





**ORIGINAL RESEARCH**

# Mendelian Randomization Analyses Suggest Childhood Body Size Indirectly Influences End Points From Across the Cardiovascular Disease Spectrum Through Adult Body Size

Grace M. Power , MSc; Jessica Tyrrell , PhD; Timothy M. Frayling , PhD; George Davey Smith , FRS; Tom G. Richardson , PhD

**BACKGROUND:** Obesity is associated with long-term health consequences including cardiovascular disease. Separating the independent effects of childhood and adulthood obesity on cardiovascular disease risk is challenging as children with obesity typically remain overweight throughout the lifecourse.

**METHODS AND RESULTS:** This study used 2-sample univariable and multivariable Mendelian randomization to estimate the effect of childhood body size both independently and after accounting for adult body size on 12 endpoints across the cardiovascular disease spectrum. Univariable analyses identified strong evidence of a total effect between genetically predicted childhood body size and increased risk of atherosclerosis, atrial fibrillation, coronary artery disease, heart failure, hypertension, myocardial infarction, peripheral artery disease, and varicose veins. However, evidence of a direct effect was weak after accounting for adult body size using multivariable Mendelian randomization, suggesting that childhood body size indirectly increases risk of these 8 disease outcomes via the pathway involving adult body size.

**CONCLUSIONS:** These findings suggest that the effect of genetically predicted childhood body size on the cardiovascular disease outcomes analyzed in this study are a result of larger body size persisting into adulthood. Further research is necessary to ascertain the critical timepoints where, if ever, the detrimental impact of obesity initiated in early life begins to become immutable.

**Key Words:** cardiovascular disease ■ genetic epidemiology ■ lifecourse ■ Mendelian randomization ■ obesity

Approximately 2.6 million people worldwide die as a result of obesity related diseases each year, including cardiovascular diseases (CVDs), such as heart disease and stroke.<sup>1</sup> The World Health Organization posits that obesity results from and might influence social disparities.<sup>2</sup> Therefore, decreasing the frequency of obesity and thus reducing associated long-term adverse health consequences is key

to reducing health inequity, with the goal of achieving health attainment as well as poverty reduction globally.

The extent and prevalence of obesity have been growing steadily in both pediatric and adult populations over the past 4 decades.<sup>3</sup> In a 2017 meta-analysis, pooled estimates from 21 cohort and case-control studies suggest that childhood obesity may be a risk factor for selected adult CVD risk factors;

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## CLINICAL PERSPECTIVE

### What Is New?

- This Mendelian randomization investigation provides univariable evidence that genetically predicted childhood obesity increases risk of 8 types of cardiovascular disease.
- Evidence of total effects substantially attenuated upon accounting for body size in adulthood.

### What Are the Clinical Implications?

- These findings suggest that childhood obesity influences cardiovascular disease risk as a result of the long-term effect of adiposity persisting into adulthood.
- Risks associated with childhood adiposity may therefore potentially be reversed by early resolution of obesity in prepubertal children.
- Further research is required to elucidate whether there are critical timepoints in the lifecourse where the effects of childhood obesity may be reversed through lifestyle modifications.

## Nonstandard Abbreviations and Acronyms

<b>FDR</b>	false discovery rate
<b>MR</b>	Mendelian randomization

however, causal effects independent of adult adiposity could not be established.<sup>4</sup> This is in part due to the inherent problems with observational investigations, in which standard statistical techniques used to adjust for confounding do not fully negate bias, which may lead to spurious findings.<sup>5</sup> Furthermore, whether prepubertal childhood obesity has a lasting effect on different types of cardiovascular disease or whether those who become nonobese by adulthood have a similar risk to individuals who were never obese<sup>6,7</sup> is yet to be determined.

A lifecourse approach crucially investigates the contribution of early and later life factors together to identify risk and protective mechanisms across the lifespan.<sup>8</sup> The issues described relating to observational studies make separating the effects of obesity at different stages throughout the lifecourse challenging, which is one of the motivations behind using human genetics through the application of an approach known as Mendelian randomization (MR).<sup>9</sup> MR is often implemented as an instrumental variable analysis that exploits the random assortment of genetic variants at birth.<sup>10</sup> Thus, by using this approach, it is possible to estimate the

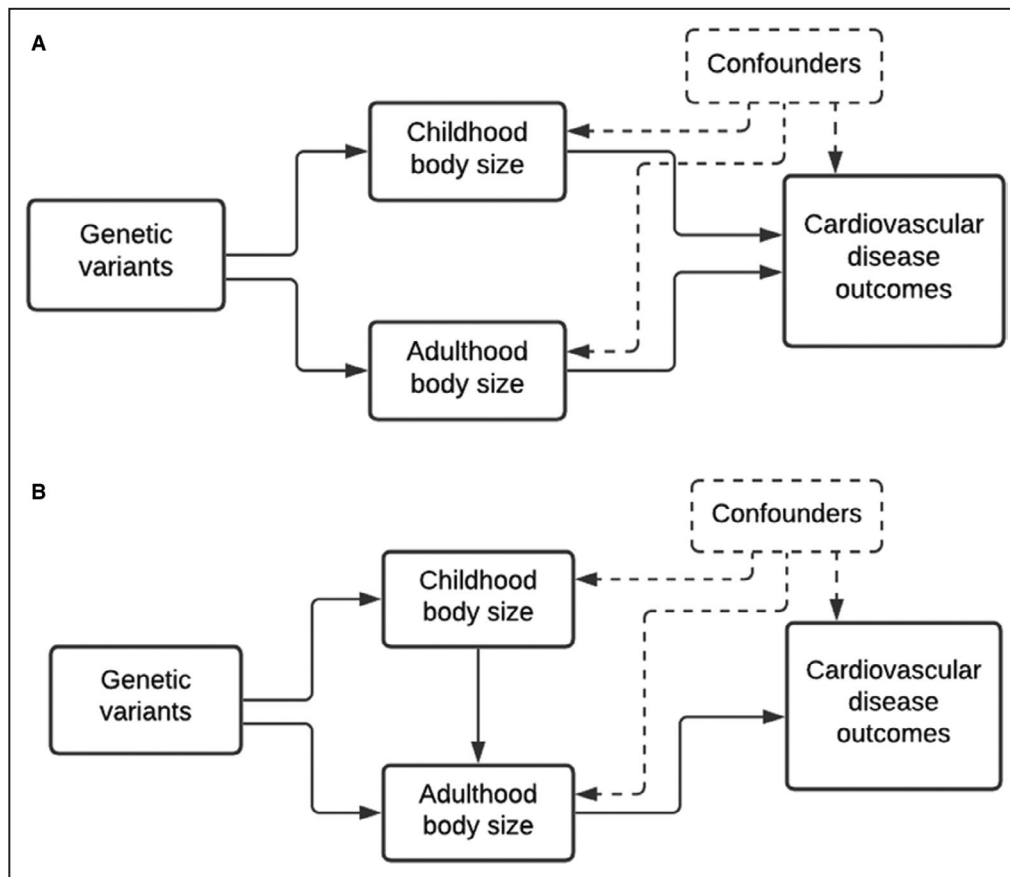
causal effects between closely related exposures and disease outcomes of interest, while mitigating the influence of common observational epidemiological issues relating to confounding and reverse causation.<sup>5</sup>

Multivariable MR is an extension of this approach that uses multiple genetic variants associated with multiple exposures to concurrently estimate the causal effect of each risk factor on an outcome. It has previously been applied to separate the independent effects of childhood and adult body size on disease risk,<sup>9</sup> using genetic instruments for self-reported perceived body size at age 10 and body mass index (BMI) in adulthood (average age 56.5 years).<sup>11,12</sup> In addition, these childhood effects have been replicated using measured BMI data from the Young Finns Study<sup>13</sup> and the HUNT Study (Nord-Trøndelag Health Study).<sup>14</sup> Childhood body size has been shown to have an effect on coronary artery disease using univariable MR (odds ratio [OR], 1.49; 95% CI, 1.33–1.68). However, after accounting for adult body size using multivariable MR, this effect attenuated (OR, 1.02; 95% CI, 0.86–1.22), suggesting that the childhood effects are because of sustained effects of adiposity over time.<sup>9</sup> This approach has not yet been applied to comprehensively evaluate end points throughout the CVD spectrum, however.

This investigation sets out to examine whether genetically predicted childhood body size has a direct effect on a comprehensive list of CVD outcomes, independent of adult body size, that have been linked previously to obesity. Initially, univariable MR was applied to estimate the “total effect” of early life body size on 12 CVD outcomes (ie, without accounting for adult body size). Multivariable MR was then used to estimate the “direct” (Figure 1A) and “indirect” (Figure 1B) effect of early life body size on the CVD outcomes. Estimating the independent effects of childhood and adult body size on a spectrum of CVD outcomes is of public health importance to better understand whether risks associated with childhood adiposity are lasting or can be minimized, suspended, or even reversed by resolution of obesity in early life.<sup>15</sup>

## METHODS

The data that support the findings of this study are all available from within the supplementary materials or publicly accessible from the resources cited. Data were obtained from the UKBB (UK Biobank) study, which obtained ethics approval from the Research Ethics Committee (REC; approval number: 11/NW/0382) and informed consent from all participants enrolled in UKBB.<sup>7</sup>



**Figure 1.** Directed acyclic graphs indicating 2 scenarios to explain the causal effect between childhood body size and disease outcomes in later life.

Childhood body size has a direct effect on cardiovascular disease (CVD) risk independent of body size in adulthood (A), and childhood body size has an indirect effect on CVD risk, through body size in adulthood (B).

## DATA RESOURCES

### Genetic Variants for Childhood and Adult Body Size

Genetic instruments for childhood and adult body size were identified previously, where 295 and 557 independent genetic variants were identified, respectively (using  $P < 5 \times 10^{-8}$  and  $r^2 < 0.001$ ) from a large-scale genome-wide association study (GWAS) of 453 169 participants in the UKBB study.<sup>11,12</sup> Adulthood measured BMI (mean age=56.5 years) was obtained at baseline using height (measured in cm) and weight (to the nearest 0.1 kg). In addition, participants were asked the question “When you were 10 years old, compared to average would you describe yourself as thinner, about average, or plumper?” For comparability purposes, BMI in adults was transformed into a categorical variable comprising 3 groups indicating body sizes indicative of being “thinner” (21.1–25 kg/m<sup>2</sup>), “about average” (25–31.7 kg/m<sup>2</sup>), and “plumper” (31.7–59.9 kg/m<sup>2</sup>). Throughout this study, these measures

are described as childhood and adult body size, respectively. The estimates derived in our analysis thus reflect a change in the odds of each change in weight category within childhood and adult groups (eg, from “thinner” to “about average” or from “about average” to “plumper”).

GWAS were conducted on individuals who had both measures available adjusting for age, sex, and the genotyping chip used to measure genetic data in the UKBB. This analysis applied linear regression and thus assumes that the effect of a single nucleotide polymorphism from the lowest to the middle category of the body size variables is the same as the effect from the middle to the highest. The GWAS used for childhood body size was also adjusted for month of birth. Conditional F-statistics generated for childhood ( $F=13.6$ ) and adult ( $F=16.0$ ) body size instruments suggested that weak instrument bias was unlikely to influence findings from these analyses.<sup>9</sup> Validation and simulation analyses for measures have been performed and comparisons of genome-wide effect

estimates between early life and adult body size in the UKBB made<sup>9</sup> (Table S1). Scores have been validated in the Young Finns Study.<sup>13</sup> This study indicated that the genetic score for childhood body size was a stronger predictor of childhood BMI compared with the adult body size score (area under the curve coefficients, 0.74; 95% CI, 0.65–0.82 versus 0.62, 0.53–0.72;  $P=0.02$ ) and the adult genetic score was a stronger predictor of adult BMI than the childhood body size score (area under the curve coefficients, 0.62; 95% CI, 0.58–0.65 versus 0.57, 0.54–0.60;  $P=0.02$ ). In addition, findings from the HUNT Study validated the childhood and adult gene scores for BMI with repeated BMI measurements of a Norwegian population aged 12 to 70 over 6 decades, confirming that both polygenetic risk scores were valid instruments. This study showed that the predictive performance of the childhood score was better in those aged 12 to 15.9 years compared with 24 to 29.9 years (polygenic risk scores 6.7% versus 2.4%) and that of the adult score was better in those aged 24 to 29.9 years compared to 12 to 15.9 years (3.9% versus 3.6%).<sup>14</sup> Thus, the predictive ability of these BMI scores have been validated in 2 further population groups in addition to validation analyses undertaken in the original study that conducted the GWAS.<sup>13,14</sup>

## Genetic Effects on Cardiovascular Disease Outcomes

The CVD end points analyzed in this study comprised those available from GWAS that BMI has been shown to influence previously.<sup>16–18</sup> Genetic estimates on coronary artery disease and myocardial infarction were obtained from the Coronary Artery Disease Genome-wide Replication and Meta-analysis plus the Coronary Artery Disease Genetics (CARDIOGRAMplusC4D) consortium.<sup>19</sup> Effect estimates on stroke were obtained from a GWAS undertaken by the MEGASTROKE consortium.<sup>20</sup> These GWAS were additionally selected as they did not include the UKBB study, to avoid overlapping samples with our instrument identification data set. Genetic estimates for the remaining CVD outcomes (all  $N>1000$  cases) had also been associated with BMI in the literature and were obtained from the FinnGen (FinnGen-tutkimushanke vie suomalaiset löytöretkelle genomitietoon) study (freeze 4), which brings together the nationwide network of Finnish biobanks and digital health care data. *International Classification of Diseases, Tenth Revision (ICD-10)* codes are available for these outcomes<sup>21</sup> (Table S2).

## Statistical Analysis

The “total effects” of genetically predicted childhood body size on each of the 12 CVD outcomes

were estimated in a 2-sample setting using the “TwoSampleMR” R package.<sup>22</sup> We initially applied the inverse variance weighted method, which provides an overall weighted estimate of causal effects of an exposure on an outcome by combining estimates using each variant in a fixed effect meta-analysis model.<sup>23</sup> Weighted median and MR-Egger methods were additionally used in this study to assess the robustness of univariable results to horizontal pleiotropy, the phenomenon whereby genetic variants influence multiple traits or disease outcomes via independent biological pathways.<sup>24,25</sup>

To mitigate false positive rates due to multiple testing, false discovery rate (FDR) corrections were used to adjust the  $P$  values computed for the univariable MR estimates using the inverse variance weighted method. For comparative purposes, we also undertook univariable MR analyses of adult body size for all 12 outcomes.

Multivariable MR using the inverse variance weighted method was conducted to fit childhood and adult body size as simultaneous risk factors on the remaining CVD outcomes, which were robust to FDR corrections in the previous analysis. This enabled the estimation of the “direct” effect of childhood body size on the CVD outcomes after accounting for adult body size.

Forest plots were generated using the R package “ggplot2.”<sup>26</sup> All analyses were undertaken using R (version 3.5.1).

## RESULTS

The total effects through univariable analyses indicated strong evidence of an effect between genetically predicted childhood body size and atherosclerosis (OR, 1.76; 95% CI, 1.37–2.27;  $P=1.25\times 10^{-5}$ ), atrial fibrillation and flutter (OR, 1.69; 95% CI, 1.39–2.06;  $P=2.00\times 10^{-7}$ ), coronary artery disease (OR, 1.53; 95% CI, 1.36–1.72;  $P=1.61\times 10^{-12}$ ), heart failure (OR, 1.72; 95% CI, 1.45–2.05;  $P=5.5\times 10^{-10}$ ), hypertension (OR, 1.77; 95% CI, 1.53–2.04;  $P=6.30\times 10^{-15}$ ), myocardial infarction (OR, 1.51; 95% CI, 1.36–1.74;  $P=8.85\times 10^{-11}$ ), peripheral artery disease (OR, 1.89; 95% CI, 1.48–2.42;  $P=4.69\times 10^{-7}$ ), and varicose veins (OR, 1.57; 95% CI, 1.29–1.91;  $P=6.7\times 10^{-6}$ ). These 8 outcomes were robust to FDR  $<0.05$  corrections. Additionally, there was little evidence of an effect between genetically predicted childhood body size and pulmonary heart disease (OR, 1.28; 95% CI, 0.97–1.69;  $P=0.09$ ), angina pectoris (OR, 1.15; 95% CI, 0.95–1.37;  $P=0.15$ ), pulmonary embolism (OR, 1.27; 95% CI, 0.95–1.72;  $P=0.11$ ), and stroke (OR, 1.57; 95% CI, 0.93–1.16;  $P=0.50$ ) (Table S3) based on FDR  $<0.05$ . For comparison, univariable estimates for adult body size on these 12 CVD end points can be found in Table S4.

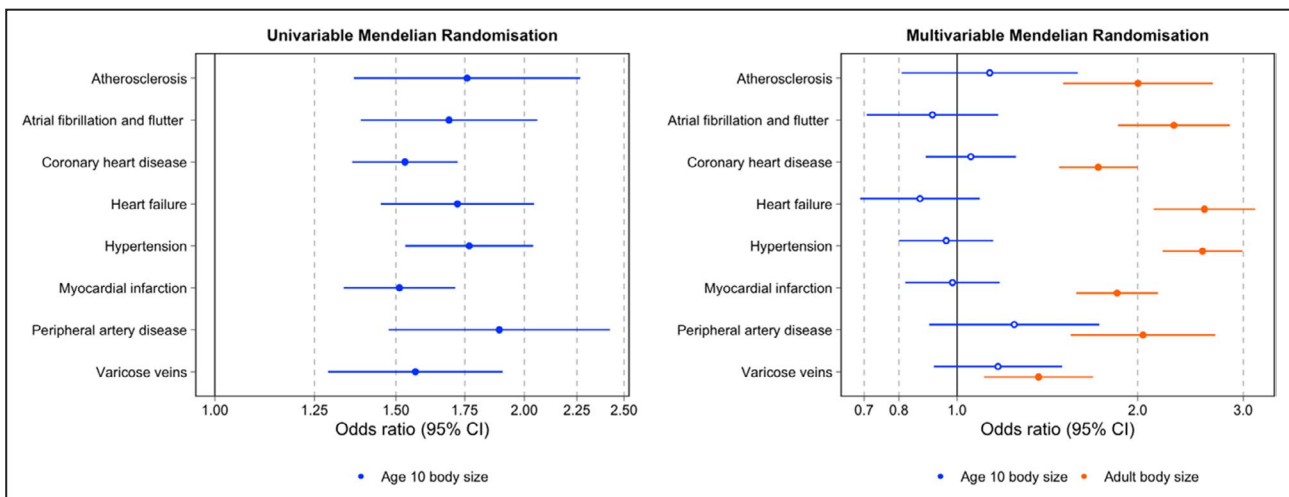
Consistent patterns of associations were observed using the weighted median method employed for robustness (Table S5). The MR-Egger method did not suggest that horizontal pleiotropy was responsible for the estimates derived, with the possible exception of the estimate between childhood body size and atrial fibrillation and flutter (Table S6).

Upon accounting for adult body size using multivariable MR, estimates for all 8 end points that survived FDR corrections in the univariable analysis substantially attenuated (Figure 2A). These estimates provided little evidence of a direct effect between genetically predicted childhood body size and atherosclerosis (OR, 1.13; 95% CI, 0.81–1.59;  $P=0.468$ ), atrial fibrillation and flutter (OR, 0.91; 95% CI, 0.71–1.17;  $P=0.462$ ), coronary heart disease (OR, 1.05; 95% CI, 0.89–1.25;  $P=0.551$ ), heart failure (OR, 0.87; 95% CI, 0.69–1.09;  $P=0.224$ ), hypertension (OR, 0.96; 95% CI, 0.90–1.15;  $P=0.650$ ), myocardial infarction (OR, 0.98; 95% CI, 0.82–1.18;  $P=0.848$ ), peripheral artery disease (OR, 1.25; 95% CI, 0.90–1.73;  $P=0.118$ ), and varicose veins (OR, 1.17; 95% CI, 0.92–1.50;  $P=0.211$ ). In contrast, multivariable analyses provided strong evidence that adult body size directly increases risk of the 8 CVD disease outcomes analyzed (Figure 2B). Lastly, although there was little evidence of an effect between childhood body size and the 4 outcomes not included in multivariable analyses, adult body size provided strong evidence of a total effect on angina pectoris (OR, 1.67; 95% CI, 1.36–2.05;  $P=1.28 \times 10^{-6}$ ), pulmonary embolism (OR, 1.61; 95% CI, 1.15–2.25;  $P=0.005$ ), pulmonary heart disease (OR, 1.77; 95% CI, 1.30–2.42;  $P=2.96 \times 10^{-4}$ ), and stroke (OR, 1.56; 95% CI, 1.36–1.79;  $P=1.36 \times 10^{-10}$ ) (Table S7).

## DISCUSSION

In the present MR investigation, we applied a lifecourse approach to investigate the mechanisms underlying the causal effect of genetically predicted childhood body size on the risk of a spectrum of later life CVD outcomes linked to obesity. This was to determine whether childhood body size has an independent effect on CVD risk or whether its influence can be explained by accounting for body size in adulthood. We report results based on direct or indirect effects as described previously in the multivariable Mendelian randomization literature.<sup>27</sup> A consistent relationship between higher childhood body size and an increase in the odds of CVD was identified in univariable analyses. When accounting for adult body size, however, estimates attenuated to include the null (and in some cases reversed direction of effect), indicating weak evidence of a direct effect between childhood body size and CVD outcomes in multivariable analyses. There was strong evidence indicating the influence of adult body size on CVD outcomes in both univariable and multivariable analyses.

Results from this study are in line with previous clinical and epidemiological observational research, indicating that childhood adiposity is a risk factor for several disease outcomes, including type 2 diabetes mellitus, hypertension, dyslipidemia and carotid-artery atherosclerosis, only if individuals remain overweight into puberty or later ages.<sup>6,7</sup> These findings therefore highlight the importance of prevention efforts to reduce adiposity in prepubescent children to help mitigate adverse cardiovascular consequences in later life.<sup>28</sup> Ensuring socially disadvantaged groups benefit from relevant public health interventions aimed at



**Figure 2. Univariable for childhood body size (A) and multivariable for childhood and adult body size (B) Mendelian randomization onto CVD outcomes.** CVD indicates cardiovascular disease.

reducing obesity is especially key in both policy and practice, because obesity levels in high-income countries disproportionately affect ethnic minority, low-income, and other socially marginalized populations.<sup>29</sup> For example, in the context of the United States, the prevalence of a BMI above the 85th percentile for age and sex rose to 35% in Hispanic and Black children compared with 20% in their counterparts of European ancestry.<sup>28</sup>

In addition, findings from this report highlight the advantages of considering the long-term effects of childhood and early adult risk factors on later disease to elucidate processes operating across the lifecourse, that influence the development of disease risk.<sup>8</sup> Previous longitudinal research has investigated adverse outcomes in overweight individuals at multiple different stages throughout early life. For example, a retrospective cohort study comprising individuals born between 1930 and 1989 in Copenhagen, Denmark, assessed the adverse effects of weight gain in childhood (7 years of age), adolescence (13 years of age) and early adulthood on type 2 diabetes mellitus risk.<sup>7</sup> Whereas those who were overweight between 7 to 13 years who had subsequently maintained normal weight in early adulthood had a risk of type 2 diabetes mellitus similar to those with normal weights at all ages, those who were overweight between 13 and early adulthood had a risk of type 2 diabetes mellitus higher than those who had never been overweight. In addition, a prospective cohort study completed on the Israeli Defence Force Medical Corps revealed that elevated BMI in both adolescence (mean 17.44±0.46 years) and adulthood (mean 30.59±5.30 years) were independently associated with angiography-proven coronary heart disease.<sup>30</sup> Furthermore, in this study we found that the effect sizes of childhood body size estimates on CVD were consistently smaller than adulthood body size in univariable analyses. Although the magnitude of total effect estimates are relevant from a lifecourse perspective, only through multivariable analyses can evidence of direct and indirect effects be inferred. Future investigations using genetics would benefit from developing genetic scores for multiple age groups to assess the causal effects of increased body size at specific ages on adverse outcomes related to obesity.

### Strengths and Limitations

Although the association between obesity and CVD risk has been investigated longitudinally in observational research, this is a unique study in that it estimates effects on various endpoints throughout the CVD disease spectrum, using genetically predicted exposures at separate timepoints in the lifecourse. Doing so means that our effect estimates should

be more robust to reverse causation and confounding compared with previous observational estimates. In addition, this investigation leverages large sample sizes available through the UKBB study (n=453 169) for measures of early and later life body size and the CARDIOGRAMplusC4D consortium (n=185 000), MEGASTROKE consortium (n=521 612), and FinnGen study (n=269 077) for measures of CVD outcomes, increasing study power. This study also uses a 2-sample approach, where the risk factor and outcome are taken from nonoverlapping data sets, minimizing the potential for bias from overfitting.<sup>31</sup> Furthermore, weighted median and MR-Egger methods were used to assess the robustness of univariable results to horizontal pleiotropy.

This study, however, also has important limitations. First, participants' self-reporting of their body size in childhood may have resulted in differential social desirability bias, with respect to retrospective weight recall at age 10. Furthermore, the age of participants in adulthood when reporting this information could potentially influence the childhood body size measurement, because individuals recalled their body weight at different ages in midlife, resulting in different lengths of time since they were children. To account for this, GWAS were conducted on individuals who had both measures available adjusting for age, as well as sex and the genotyping chip. Though, as described earlier using measured BMI data from the Young Finns Study<sup>13</sup> and the HUNT Study,<sup>14</sup> the genetic score for early life body size has been shown to be a better predictor of childhood BMI and the score for adult body size a better predictor of adult BMI. Second, although effect estimates in this study were positive, there was weak evidence of a genetically predicted effect between childhood body size and 4 of the 12 risk factors in univariable analyses. This may be because of a lack of power based on the number of cases for these endpoints in the FinnGen dataset. However, this could also potentially indicate that having a larger body size does not begin to exert its effect on angina pectoris, pulmonary embolism, pulmonary heart disease, and stroke as early in the lifecourse as other outcomes assessed. This requires further investigation. Third, this study uses genetically determined body size, which may not translate directly into weight loss or gain from lifestyle reforms.<sup>9</sup> Fourth, selection bias using the UKBB is an important limitation, because participants in the UKBB are more likely to be older, female, and live in less socioeconomically deprived areas than participants in nationally representative data sources.<sup>32</sup> Underrepresentation of younger, male, nonbinary, or any other gender identity and the lowest socioeconomic position group is therefore problematic, with the potential to cause issues for instrumental variable

analyses.<sup>33</sup> Furthermore, because allele frequencies and disease or exposure rates vary between different subgroups of the population, introducing the potential for confounding, this study performs analyses in homogeneous populations of European ancestry.<sup>34</sup> This therefore provides evidence of the causal effects identified only within this single ancestry group and may thus not be generalizable to other ancestry populations. Future research should therefore investigate estimates derived in this study across a broader range of different ancestries. Lastly, genetic correlation has been shown to exist in the UKBB between birth location and several health outcomes relevant to our study, after adjusting for population structure, including hypertension and BMI.<sup>35</sup> Future work to assess the extent to which environmental factors confounded with location may influence findings from UKBB analyses would be worthwhile.

## CONCLUSIONS

These findings provide evidence that the total effect of childhood body size on CVD outcomes is a result of larger body size persisting into adulthood, suggesting that childhood obesity is unlikely to have a direct causal effect on the CVD outcomes assessed in this work. Importantly, elevated risk of these types of CVD associated with childhood adiposity may therefore putatively be mitigated or potentially reversed by early resolution of obesity in early life.

## ARTICLE INFORMATION

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## Supplementary Material

Table S1–S7

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# **SUPPLEMENTAL MATERIAL**

















rs4739558	8	38337264	FGFR1	A	G	0.00809748	0.00140056	7.4E-09	0.00829517	0.00143069	6.7E-09	0.446523149
rs73982435	17	31473455	ASIC2	C	T	0.00942922	0.00166802	1.6E-08	0.00756369	0.00170321	0.000009	0.465811913
rs512121	18	7548501	PTPRM	T	C	0.0105713	0.00174913	1.5E-09	0.00930527	0.00178584	0.00000019	0.476966036
rs7453694	6	51739528	PKHD1	C	T	-0.00979363	0.00152053	1.2E-10	-0.00598175	0.00155374	0.00012	0.477819349
rs12045879	1	15817090	CELA2B	C	T	0.0061829	0.00147365	0.000027	0.00988708	0.00150652	5.3E-11	0.47958885
rs59714050	3	141267294	RASA2	T	A	-0.019371	0.00275265	2E-12	-0.0228386	0.00281497	4.9E-16	0.4870535858
rs1633418	22	20091756	DGCR8	T	C	0.00792126	0.00141049	0.00000002	0.004885	0.00143933	0.00069	0.491327207
rs3861871	9	129424719	LMX1B	A	G	-0.00828546	0.00139067	2.6E-09	-0.00711657	0.00142047	0.00000054	0.493601675
rs11496125	7	103417557	RELN	C	T	-0.0109238	0.00139455	4.8E-15	-0.00854189	0.00142469	0.000000002	0.500013878
rs7951870	11	46373311	DGKZ	T	C	-0.00715047	0.00182188	0.000087	-0.0115536	0.00186108	5.4E-10	0.52090774
rs12798028	11	47604639	NDUFS3	C	T	-0.0150337	0.00139188	3.4E-27	-0.0145642	0.00142183	1.3E-24	0.527357034
rs559231	18	39644247	PIK3C3	G	T	-0.00952495	0.00141154	1.5E-11	-0.00909768	0.00144117	2.7E-10	0.531546264
rs73026723	19	31017177	ZNF536	C	T	0.0140677	0.00190031	1.3E-13	0.0094854	0.00194001	0.000001	0.542994723
rs4148155	4	89054667	ABCG2	A	G	0.0143494	0.00215753	2.9E-11	0.00641588	0.0022505	0.0036	0.5456516121
rs7656673	4	30840331	PCDH7	A	G	-0.00828306	0.00139847	3.2E-09	-0.011556	0.00142927	6.2E-16	0.551539336
rs3810291	19	47569003	ZC3H4	G	A	-0.0157949	0.00146479	4.1E-27	-0.0147393	0.00149539	6.4E-23	0.571383505
rs72892910	6	50816887	TFAP2B	G	T	-0.0252844	0.00181803	5.7E-44	-0.0246629	0.00185774	3.2E-40	0.573603603
rs7711823	5	158489315	EBF1	A	G	0.00657182	0.00142907	0.0000043	0.00838771	0.00146043	9.3E-09	0.578259633
rs34722008	4	38659594	AC021860.1	G	A	0.00699237	0.00143592	0.0000011	0.00826538	0.00146755	0.000000018	0.582424518
rs75706763	2	145669168	ZEB2	A	G	-0.0177039	0.00313665	1.7E-08	-0.0121363	0.00320738	0.00015	0.586664804
rs12484438	22	40558064	TNRC6B	T	C	0.0128869	0.00145125	6.7E-19	0.0117799	0.00148093	1.8E-15	0.593098027
rs5558481	2	219284215	VIL1	G	A	-0.0089689	0.00144403	5.3E-10	-0.00815869	0.00147766	0.00000033	0.605224249
rs11976804	7	137437156	DGKI	C	T	-0.00856668	0.00151882	1.7E-08	-0.0066061	0.00155165	0.000021	0.610879573
rs58084604	18	57849429	MC4R	C	T	-0.0351865	0.00162237	2.6E-104	-0.0331788	0.00165642	3E-89	0.639182079
rs1852006	7	77829768	MAGI2	G	A	0.00883089	0.00143031	6.7E-10	0.00877312	0.00146122	1.9E-09	0.647257549
rs2712667	12	99588917	ANKS1B	G	C	0.00962407	0.00143716	2.1E-11	0.00848645	0.00146746	7.3E-09	0.658849548
rs55896564	8	11447093	BLK	G	A	0.0116966	0.00138218	2.6E-17	0.00911305	0.00141192	1.1E-10	0.680319936
rs55838622	5	95711605	PCSK1	A	C	-0.00989605	0.00164361	1.7E-09	-0.00673263	0.00167968	0.000061	0.688876447
rs1422067	5	77424836	AP3B1	C	T	0.00870177	0.00160988	6.5E-08	0.0108803	0.00164522	3.8E-11	0.690202603
rs9922288	16	24550930	RBBP6	A	G	0.00938916	0.00163749	9.8E-09	0.0105391	0.00167252	3E-10	0.692806621
rs10791902	11	67093360	SSH3	C	T	-0.00563275	0.00140655	0.000062	-0.00791481	0.00143682	0.00000036	0.696581727
rs11150745	17	78757626	RPTOR	A	G	0.0137948	0.00147616	9.2E-21	0.0121511	0.00150731	7.5E-16	0.702479635
rs72618637	2	48953979	GTF2A1L	T	A	0.0099921	0.00177487	1.8E-08	0.00628905	0.00181489	0.00053	0.705135669
rs7752998	6	34398358	RPS10	A	T	0.0102464	0.00174849	4.6E-09	0.00734414	0.00178668	0.000039	0.706890342
rs111768603	3	42329113	CKK	G	T	0.0159053	0.00219022	3.8E-13	0.0154313	0.00223981	5.6E-12	0.750423451
rs7619139	3	25110415	RARB	T	A	-0.00884007	0.00139518	2.4E-10	-0.00979985	0.00142677	6.5E-12	0.757971664
rs3931548	9	103113652	TEX10	C	A	-0.0105077	0.0014385	2.8E-13	-0.00540991	0.00146933	0.00023	0.761641771
rs80082536	3	35195311	ARPP21	A	G	-0.0128944	0.00212463	1.3E-09	-0.00715424	0.00217273	0.00099	0.771183462
rs7827182	8	8380471	SGK223	G	C	-0.0112266	0.00137268	2.9E-16	-0.00848727	0.00140221	1.4E-09	0.776826066
rs4836133	5	124332103	ZNF608	C	A	-0.00836449	0.00141129	3.1E-09	0.00231309	0.00246539	0.35	0.786351589
rs62004865	15	74207695	LOXLI	T	A	-0.0135621	0.00224169	1.4E-09	-0.0117753	0.00228856	0.00000027	0.814628514
rs7928320	11	116942753	SIK3	C	G	-0.0172858	0.00297269	6.1E-09	-0.00223066	0.00303665	0.46	0.836253954
rs59428052	2	53861389	GPR75-ASB3	A	G	0.0114661	0.00199987	9.8E-09	0.00833123	0.00204497	0.000046	0.867118662
rs8089514	18	69224478	RP11-723G8.2	T	A	-0.0081679	0.00143938	1.4E-08	-0.00731918	0.00146959	0.00000063	0.876197736
rs1576655	13	79587841	RBM26	A	C	-0.0113489	0.00142746	1.9E-15	-0.0118472	0.00145793	4.4E-16	0.886607189
rs12606230	18	52492252	RAB27B	T	C	-0.0116875	0.00262392	6.2E-13	-0.0127194	0.001658	1.7E-14	0.911819108
rs72673947	8	118884379	EXT1	A	G	-0.0140208	0.00223036	3.3E-10	-0.0118252	0.00227835	0.00000021	0.923011464
rs61992671	14	101531854	AL117190.3	A	G	0.00988005	0.00143461	5.7E-12	0.00757897	0.001465	0.00000023	0.925555966
rs62048187	15	38117049	TMCO5A	G	C	-0.00601476	0.00150076	0.000061	-0.00838898	0.00153213	0.00000044	0.934936884
rs57636386	18	58048295	MC4R	T	C	0.0247018	0.00248459	2.7E-23	0.0235012	0.00253674	2E-20	0.947256486
rs1423534	5	63977000	FAM159B	G	A	0.00770872	0.00139391	3.2E-08	0.00714486	0.00142451	0.00000053	0.948333389
rs35775580	7	130420740	KLF14	A	G	0.0180149	0.00324057	2.7E-08	0.0132438	0.00331061	0.000063	0.948565676
rs112253053	19	19425145	SUGP1	T	A	0.013771	0.00186963	1.8E-13	0.0101428	0.00190869	0.00000011	0.967308093
rs28350	3	42418446	LYZL4	A	G	0.0126363	0.00179146	1.7E-12	0.00969738	0.00183201	0.00000012	0.969187358
rs1834144	18	40744790	RIT2	C	A	0.00792997	0.00142258	2.5E-08	0.00681807	0.00145244	0.00000027	0.990302683
rs12140153	1	62579891	TNADL	G	T	0.0214472	0.00240105	4.2E-19	0.021828	0.0024546	6E-19	0.994017345
rs9317002	13	59175727	PCDH17	C	A	-0.0113783	0.00138238	1.9E-16	-0.0115024	0.00141189	3.7E-16	0.996218241

SNP - single nucleotide polymorphism identifier, Beta - effect estimate coefficient for SNP on body size, SE - standard error of the effect estimate, P - corresponding p-value

**Table S2. A summary of the genetic datasets used in this study.**

Outcome	Sample size	Cases	Control	Year	Ancestry	Study	ICD-10 codes
Angina pectoris	167333	14712	152621	2020	European	FinnGen study	I20
Atherosclerosis	172780	4937	167843	2020	European	FinnGen study	I70
Atrial fibrillation and flutter	114539	17325	97214	2020	European	FinnGen study	I48
Coronary artery disease	184305	60801	123504	2015	Mixed	CARDIoGRAMplusC4D consortium	
Heart failure	168862	9576	159286	2020	European	FinnGen study	I50
Hypertension	176899	43576	133323	2020	European	FinnGen study	I10
Myocardial infarction	171875	43676	128199	2015	Mixed	CARDIoGRAMplusC4D consortium	
Peripheral artery disease	173166	5323	167843	2020	European	FinnGen study	I73.9
Pulmonary embolism	176613	3016	173597	2020	European	FinnGen study	I26
Pulmonary heart disease	176899	3302	173597	2020	European	FinnGen study	I27
Stroke	446696	40585	406111	2015	Mixed	MEGASTROKE consortium	
Varicose veins	167879	13928	153951	2020	European	FinnGen study	I83

**Table S3. Inverse variance weighted method results for univariable Mendelian randomization analyses for childhood body size on cardiovascular disease outcomes.**

<b>Outcome</b>	<b>F-stat</b>	<b>nSNPs</b>	<b>Beta</b>	<b>SE</b>	<b>P</b>	<b>OR</b>	<b>FDR</b>
Angina pectoris	13.6	302	0.136	0.093	0.145	1.145	0.289
Atherosclerosis	13.6	302	0.565	0.129	0.000	1.759	0.000
Atrial fibrillation and flutter	13.6	302	0.524	0.101	0.000	1.690	0.000
Coronary heart disease	13.6	276	0.426	0.060	0.000	1.531	0.000
Heart failure	13.6	302	0.543	0.088	0.000	1.722	0.000
Hypertension	13.6	302	0.570	0.073	0.000	1.768	0.000
Myocardial infarction	13.6	276	0.413	0.064	0.000	1.512	0.000
Peripheral artery disease	13.6	302	0.637	0.126	0.000	1.891	0.000
Pulmonary embolism	13.6	302	0.242	0.152	0.111	1.274	0.243
Pulmonary heart disease	13.6	302	0.245	0.143	0.087	1.278	0.208
Stroke	13.6	278	0.039	0.058	0.502	1.040	0.635
Varicose veins	13.6	302	0.449	0.100	0.000	1.567	0.000

**Table S4. Inverse variance weighted method results for univariable Mendelian randomization analyses for adult body size on cardiovascular disease.**

<b>Outcome</b>	<b>F-stat</b>	<b>nSNPs</b>	<b>Beta</b>	<b>SE</b>	<b>P</b>	<b>OR</b>
Angina pectoris	16	562	0.389	0.076	0.000	1.476
Atherosclerosis	16	562	0.761	0.105	0.000	2.141
Atrial fibrillation and flutter	16	562	0.769	0.077	0.000	2.157
Coronary heart disease	16	505	0.569	0.055	0.000	1.766
Heart failure	16	562	0.865	0.073	0.000	2.374
Hypertension	16	562	0.919	0.055	0.000	2.507
Myocardial infarction	16	505	0.598	0.058	0.000	1.818
Peripheral artery disease	16	562	0.844	0.101	0.000	2.326
Pulmonary embolism	16	562	0.420	0.123	0.001	1.522
Pulmonary heart disease	16	562	0.493	0.114	0.000	1.637
Stroke	16	511	0.298	0.050	0.000	1.347
Varicose veins	16	562	0.414	0.072	0.000	1.513

**Table S5. Weighted median results for univariable Mendelian randomization analyses for childhood and adult body size on cardiovascular disease outcomes.**

<b>Exposure</b>	<b>Outcome</b>	<b>nSNPs</b>	<b>Beta</b>	<b>SE</b>	<b>P</b>	<b>OR</b>
Age 10 body size	Angina pectoris	302	0.326	0.156	0.036	1.386
Age 10 body size	Atherosclerosis	302	0.571	0.205	0.005	1.770
Age 10 body size	Atrial fibrillation and flutter	302	0.430	0.153	0.005	1.538
Age 10 body size	Coronary heart disease	276	0.487	0.089	0.000	1.627
Age 10 body size	Heart failure	302	0.605	0.151	0.000	1.832
Age 10 body size	Hypertension	302	0.634	0.095	0.000	1.885
Age 10 body size	Myocardial infarction	276	0.519	0.106	0.000	1.681
Age 10 body size	Peripheral artery disease	302	0.482	0.188	0.010	1.619
Age 10 body size	Pulmonary embolism	302	0.433	0.255	0.090	1.542
Age 10 body size	Pulmonary heart disease	302	0.495	0.236	0.036	1.641
Age 10 body size	Stroke	278	0.013	0.090	0.886	1.013
Age 10 body size	Varicose veins	302	0.707	0.141	0.000	2.027
Adult body size	Angina pectoris	562	0.384	0.128	0.003	1.469
Adult body size	Atherosclerosis	562	0.662	0.163	0.000	1.939
Adult body size	Atrial fibrillation and flutter	562	0.841	0.122	0.000	2.319
Adult body size	Coronary heart disease	505	0.639	0.087	0.000	1.895
Adult body size	Heart failure	562	0.846	0.133	0.000	2.331
Adult body size	Hypertension	562	1.057	0.076	0.000	2.876
Adult body size	Myocardial infarction	505	0.578	0.088	0.000	1.782
Adult body size	Peripheral artery disease	562	0.774	0.166	0.000	2.168
Adult body size	Pulmonary embolism	562	0.579	0.214	0.007	1.783
Adult body size	Pulmonary heart disease	562	0.767	0.207	0.000	2.152
Adult body size	Stroke	511	0.226	0.078	0.004	1.253
Adult body size	Varicose veins	562	0.562	0.116	0.000	1.755

**Table S6. MR-Egger results for univariable Mendelian randomization analyses for childhood and adult body size on cardiovascular disease outcomes.**

Exposure	Outcome	nSNPs	Beta	SE	P	OR
Age 10 body size	Angina pectoris	302	0.234	0.215	0.277	1.264
Age 10 body size	Atherosclerosis	302	1.180	0.297	0.000	3.253
Age 10 body size	Atrial fibrillation and flutter	302	0.391	0.233	0.095	1.478
Age 10 body size	Coronary heart disease	276	0.554	0.137	0.000	1.741
Age 10 body size	Heart failure	302	0.554	0.203	0.007	1.740
Age 10 body size	Hypertension	302	0.766	0.169	0.000	2.150
Age 10 body size	Myocardial infarction	276	0.650	0.145	0.000	1.916
Age 10 body size	Peripheral artery disease	302	1.132	0.291	0.000	3.102
Age 10 body size	Pulmonary embolism	302	-0.172	0.351	0.623	0.842
Age 10 body size	Pulmonary heart disease	302	-0.030	0.331	0.927	0.970
Age 10 body size	Stroke	278	0.069	0.132	0.603	1.071
Age 10 body size	Varicose veins	302	0.475	0.231	0.040	1.609
Adult body size	Angina pectoris	562	0.493	0.221	0.026	1.636
Adult body size	Atherosclerosis	562	1.244	0.303	0.000	3.471
Adult body size	Atrial fibrillation and flutter	562	0.749	0.224	0.001	2.114
Adult body size	Coronary heart disease	505	0.877	0.165	0.000	2.403
Adult body size	Heart failure	562	1.087	0.210	0.000	2.966
Adult body size	Hypertension	562	1.177	0.160	0.000	3.245
Adult body size	Myocardial infarction	505	0.814	0.173	0.000	2.258
Adult body size	Peripheral artery disease	562	1.285	0.291	0.000	3.614
Adult body size	Pulmonary embolism	562	0.838	0.355	0.019	2.311
Adult body size	Pulmonary heart disease	562	1.062	0.329	0.001	2.891
Adult body size	Stroke	511	0.110	0.149	0.461	1.116
Adult body size	Varicose veins	562	0.745	0.209	0.000	2.107

**Table S7. Inverse variance weighted method results for multivariable Mendelian randomization analyses for childhood and adult body size on cardiovascular disease outcomes.**

Exposure	Outcome	nSNPs	Beta	SE	OR	LCI	UCI	P
Age 10 body size	Angina pectoris	263	-0.175	0.124	0.839	0.657	1.071	0.159
Age 10 body size	Atherosclerosis	263	0.125	0.172	1.133	0.808	1.589	0.468
Age 10 body size	Atrial fibrillation and flutter	263	-0.095	0.129	0.910	0.707	1.171	0.462
Age 10 body size	Coronary heart disease	241	0.053	0.088	1.054	0.886	1.254	0.551
Age 10 body size	Heart failure	263	-0.142	0.117	0.867	0.689	1.091	0.224
Age 10 body size	Hypertension	263	-0.042	0.092	0.959	0.801	1.149	0.650
Age 10 body size	Myocardial infarction	241	-0.018	0.092	0.983	0.820	1.178	0.848
Age 10 body size	Peripheral artery disease	263	0.219	0.167	1.245	0.899	1.726	0.188
Age 10 body size	Pulmonary embolism	263	-0.022	0.201	0.979	0.660	1.451	0.915
Age 10 body size	Pulmonary heart disease	263	-0.078	0.186	0.925	0.642	1.332	0.676
Age 10 body size	Stroke	243	-0.271	0.080	0.762	0.652	0.892	0.001
Age 10 body size	Varicose veins	263	0.157	0.126	1.170	0.915	1.496	0.211
Adult body size	Angina pectoris	522	0.512	0.106	1.669	1.357	2.054	0.000
Adult body size	Atherosclerosis	522	0.694	0.147	2.002	1.502	2.669	0.000
Adult body size	Atrial fibrillation and flutter	522	0.832	0.109	2.298	1.854	2.848	0.000
Adult body size	Coronary heart disease	472	0.542	0.077	1.719	1.479	1.997	0.000
Adult body size	Heart failure	522	0.949	0.100	2.584	2.126	3.140	0.000
Adult body size	Hypertension	522	0.942	0.078	2.565	2.200	2.990	0.000
Adult body size	Myocardial infarction	472	0.614	0.080	1.848	1.580	2.162	0.000
Adult body size	Peripheral artery disease	522	0.713	0.142	2.041	1.546	2.693	0.000
Adult body size	Pulmonary embolism	522	0.474	0.171	1.607	1.150	2.246	0.005
Adult body size	Pulmonary heart disease	522	0.573	0.158	1.773	1.300	2.419	0.000
Adult body size	Stroke	476	0.444	0.069	1.559	1.361	1.785	0.000
Adult body size	Varicose veins	522	0.313	0.107	1.367	1.109	1.685	0.003