome data sets

Exposure factors/outcome variables	Source	Year	Population	Sample size	Cases	Controls	SNP	Web source
Childhood obesity	IEU OpenGWAS	2020	European	453,169	…	…	12,321,875	https://gwas.mrcieu.ac.uk/
Childhood obesity(validation)	EGG	2012	European	13,848	5530	8318	2,442,739	http://egg-consortium.org/
Coronary atherosclerosis	Finngen	2024	European	479,478	63,307	416,171	21,326,795	https://r12.finngen.fi/pheno/I9_CORATHER
Cardiovascular diseases	Finngen	2024	European	500,348	247,538	252,810	21,327,062	https://r12.finngen.fi/pheno/FG_CVD
Hard cardiovascular diseases	Finngen	2024	European	500,348	80,527	419,821	21,327,062	https://r12.finngen.fi/pheno/I9_CVD_HARD
Ischaemic heart disease	Finngen	2024	European	500,348	84,088	416,260	21,327,062	https://r12.finngen.fi/pheno/I9_IHD
Angina pectoris	Finngen	2024	European	460,759	44,588	416,171	21,326,557	https://r12.finngen.fi/pheno/I9_ANGINA
Unstable angina pectoris	Finngen	2024	European	460,589	17,428	443,161	21,326,551	https://r12.finngen.fi/pheno/I9_UAP
Myocardial infarction	Finngen	2024	European	447,837	31,666	416,171	21,326,401	https://r12.finngen.fi/pheno/I9_MI_STRICT
Heart failure	Finngen	2024	European	500,348	37,653	462,695	21,327,062	https://r12.finngen.fi/pheno/I9_HEARTFAIL
Cardiac arrest	Finngen	2024	European	255,821	3011	252,810	21,320,096	https://r12.finngen.fi/pheno/I9_CARDARR
Major coronary heart disease event	Finngen	2024	European	500,348	56,650	443,698	21,327,062	https://r12.finngen.fi/pheno/I9_CHD
Cardiac arrhythmias	Finngen	2024	European	381,142	92,926	288,216	21,325,120	https://r12.finngen.fi/pheno/CARDIAC_ARRHYTM
Atrial fibrillation and flutter	Finngen	2024	European	316,342	63,532	252,810	21,323,076	https://r12.finngen.fi/pheno/I9_AF
Coronary revascularization (ANGIO or CABG)	Finngen	2024	European	444,971	28,800	416,171	21,326,322	https://r12.finngen.fi/pheno/I9_REVASC
Coronary angioplasty	Finngen	2024	European	434,419	18,248	416,171	21,326,147	https://r12.finngen.fi/pheno/I9_ANGIO
Coronary artery bypass grafting	Finngen	2024	European	429,852	13,681	416,171	21,326,086	https://r12.finngen.fi/pheno/I9_CABG
Stroke	Finngen	2024	European	413,834	53,492	360,342	21,325,813	https://r12.finngen.fi/pheno/C_STROKE
Stroke (excluding SAH)	Finngen	2024	European	484,133	34,110	450,023	21,326,904	https://r12.finngen.fi/pheno/I9_STR
Embolic stroke	Finngen	2024	European	455,636	1808	453,828	21,326,475	https://r12.finngen.fi/pheno/I9_STR_EMBOLIC
Subarachnoid haemorrhage	Finngen	2024	European	454,456	4180	450,276	21,326,485	https://r12.finngen.fi/pheno/I9_SAH
Intracerebral haemorrhage	Finngen	2024	European	455,128	5112	450,016	21,326,511	https://r12.finngen.fi/pheno/I9_ICH

SNP single nucleotide polymorphism

current complications following acute myocardial infarction, angina pectoris, etc. (https://r12.finngen.fi/pheno/I9_CHD). Cardiovascular diseases primarily include hypertension, ischemic heart diseases, pulmonary embolism, paroxysmal tachycardia, etc., while excluding rheumatic diseases. Coronary revascularization (ANGIO or CABG) refers to coronary angioplasty and coronary artery bypass grafting in the Finngen database. Refer to Table 1 for further information.

In order to verify the reliability of the research results, we conducted a replication analysis of the exposure factors. The GWAS data for childhood obesity (validation) were sourced from the EGG database (http://egg-consortium.org/), comprising 13,848 samples. The genetic loci linked to childhood obesity, as identified through GWAS analysis of this dataset, were published in 2012 in Nat Genet [22], See Table 1 for details. All population data were derived from European cohorts.

Selection criteria for IVs

In the primary analysis, we identified significant SNPs from the GWAS data one childhood obesity, employing a threshold of $P < 5 \times 10^{-8}$. During the replication analysis validation, applying the same threshold resulted in fewer

than 10 SNPs being associated with childhood obesity (validation). Since MR studies require at least 10 SNPs [23], we chose a more lenient threshold ($P < 5 \times 10^{-6}$). In the primary analysis and replication analysis, in order to eliminate linkage disequilibrium, the parameters of r^2 threshold<0.001 and window size = 10,000 kb were used to ensure the independence of each SNP and exclude the potential influence of gene pleiotropy on the outcomes.

In the primary analysis, weak IVs with F -statistic less than 10 were excluded to mitigate potential bias. The F-statistic is calculated as follows: $F=[(n-K-1)/K*R^2/(1-R^2)]$ [24], $R^2 = 2\times eaf\times(1 - eaf)\times beta^2$. Where n represents the sample size, k represents the number of SNPs, R^2 represents the exposure variance explained by the genetic instrument, eaf is the effect allele frequency, and beta is the effect size of the SNP on the exposure. In the replication analysis validation, due to missing allele frequency data for certain IVs, we were unable to calculate the traditional F-statistic to evaluate bias in weak IVs.

Extract the above-screened SNPs from the GWAS data of CCVD. Missing SNPs were replaced with those having high linkage (r^2 >0.8), while SNPs without suitable replacement sitesand those directly linked to 20 types of CCVD were eliminated ($P < 5 \times 10^{-8}$). Prior to analysis, we performed MR-PRESSO analysis to exclude any outliers with potential pleiotropy [25], See Supplementary File 1 (Table 1).The remaining SNPs were finally used as IVs.

MR analysis

Inverse variance weighted (IVW) served as the principal approach for evaluating the causal relationship between childhood obesity and CCVD, and provides an estimate for effective IVs [26]. To complement these findings, additional analyses were conducted using MR-Egger regression, the weighted median, the simple mode, and the weighted mode. The results presented as odds ratios (ORs) with 95% confidence intervals (CI), and a *P*-value of less than 0.05 was considered indicative of a causal effect. Visualization of the data was achieved through the use of forest plots and scatter plots.

Cochran's Q test was employed to assess the heterogeneity of the IVW model, a P-value of less than 0.05 was indicative of significant heterogeneity, warranting increased scrutiny of the IVW results. The MR-Egger intercept was utilized to evaluate horizontal pleiotropy, with a P-value greater than 0.05 suggesting the absence of horizontal pleiotropy, thereby affirming the reliability of the results. Funnel plot was constructed for visualization purposes. Leave-one-out sensitivity analysis was conducted to ascertain the impact of excluding individual SNPs on the overall results. If the results excluding a particular SNP did not significantly differ from the complete MR results, it was concluded that the MR results were robust. Furthermore, when the P value of the Steiger directional test was less than 0.001, the causal direction from exposure to outcome was considered statistically significant. To address the potential for false-positive results arising from multiple comparisons in this study, we computed false discovery rate (FDR)-adjusted P-values for the primary analysis.

Finally, the outcome variables were analyzed repeatedly related to childhood obesity (validation) for validation purposes. Statistical analysis was performed using R software (version 4. 4. 2).

GBD study

Data sources

The GBD study seeks to evaluate the burden of disease, injuries, and risk factors worldwide (https://www.healthdata.org/data-tools-practices/data-sources). Led by the Institute for Health Metrics and Evaluation at the University of Washington, This comprehensive research initiative systematically quantifies the impact of disease, injury, and risk factors on human health worldwide. The study encompasses more than 200 countries and regions, examining 371 diseases and injuries alongside over 88 risk factors [27]. The study utilized the most recent data available from 2021, examining eight categories risk factors, including high alcohol use, tobacco, high systolic blood pressure, diet Low in omega-6 polyunsaturated fatty acids, high fasting plasma glucose, obesity (specifically refers to a high body-mass index), diet low in seafood omega-3 fatty acids and high low-density lipoprotein (LDL) cholesterol. Additionally, the study encompassed eight types of CCVD, including atrial fibrillation and flutter, stroke, aortic aneurysm, lower extremity peripheral arterial disease, ischemic heart disease, ischemic stroke, subarachnoid hemorrhage and intracerebral hemorrhage. The GBD study categorizes all countries into 21 distinct regions; while simultaneously stratifying them into five levels of socio-demographic index (SDI) according to the comprehensive indicators of national or regional development status.

GBD analysis

To assess the global health impact of obesity and other risk factors on the eight categories of CCVD, we extracted data on deaths and DALYs from the GBD 2021 dataset, stratified by various SDI regions and GBD areas. DALYs measure the number of healthy years lost as a result of illness or injury. This metric is derived by summing the years lived with disability (YLD) and years of life lost (YLL). YLD quantify the number of years of quality life forfeited as a result of illness or disability. They are calculated by multiplying the number of people with the risk factor-related disease by an appropriate disability weight. YLL quantify the number of years lost due to premature mortality. This metric is determined by

subtracting the age at death of each individual from the standard life expectancy, and then summing these differences across all deceased individuals within the population. The SDI reflects the mean values across all regions in the GBD study concerning per capita income, average educational attainment, and fertility rate. The SDI quantified on a scale from 0 to 1, serving as an indicator of social development levels. It is classified into five categories: high (>0.81), high-middle (0.70–0.81), middle (0.61–0.69), lower-middle (0.46–0.60), and low (<0.46) [28]. This facilitates a comprehensive understanding of the disparities in disease burden across regions with varying levels of economic development, thereby enabling the formulation of region-specific intervention programs. Deaths and DALYs from risk factor-related diseases were calculated to assess their global burden across SDI and GBD regions.

Ethics statement

This study utilized exclusively publicly available, de-identified summary-level data. Summary data sourced from IEU OpenGWAS, EGG, Finngen, GBD project have been granted necessary permissions by respective review boards, in addition to having received informed consent from individual participants. As our analysis did not involve any direct interaction with human subjects or access to individual-level data, no additional ethical approval or informed consent was required for this study.

Result

Characteristics of IVs

Following a systematic screening of SNPs, relevant SNPs were identified from GWAS data pertaining to childhood obesity and matched with data on CCVD to further ascertain IVs. Similarly, the SNPs ultimately incorporated in the MR replication analysis were identified with in the GWAS data for childhood obesity (validation), serving as a validation step. Comprehensive details regarding these SNPs are available in Supplementary Files. 2–3.

Positive causal relationship between childhood obesity and CCVD

The forest plot (Figs. 1 and 2) indicated that genetically predicted childhood obesity is associated with an elevated risk of various CCVD. The results of IVW analysis demonstrated a positive causal relationship between childhood obesity and coronary atherosclerosis (OR = 1.339, 95% CI = 1.208–1.485, *P* = 2.586E-08), cardiovascular diseases (OR = 1.515, 95% CI = 1.401–1.640, *P* = 4.160E-25), hard cardiovascular diseases (OR = 1.315, 95% CI = 1.197–1.444, *P* = 1.205E-08), ischemic heart disease (OR = 1.294, 95% CI = 1.174–1.426, *P* = 2.068E-07),

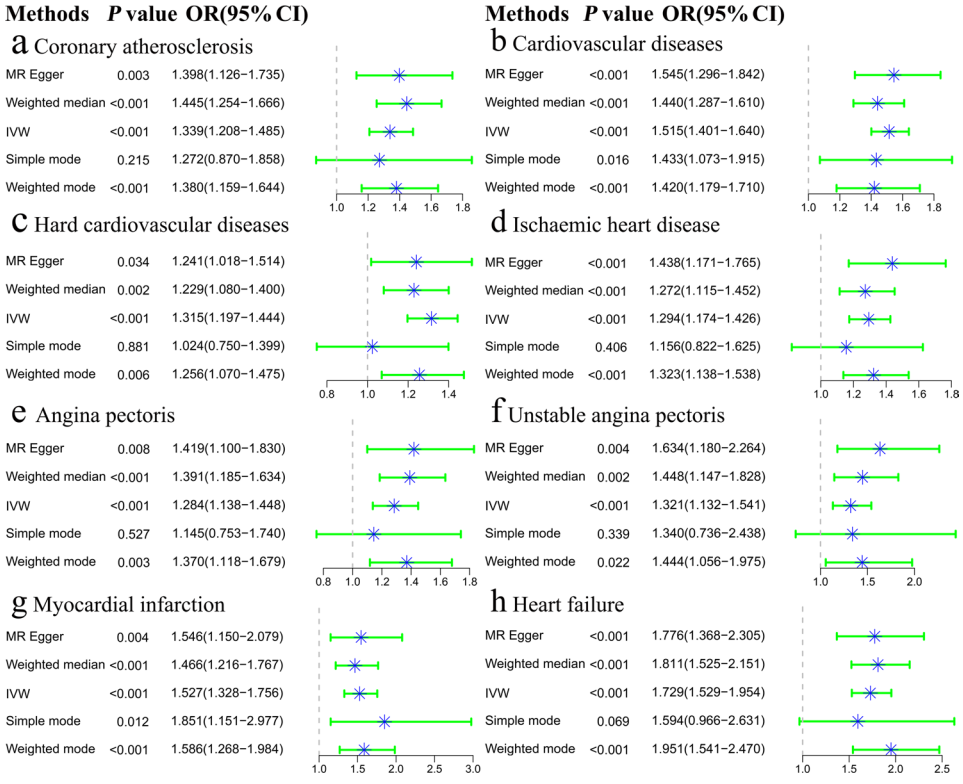


Fig. 1 Forest plots of the causal effects. SNP effects on childhood obesity and coronary atherosclerosis (**a**), cardiovascular diseases (**b**), hard cardiovascular diseases (**c**), ischaemic heart disease (**d**), angina pectoris (**e**), unstable angina pectoris (**f**), myocardial infarction (**g**), and heart failure (**h**). OR: Odds Ratio; CI: Confidence Interval; SNP: Single Nucleotide Polymorphism

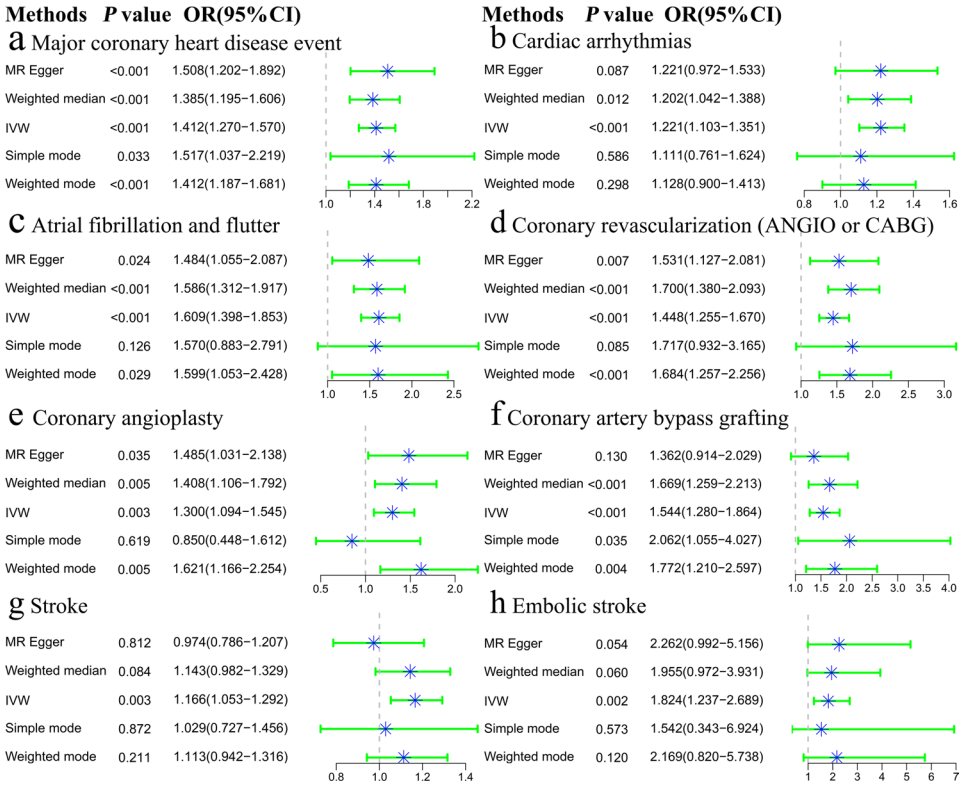


Fig. 2 Forest plots of the causal effects. SNP effects on childhood obesity and major coronary heart disease event (**a**), cardiac arrhythmias (**b**), atrial fibrillation and flutter (**c**), coronary revascularization (ANGIO or CABG) (**d**), coronary angioplasty (**e**), coronary artery bypass grafting (**f**), stroke (**g**), and embolic stroke (**h**). OR: Odds Ratio; CI: Confidence Interval; SNP: Single Nucleotide Polymorphism

angina pectoris (OR = 1.284, 95% CI = 1.138–1.448, *P* = 4.757E-05), unstable angina pectoris (OR = 1.321, 95% CI = 1.132–1.541, *P* = 4.111E-04), myocardial infarction (OR = 1.527, 95% CI = 1.328–1.756, *P* = 2.953E-09), heart failure (OR = 1.729, 95% CI = 1.529–1.954, *P* = 2.132E-18), major coronary heart disease event (OR = 1.412, 95% CI = 1.270–1.570, *P* = 1.796E-10), cardiac arrhythmias (OR = 1.221, 95% CI = 1.103–1.351, *P* = 1.121E-04), atrial fibrillation and flutter (OR = 1.609, 95%CI = 1.398–1.853, *P* = 3.693E-11), coronary revascularization (ANGIO or CABG) (OR = 1.448, 95% CI = 1.255–1.670, *P* = 3.878E-07), coronary angioplasty (OR = 1.300, 95% CI = 1.094–1.545, *P* = 0.003), coronary artery bypass grafting (OR = 1.544, 95% CI = 1.280–1.864, *P* = 5.878E-06), stroke (OR = 1.166, 95% CI = 1.053–1.292, *P* = 0.003), and embolic stroke (OR = 1.824, 95% CI = 1.237–2.689, *P* = 0.002). The causal associations between childhood obesity and these CCVD remained significant after adjusting for the FDR (all *P* < 0.05), as detailed in Supplementary File 1 (Table 2). The Steiger directional test substantiated the causal hypothesis linking childhood obesity to CCVD, demonstrating that the influence of childhood obesity on CCVD was aligned with the hypothesized causal direction (all *P* < 0.001), see Supplementary File 1 (Table 3). In contrast, no causal relationships was identified between childhood obesity and cardiac arrest, stroke (excluding SAH), subarachnoid haemorrhage, and intracerebral haemorrhage (all *P*>0.05). The majority of the results observed in the supplementary methods demonstrated consistency. Furthermore, the scatter plot indicated a positive causal relationship between childhood obesity and multiple CCVD. The direction of causal effects, as determined by the five methods, was largely consistent, See Figs. 3, 4, 5 and 6 for details.

Sensitivity analysis

Cochrane's Q test suggested potential heterogeneity between childhood obesity and the aforementioned CCVD (excluding cardiac arrest, embolic stroke, subarachnoid haemorrhage, and intracerebral haemorrhage) in the MR analysis. However, the MR-Egger intercept test suggested the absence of horizontal pleiotropy in these analyses (*P* > 0.05), excluding stroke (excluding SAH), and intracerebral haemorrhage. as detailed in Table 2. Additionally, as illustrated in Supplementary File 4 (Figs. 1–8, 10–16, 18), the funnel plots displayed significant symmetry, underscoring the robustness of this study.

The findings from the leave-one-out analysis indicated that, upon sequential exclusion of each SNP, the residual SNPs consistently clustered on one side of the zero line. This suggests that no individual SNP exerts a decisive influence on causal reasoning, with the exceptions

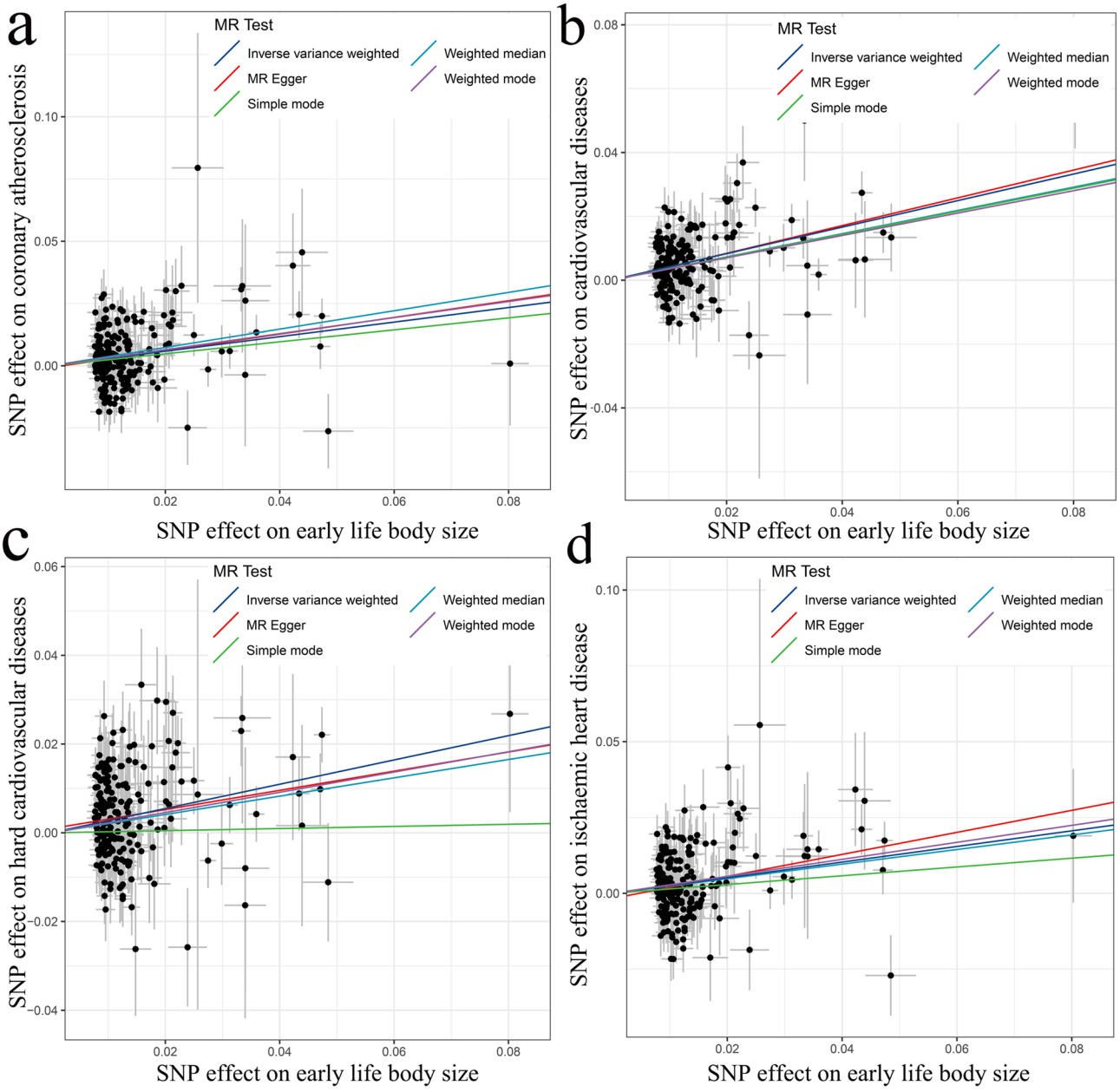


Fig. 3 Scatter plots of the causal effects. SNP effects on childhood obesity and coronary atherosclerosis (**a**), cardiovascular diseases (**b**), hard cardiovascular diseases (**c**), and ischaemic heart disease (**d**). SNP: Single Nucleotide Polymorphism; MR: Mendelian Randomization

of cardiac arrest, stroke (excluding SAH), subarachnoid haemorrhage, and intracerebral haemorrhage, see Supplementary File 4(Figs. 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39 and 40) for further details.

Replication analysis

To assess the stability of the findings, SNPs associated with childhood obesity (validation) were extracted from the EGG database to repeat the validation of the outcome variables and obtain consistent results. As demonstrated in Supplementary File 1 (Table 4, and 5), the primary IVW MR analysis reveals a genetically predicted positive causal relationship between childhood obesity (validation) and an increased risk of various CCVD. These conditions include coronary atherosclerosis, cardiovascular diseases, hard cardiovascular diseases, ischemic heart disease, angina pectoris, unstable angina pectoris, myocardial infarction, heart failure, major coronary heart disease event, cardiac arrhythmia, atrial fibrillation and flutter, coronary revascularization (ANGIO or CABG), coronary angioplasty, coronary artery bypass grafting, stroke, and embolic stroke, with all associations achieving statistical significance ($P<0.05$). After adjusting for

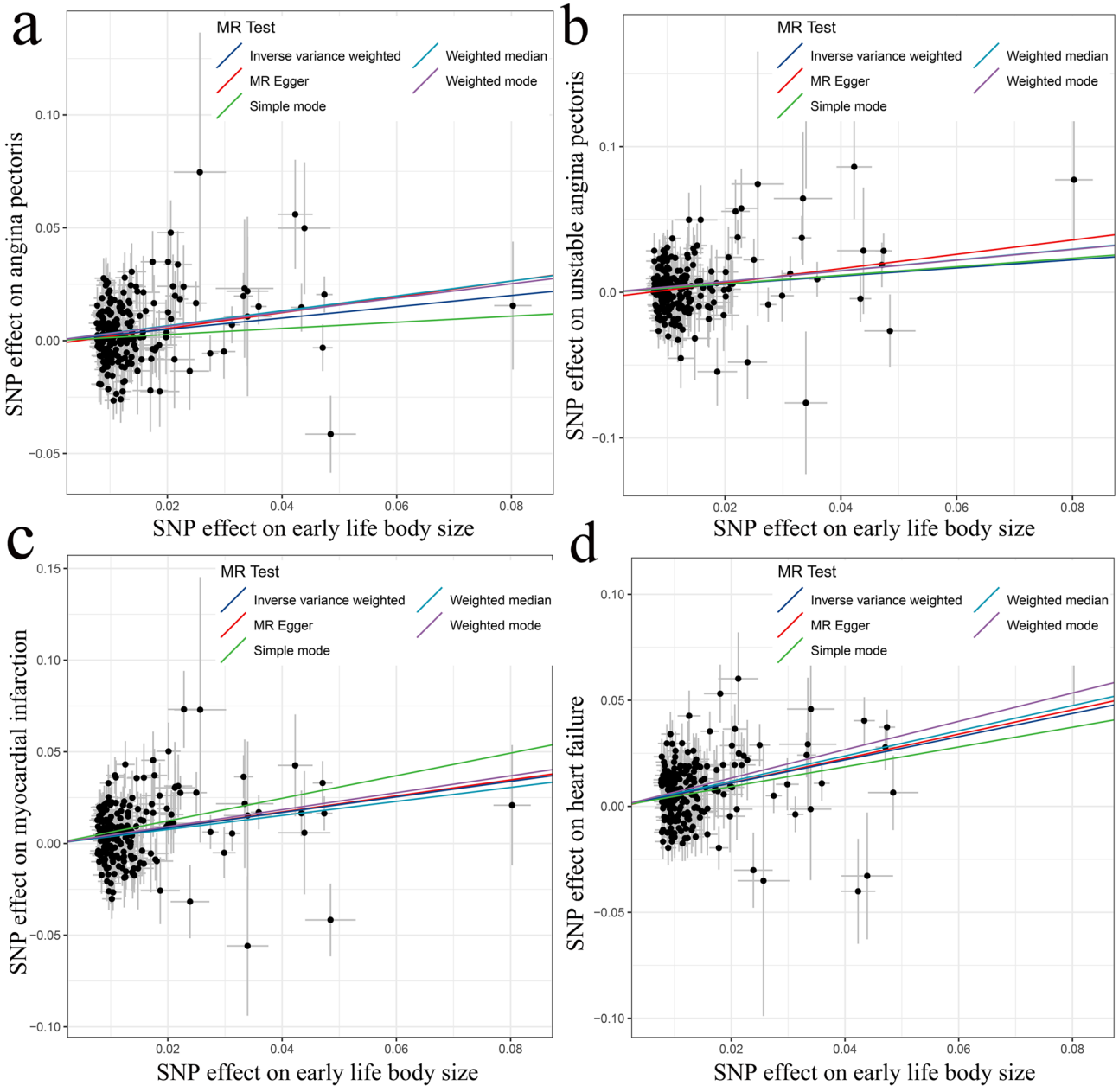


Fig. 4 Scatter plots of the causal effects. SNP effects on childhood obesity and angina pectoris (**a**), unstable angina pectoris (**b**), myocardial infarction (**c**), and heart failure (**d**). SNP: Single Nucleotide Polymorphism; MR: Mendelian Randomization

the FDR, these causal relationships continued to demonstrate statistical significance (all $P<0.05$), as detailed in Supplementary File 1 (Table 2). The Steiger directional test validated the causal hypothesis of childhood obesity-CCVD was in the correct direction (all $P<0.001$), see Supplementary File 1 (Table 3). In contrast, no causal relationship was observed between childhood obesity (validation) and cardiac arrest, stroke (excluding SAH), subarachnoid haemorrhage, and intracerebral haemorrhage (all $P>0.05$). Forest plots (Supplementary File 5: Figs. 1–20) and scatter plots (Supplementary File 5: Figures 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39 and 40) provide a visual representation of the impact of the IVs on exposure and outcome. Cochran's Q test indicated that there was no heterogeneity between the IVs and the outcomes of various CCVD, with the exception of heart failure, cardiac arrhythmias, and coronary revascularization (ANGIO or CABG) (all $P>0.05$). Additionally, no evidence of horizontal pleiotropy was detected (all $P>0.05$), see Supplementary File 1 (Table 6). As illustrated in Supplementary File 5 (Figs. 41, 42, 43, 44, 45, 46, 47 and 48, 50–56, 58), most funnel plots

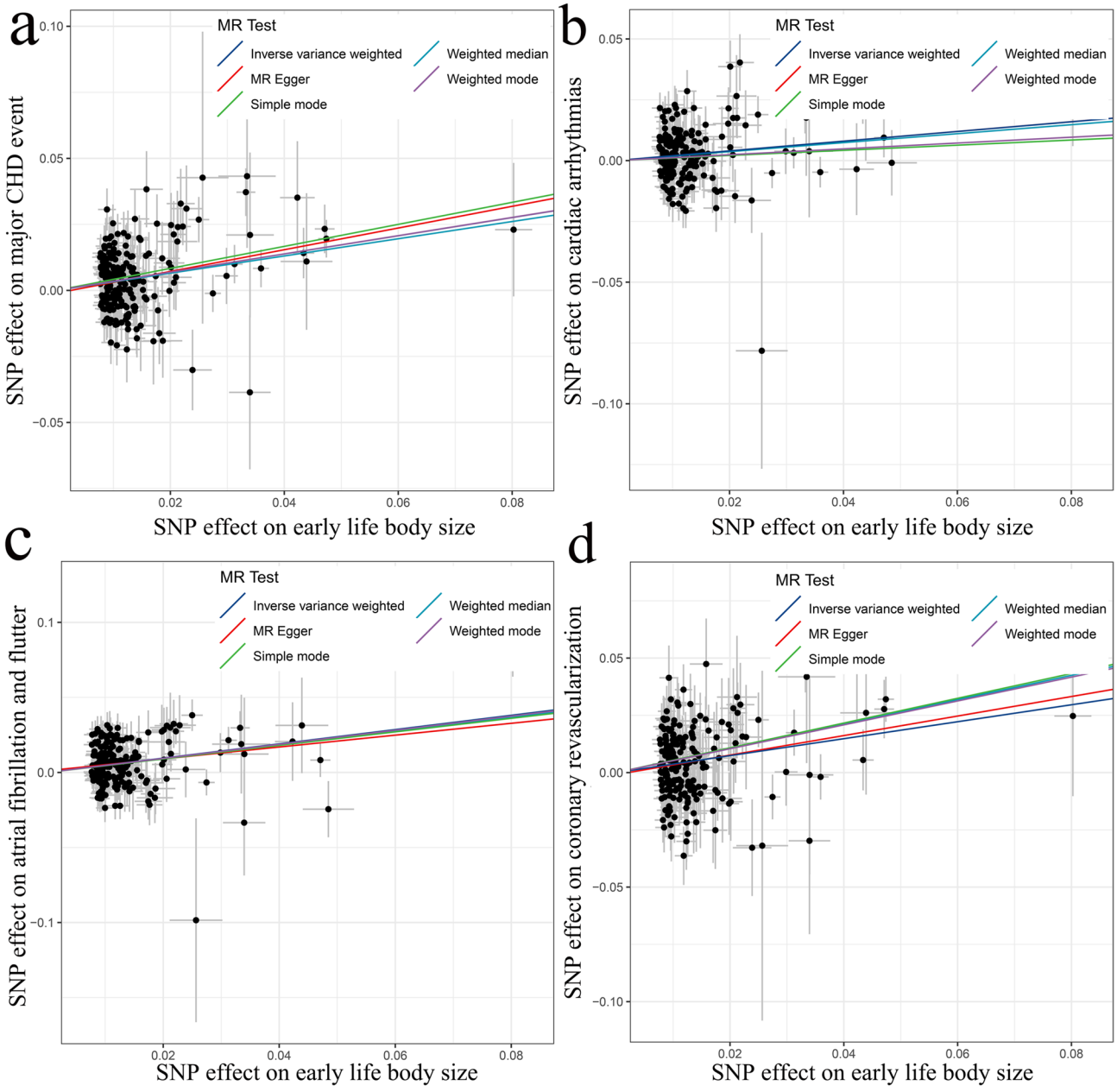


Fig. 5 Scatter plots of the causal effects. SNP effects on childhood obesity and major coronary heart disease event (**a**), cardiac arrhythmias (**b**), atrial fibrillation and flutter (**c**), and coronary revascularization (ANGIO or CABG) (**d**). SNP: Single Nucleotide Polymorphism; MR: Mendelian Randomization

were symmetrical, except for Fig. 51 (cardiac arrhythmias). Furthermore, leave-one-out analysis revealed that removing individual SNPs did not significantly alter the results, except for cardiac arrest, stroke (excluding SAH), embolic stroke, subarachnoid haemorrhage, and intracerebral haemorrhage, demonstrating result stability (Supplementary File 5: Figures 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79 and 80).

Relationship between obesity and prognosis of CCVD

To clarify the link between obesity and CCVD prognosis, we conducted a GBD study, and the results showed that obesity was a key risk factor for deaths and DALYs in patients with 8 types of CCVD, whether globally, in the five SDI regions, or in the 21 GBD regions, See Table 3, Supplementary File 1 (Figs. 2 and 3). The effects of the remaining seven risk factors on deaths and DALYs in patients with 8 types of CCVD are detailed in Table 3.

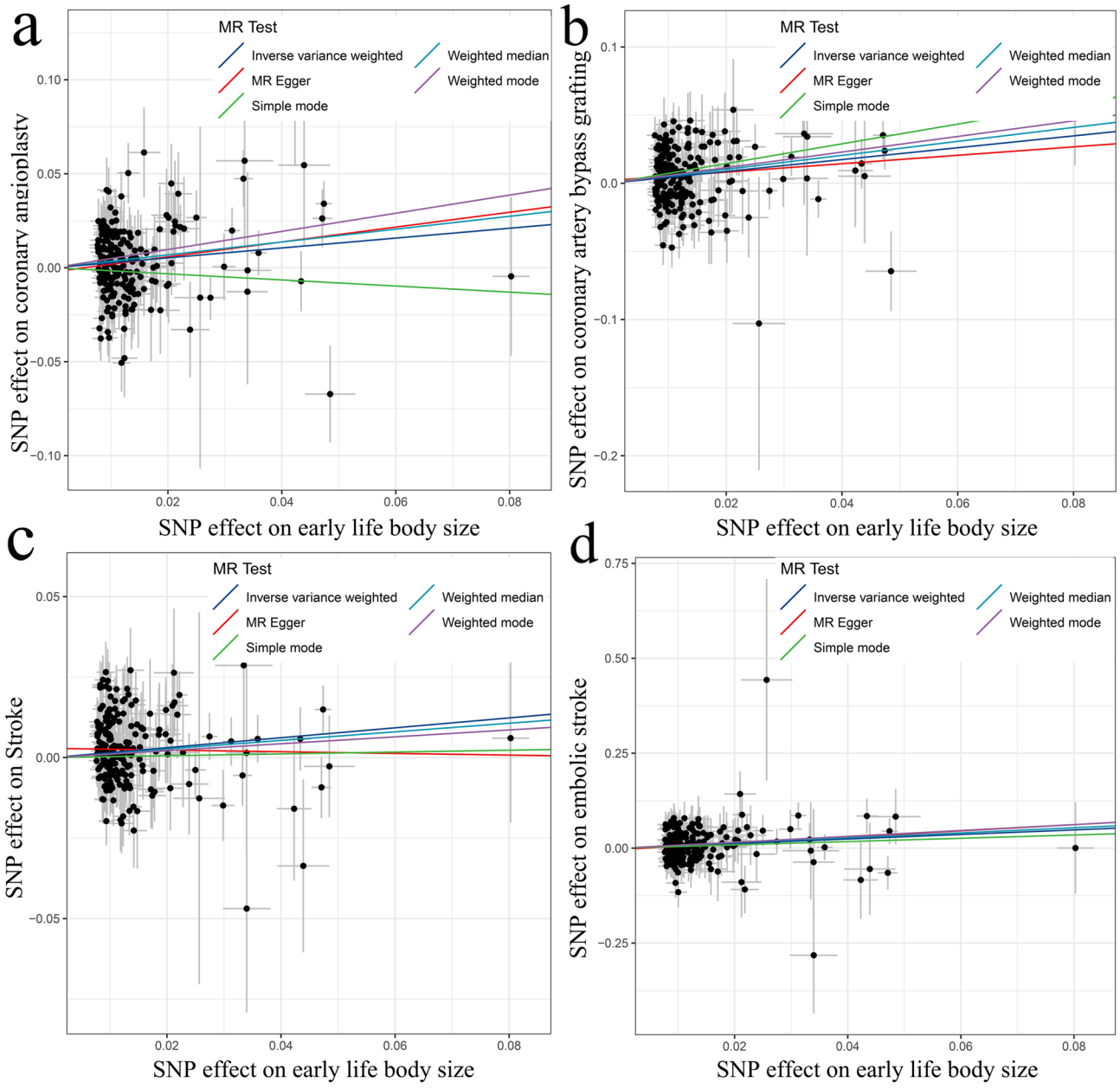


Fig. 6 Scatter plots of the causal effects. SNP effects on childhood obesity and coronary angioplasty (**a**), coronary artery bypass grafting (**b**), stroke (**c**), and embolic stroke (**d**). SNP: Single Nucleotide Polymorphism; MR: Mendelian Randomization

Discussion

This study employed the MR analysis method utilizing SNPs associated with childhood obesity as IVs based on GWAS data to assess the causal relationship between childhood obesity and CCVD. To evaluate the robustness and scalability of the results, sensitivity analyses were conducted, and the GWAS data on childhood obesity from external databases were repeatedly analyzed and validated. The results suggested a positive causal relationship between childhood obesity and various CCVD ($P < 0.05$). Furthermore, the findings of this study are robust and reliable.

Several previous studies have explored the relationship between childhood obesity and CCVD, yet the findings remain controversial. Bjerregaard et al. [29] demonstrated that excessive weight gain during childhood can exacerbate cardiovascular risk factors, alter heart structure, and elevate the risk of coronary heart disease in later life. A substantial cohort study conducted in China, which tracked 64,454 children over a period of 10.7 years, identified a positive correlation between childhood obesity and the risk of ischaemic heart disease (OR=1.10; 95% CI: 1.02 ~ 1.18) [30]. Prior studies have indicated a negative correlation between the severity of childhood obesity

Table 2 Examination of Pleiotropy of selected SNPs and the heterogeneity among these SNPs

Outcomes	Cochrane's Q test		Pleiotropy test	
	Q	*P* value	Egger intercept	*P* value
Coronary atherosclerosis	309.514	2.568E-07	−0.001	0.662
Cardiovascular diseases	319.553	6.980E-09	−2.928E-04	0.812
Hard cardiovascular diseases	337.903	1.254E-09	0.001	0.521
Ischaemic heart disease	363.494	3.795E-12	−0.002	0.253
Angina pectoris	341.232	1.070E-09	−0.002	0.384
Unstable angina pectoris	259.227	0.003	−0.003	0.148
Myocardial infarction	342.869	7.499E-10	−1.9904E-04	0.925
Heart failure	341.516	2.317E-09	−4.234E-04	0.820
Cardiac arrest	198.926	0.528	−0.001	0.763
Major coronary heart disease event	321.029	3.328E-08	−0.001	0.518
Cardiac arrhythmias	335.779	4.774E-10	−4.696E-06	0.998
Atrial fibrillation and flutter	316.123	3.202E-08	0.001	0.610
Coronary revascularization (ANGIO or CABG)	309.870	4.935E-07	−0.001	0.686
Coronary angioplasty	317.719	1.762E-07	−0.002	0.420
Coronary artery bypass grafting	286.676	4.627E-05	0.002	0.484
Stroke	285.649	3.695E-05	0.003	0.063
Stroke (excluding SAH)	252.823	0.005	0.004	0.026
Embolic stroke	179.376	0.861	−0.003	0.562
Subarachnoid haemorrhage	227.017	0.101	0.003	0.522
Intracerebral haemorrhage	214.619	0.258	0.008	0.026

and the left ventricular ejection fraction, alongside an increased risk of heart failure in adulthood. Obese children need more clinical attention to avert the onset and progression of diminished cardiac function [16, 31, 32]. However, a cross-sectional observational study indicated that obesity in children does not elevate atherosclerosis-related cardiovascular risk [33]. Similarly, a meta-analysis focusing on children aged 2 to 18 years within European and American populations demonstrated a moderate correlation between childhood body-mass index and the incidence of stroke in adulthood (OR = 1.04; 95% CI: 1.02 ~ 1.07) [34]. Conversely, other research has suggested that childhood obesity may predict a reduced risk of certain adult diseases while being linked to an increased risk of coronary heart disease and diabetes in later life, but not to stroke [35]. Given the inherent biases present in epidemiological studies, it remains uncertain whether these findings accurately represent the causal relationship between childhood obesity and CCVD.

In recent years, advancements in MR have enhanced our understanding of the risk factors associated with CCVD. Zhao et al. [36] conducted a two-sample MR approach using data from a European database to assess the causal relationship between basal metabolic rate and various cardiovascular diseases. Their findings indicated that a one standard deviation increase in basal metabolic rate was linked to a 53% increase in the risk of heart failure and a 64% increase in the risk of aortic aneurysm, while no significant correlation was observed with coronary artery disease risk. Additionally, a study utilizing genetic data from the UK Biobank identified a negative correlation between low levels of high-density lipoprotein cholesterol and cardiovascular diseases [37]. A genetic analysis conducted in Copenhagen revealed a causal relationship between adult obesity and an elevated risk of heart failure incidence and all-cause mortality [38], corroborating the findings of Kim et al. [39]. A mediation MR analysis demonstrated that gastroesophageal reflux disease was associated with cerebrovascular

Table 3 Relationship between obesity and prognosis of CCVD

Disease/risk factors	Atrial fibrillation and flutter	Stroke	Aortic aneurysm	Lower extremity peripheral arterial disease	Ischemic heart disease	Ischemic stroke	Subarachnoid hemorrhage	Intracerebral hemorrhage
High alcohol use	√	√	×	×	√	√	×	√
Tobacco	√	√	√	√	√	√	√	√
High systolic blood pressure	√	√	√	√	√	√	√	√
Diet low in omega-6 polyunsaturated fatty acids	×	√	×	×	√	×	×	×
High fasting plasma glucose	×	√	×	√	√	√	×	√
obesity	√	√	√	√	√	√	√	√
Diet low in seafood omega-3 fatty acids	×	×	×	×	√	×	×	×
High LDL cholesterol	×	√	×	×	√	√	×	×

LDL low-density lipoprotein

disease after adjusting for metabolic factors [40]. Marini et al. [7] reported that adult abdominal obesity independently increases the risk of cerebral hemorrhage and ischemic stroke. Nonetheless, there is a paucity of research examining the causal relationship between childhood obesity and multiple CCVD. This study employed the MR approach to control for unknown confounding factors, and the findings suggested a positive correlation between childhood obesity and an increased risk of developing multiple CCVD.

The MR analysis may offer evidence supporting a causal relationship between childhood obesity and various CCVD. To explore the resulting global health impact, we conducted the GBD study to further investigate the prognostic correlation between obesity and CCVD. The findings suggested that obesity constitutes a significant risk factor for deaths and DALYs among some CCVD patients globally, across the five SDI regions, and within the 21 GBD regions. Additionally, our analysis revealed that deaths and DALYs were elevated in regions with high SDI and high-middle SDI, indicating a heavier disease burden in these areas. With socioeconomic development, the sales of high-calorie, high-fat, and high-sugar processed foods have increased, and food establishments have shifted toward more processed diets [41]. Concurrently, urbanization, the proliferation of automated transportation, increased screen time, and diminished opportunities for physical activity have contributed to a significant decline in overall physical activity levels, thereby exacerbating the obesity epidemic [42]. This has increased the incidence of CCVD and exacerbated the burden of CCVD. It can be seen that there are differences in disease burden in different SDI regions, and special attention should be paid to these regions. Childhood obesity should be considered a risk factor in adult CCVD prevention strategies. Given its readily identifiable characteristics, childhood obesity warrants consistent monitoring for any changes, thereby enabling timely preventive interventions to mitigate the risk of adult CCVD.

Childhood obesity is associated with CCVD, and its pathophysiological mechanisms remain incompletely understood. The proliferation of adipocytes in obese children leads to an elevated body mass and heightened oxygen consumption. This physiological alteration results in an increased peripheral blood volume and cardiac output, thereby augmenting both the preload and afterload on the heart, ultimately compromising cardiac function [43]. Adipose tissue has the capacity tosecrete proinflammatory cytokines and induce oxidative stress [44]. This result in a prolonged state of low-grade chronic inflammation within the body, which subsequently leads to endothelial cell dysfunction, promotes calcification and damage of the vascular walls, and diminishes vascular elasticity. Furthermore, obesity contributes to insulin resistance, which may activate the renin-angiotensin-aldosterone system, as well as promote proinflammatory and oxidative stress responses, this cascade of events can lead to vascular endothelial dysfunction, thereby facilitating the onset and progression of atherosclerosis, and subsequently increasing the risk of CCVD [45, 46]. Previous research has demonstrated that the accumulation of adipocytes leads to coagulation dysfunction, procoagulant activation, and hyperfibrinolysis, thereby further contributing to the incidence of cardiovascular and cerebrovascular events [47]. In summary, childhood obesity may elevate the risk of CCVD by damaging vascular endothelial cells through prolonged chronic inflammation, oxidative stress, insulin resistance, and coagulation dysfunction.

Our study benefits from a large sample size, which enhances the precision of the effect estimates. Additionally, the utilization of publicly available datasets contributes to the transparency and reproducibility of our findings. The robustness and generalizability of the results were further corroborated through replication analysis of outcome variables using childhood obesity-related genetic variations from an external database. Furthermore, this study employs MR utilizing genetic variants to assess the health outcomes associated with the affected phenotypes. This approach represents a relatively novel research design grounded in whole genome sequencing data, which can effectively mitigate bias, circumvent reverse causality, and elucidate causal relationships. This study extended beyond examining the association between childhood obesity and the onset of CCVD to also investigated the adverse prognosis associated with CCVD. The findings of this research hold significant implications for the early prevention of childhood obesity.

However, there are some limitations to this study. Primarily, our MR analysis relies predominantly on datasets derived from individuals of European ancestry. The findings may not be entirely generalizable to other populations due to well-documented variations in genetic architecture, allele frequencies, and linkage disequilibrium patterns across different ethnic groups. This limitation is prevalent in contemporary GWAS. Future studies incorporating diverse ancestries are needed to validate these associations and assess potential ethnic-specific effects. Secondly, the selected exposure factor was childhood obesity, due to the lack of corresponding GWAS data, a stratified analysis based on the degree of obesity, type, gender, and age was not feasible, so relevant subgroup analysis studies could not be conducted. Thirdly, although we have large-scale summary statistics in the replication analysis, the statistical power is diminished due to limited valid IVs and the inability to calculate F statistics. Once more valid IVs and computable

F statistics data are available, further MR studies are needed to verify these associations. Furthermore, despite utilizing ancestry-matched GWAS summary statistics and implementing robust MR methods alongside sensitivity analyses to address pleiotropic effects, the possibility of residual bias remains if genetic variants influence outcomes through pathways independent of the exposure. Additionally, the extent of phenotypic variation that can be explained by a single genetic tool is limited, resulting in weak IV bias. The winner's curse in SNP selection may inflate effect estimates, all of which may bias the results. Finally, MR analysis has yet to elaborate the underlying biological mechanisms, and further research is required to investigate the causal mechanism between childhood obesity and CCVD.

Conclusion

In conclusion, the causal relationship between childhood obesity and 20 types of CCVD was inferred through associations with genetic variants, suggesting a positive causal link between childhood obesity and various forms of CCVD. The GBD study 2021 identified obesity as a significant risk factor for deaths and DALYs in individuals with CCVD. The implementation of evidence-based strategies aimed at reducing the prevalence of childhood obesity may contribute to lowering the risk of developing CCVD in adulthood.

Abbreviations

CCVD	cardiovascular and cerebrovascular disease
MR	Mendelian randomization
GWAS	genome-wide association study
STROBE-MR	Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization
IVW	inverse variance weighted
SNP	single nucleotide polymorphism
IV	instrumental variable
GBD	Global Burden of Disease
DALYs	disability adjusted life years: LDL: low-density lipoprotein
SDI	socio-demographic index
YLD	years lived with disability
YLL	years of life lost
FDR	false discovery rate
OR	odds ratio
CI	confidence interval

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-025-25315-2.

Supplementary Material 1.

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Authors' contributions

C.R.C. and J.M.C. wrote the manuscript. W.K.C. conceived and designed the study. L.L.Y., S.F.Y. and L.Z. collected, managed and analyzed data. W.K.C., B.X. and L.L.Y. read and revised the manuscript. F.L.T. engaged in the revision and enhancement of the language. All authors participated in the revision of this manuscript. All authors read and approved the final manuscript.

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Data availability

GWAS data for childhood obesity were obtained from the IEU OpenGWAS database (https://gwas.mrcieu.ac.uk/). GWAS data for CCVD were obtained from the 2024 Finngen database (https://www.finngen.fi/en/access_results). GWAS data for childhood obesity (validation) were obtained from the EGG database (http://egg-consortium.org/). GBD study data are from (https://www.healthdata.org/data-tools-practices/data-sources). The above databases are registered.

Declarations

Ethics approval and consent to participate

The IEU OpenGWAS, EGG, Finngen, and GBD projects are all open-access databases where all data have been anonymized. IEU OpenGWAS database is a platform aggregating data from previously published GWAS, each contributing GWAS within this platform obtained ethical approval from its respective institutional review board. The GWAS data for childhood obesity (validation) from the EGG Consortium were obtained from ethically approved studies, with each contributing cohort receiving approval from its respective local ethics committee. Furthermore, the FinnGen study project was approved by The Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa (HUS) and a waiver of informed consent was approved. The GBD 2021 project was reviewed by the University of Washington's Institutional Review Board and a waiver of informed consent was approved. As our analysis did not involve any direct interaction with human subjects or access to individual-level data, no additional ethical approval or informed consent was required for the this study. Our study complied with relevant ethical regulations and the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Pediatrics, Huzhou Central Hospital, Fifth School of Clinical Medicine of Zhejiang Chinese Medical University, Huzhou 313000, Zhejiang, China
[2]Huzhou Central Hospital, Affiliated Central Hospital of Huzhou University, Huzhou 313000, Zhejiang, China
[3]Department of Intensive Care Unit, Huzhou Central Hospital, Fifth School of Clinical Medicine of Zhejiang Chinese Medical University, Huzhou 313000, Zhejiang, China
[4]Department of Emergency, Huzhou Central Hospital, Affiliated Central Hospital of Huzhou University, Huzhou 313000, Zhejiang, China
[5]Department of Cardiology, Huzhou Central Hospital, Fifth School of Clinical Medicine of Zhejiang Chinese Medical University, Huzhou 313000, Zhejiang, China
[6]Department of Emergency, Huzhou Central Hospital, Fifth School of Clinical Medicine of Zhejiang Chinese Medical University, Huzhou 313000, Zhejiang, China

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