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Genetic associations of birthweight, childhood, and adult BMI with metabolic dysfunction-associated steatotic liver disease: a Mendelian randomization

Xiaohui Ma[1†], Lina Chang[1†], Shuo Li[1†], Yian Gu[1], Jieying Wan[1], Hequn Sang[1], Li Ding[1*], Ming Liu[1*] and Qing He[1*]

Abstract

Purpose The causal relationship between life course adiposity with metabolic dysfunction-associated steatotic liver disease (MASLD) is ambiguous. We aimed to investigate whether there is an independent genetic causal relationship between body size at various life course and MASLD.

Methods We performed univariable and multivariable Mendelian randomization (MR) to estimate the causal effect of body size at different life stages on MASLD (i.e., defined by the clinical comprehensive diagnosis from the electronic health record [HER] codes [ICD9/ICD10] or diagnostic phrases), including birthweight, childhood body mass index (BMI), adult BMI, waist circumference (WC), waist-to-hip ratio (WHR), body fat percentage (BFP).

Results In univariate analyses, higher genetically predicted lower birthweight (OR_{IVW} = 0.61, 95%CI, 0.52 to 0.74), Childhood BMI (OR_{IVW} = 1.37, 95%CI, 1.12 to 1.64), and adult BMI (OR_{IVW} = 1.41, 95%CI, 1.27 to 1.57) was significantly associated with subsequent risk of MASLD after Bonferroni correction. The MVMR analysis demonstrated compelling proof that birthweight and adult BMI had a direct causal relationship with MASLD. However, after adjusting for birthweight and adult BMI, the direct causal relationship between childhood BMI and MASLD disappeared.

Conclusion For the first time, this MR elucidated new evidence for the effect of life course adiposity on MASLD risk, providing lower birthweight and duration of obesity are independent risk factors for MASLD. Our findings indicated that weight management during distinct time periods plays a significant role in the prevention and treatment of MASLD.

†Xiaohui Ma, Lina Chang and Shuo Li contributed equally to this work.

*Correspondence:
Li Ding
dinglitml@tmu.edu.cn
Ming Liu
mingliu@tmu.edu.cn
Qing He
heqing202108@163.com

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

Keywords Birthweight, Childhood body mass index, Adult body mass index, Metabolic dysfunction-associated steatotic liver disease, Mendelian randomization

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is defined as the presence of excess triglyceride storage in the liver in the presence of at least one cardiometabolic risk factor [1]. Currently, some studies have shown that it is reasonable to transfer the evidence on non-alcoholic fatty liver disease (NAFLD) to the MASLD population, and the terms of NAFLD and MASLD can be used interchangeably [1–4]. Therefore, in this study, the term of outcome was consistently expressed as MASLD. MASLD affects over 25% of populations in developed Western countries [5]. MASLD constitutes a group of acquired metabolic liver disorders characterized by the accumulation of intrahepatic fat [6]. It is associated with elevated risks of cardiovascular disease, metabolic syndrome, and overall mortality [7, 8]. Recent research highlights the multifaceted etiology of MASLD, involving factors such as insulin resistance, lipotoxicity, oxidative stress, gastrointestinal microbiome disturbances, genetic susceptibility and epigenetics, all of which are prevalent in obese individuals. Obesity stands as the primary risk factor associated with MASLD [8, 9].

The developmental origin hypothesis of health and disease posits that early-life prenatal conditions can irrevocably modify the structure, physiology, and metabolism of the body. Intrauterine growth retardation affects the functioning of the pancreas, adipose tissue, and liver, which are the primary organs involved in liver insulin resistance [10]. Recent observational evidence suggests that intrauterine growth retardation may modulate the occurrence of MASLD in adulthood through metabolic disorders [11].

The development of childhood adiposity is not only linked to early metabolic consequences but also associated with persistent adiposity in adulthood and an increased risk of chronic diseases, including hypertension, coronary artery disease, diabetes, and various malignancies [12–15]. Given the substantial correlations between birthweight, childhood BMI, and adult BMI, it is imperative to explore the causal effects of these three weight characteristics on MASLD. Distinguishing the independent effects of birthweight, childhood BMI, and adult BMI on MASLD is inherently challenging, particularly because individuals who are obese during childhood often remain obese in adulthood.

Mendelian randomization (MR) is an epidemiological method used to infer causal relationships between exposure factors and outcome phenotypes. It achieves this by employing genetic variation associated with significant exposure as instrumental variables (IVs) [16, 17]. Since an individual's genotype is determined at the time of fertilization, MR can effectively circumvent biases arising from confounding or reverse causation, providing valuable evidence for understanding disease etiology. Therefore, in this study, MR was employed to assess the independent effects of birthweight, childhood BMI, and adult BMI on MASLD.

Methods

Study design

In this study, we conducted both univariable and multivariable MR analyses to investigate the influence of body size at different life stages on MASLD risk (Fig. 1). We initiated a univariate MR analysis to assess the overall effect of various weight characteristics on MASLD risk, including birthweight, childhood body mass index (BMI), adult BMI, waist circumference (WC), waist-to-hip ratio (WHR), and body fat percentage (BFP). In addition to obesity, abnormalities of glucose metabolism, lipid metabolism and vitamin D deficiency all influence the development of MASLD [8, 18, 19]. Subsequently, we performed multivariable MR to determine the independent effect of birthweight, childhood BMI, and adult BMI on MASLD risk while accounting for potential confounding factors, including vitamin D, type 2 diabetes (T2D), low-density lipoprotein cholesterol (LDL-C), triglycerides, apolipoprotein B (ApoB), high-density lipoprotein cholesterol (HDL-C), and apolipoprotein A-I (ApoA-I). To minimize population stratification bias, we exclusively or predominantly utilized genome-wide association studies (GWASs) involving European ancestry participants. All original studies referenced in this work obtained informed consent and institutional ethics approval from their respective participant populations. A completed STROBE-MR checklist is provided as Supplementary Material to confirm adherence to the reporting guidelines.

GWAS data for exposure

We identified six life course body size traits: birthweight, childhood BMI, adult BMI, WC, WHR and BFP. The specific databases employed for each phenotype in this study are comprehensively detailed in Table 1. Notably, the data of the birthweight were collected from variable sources (measurements at birth, survey, obstetric records, parent-report and etc.) and the GWAS database for birthweight was derived from a mixed-ancestry population, and only data from its European ancestry participants were utilized [20]. As for childhood BMI also collected from multiple sources, it was informed by a meta-analysis of

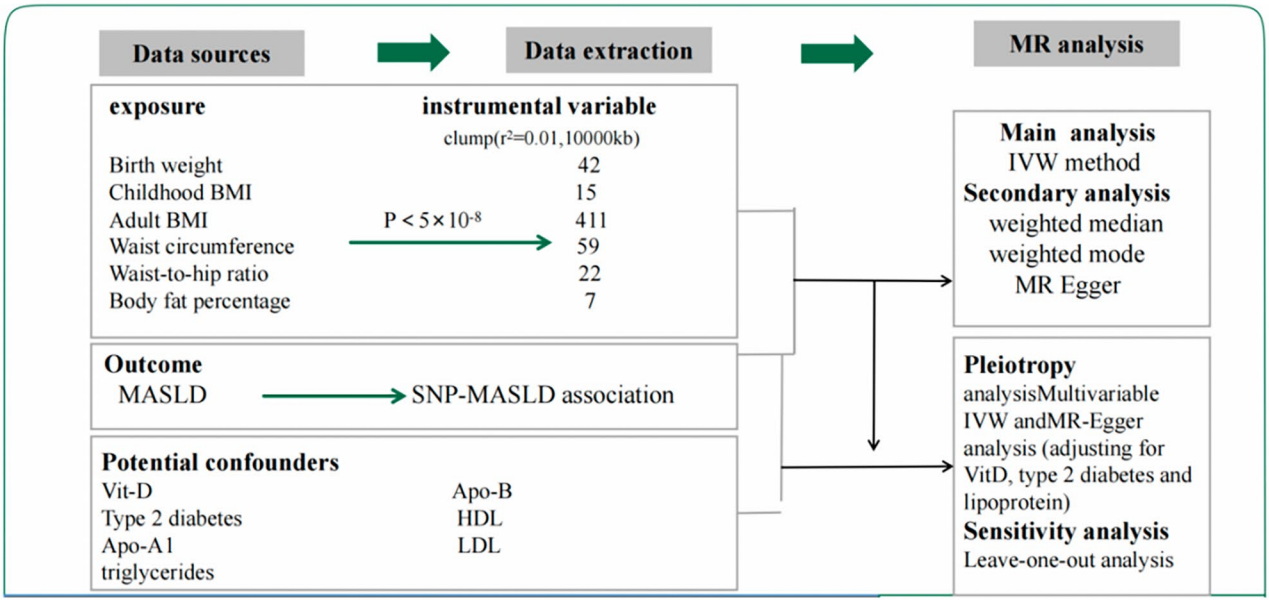

Fig. 1 The overview design of the present study
MR, Mendelian randomization. IVW, inverse-variance weighted. SNP, single nucleotide polymorphism

Table 1 GWAS data sources of the MR study

	Consortium	Sample Size	Population	PMID	Year of Publication Author
Exposures					
birthweight	NA	143,677	European	27,680,694	2016 Horikoshi M
Childhood BMI	NA	39,620	European	33,045,005	2020 Vogelezang s
Adult BMI	GIANT	681,275	European	30,124,842	2018 Yengo, L
BFP	NA	65,831	European	26,833,246	2016 Yingchang Lu
T2D	DIAGRAM	74,124/824,006	European	30,297,969	2018 Mahajan
Vitamin D	NA	79,366	European	29,343,764	2018 Jiang X
WHR	GIANT	212,244	European	25,673,412	2015 Shungin D
WC	GIANT	231,353	European	25,673,412	2015 Shungin D
LDL-C	UKB	440,546	European	32,203,549	2020 Richardson, T
ApoB	UKB	439,214	European	32,203,549	2020 Richardson, T
ApoA-1	UKB	393,193	European	32,203,549	2020 Richardson, T
HDL-C	UKB	403,943	European	32,203,549	2020 Richardson, T
Triglycerides	UKB	441,016	European	32,203,549	2020 Richardson, T
Outcome					
MASLD	eMERGE, UKB, FinnGen, Estonian Biobank	8434/770,180	European	34,841,290	2021 Ghodsian N

BMI: body mass index; BFP: body fat percentage; T2DM: type 2 diabetes mellitus; WHR: waist-to-hip ratio; WC: waist circumference; LDL-C: low-density lipoprotein cholesterol;

ApoB: apolipoprotein B; ApoA-I: apolipoprotein A-I; HDL-C: high-density lipoprotein cholesterol; MASLD: metabolic dysfunction-associated steatotic liver disease; UKB: UK Biobank; eMERGE: electronic Medical Records and Genomics

26 studies encompassing European children aged 2 to 10 years, in which the childhood BMI was collected at the latest time point (i.e., of the oldest age between 2 and 10 years) if multiple measurements were available [21]. The GWAS data for adult BMI were sourced from the Genetic Investigation of Anthropometric Traits (GIANT) consortium studies, which predominantly comprised individuals of European ancestry, with 64.3% of single nucleotide polymorphisms (SNPs) identified from the UK Biobank (UKB) [22]. The data on adult WC and WHR were obtained from a comprehensive meta-analysis of GIANT consortium studies [23]. Similarly, the GWAS data for BFP instruments were identified through a meta-analysis involving individuals of European ancestry [24]. In addition to these body size traits, GWAS data for vitamin D were secured from a meta-analysis primarily representing individuals of European ancestry [25], and data on type 2 diabetes (T2D) were procured from the DIAGRAM consortium, which specifically focused on individuals of European ancestry [26]. Furthermore, the GWAS data

pertaining to lipoprotein lipid traits, including LDL-C, triglycerides, ApoB, HDL-C and ApoA-I, were meticulously curated from the UKB [27]. The genetic variants associated with each trait were considered as IVs in this study.

GWAS data for outcome

The genetic associations with MASLD were discerned through a genome-wide meta-analysis conducted across four European cohorts [28]. The MASLD status of the enrolled patients was derived by the clinical comprehensive diagnosis from electronic health records codes [ICD9/ICD10] or diagnostic phrases, primarily sourced from Electronic Medical Records and Genomics (eMERGE), UKB, FinnGen, and Estonian Biobank. The GWAS data used in this analysis were retrieved from the GWAS Catalog under accession number GCST90091033.

Instrumental variable selection

The selection of SNPs was pivotal in ensuring the validity of the Mendelian randomization (MR) analysis. SNPs with genome-wide significance ($p<5\times10^{-8}$) were systematically extracted from the corresponding GWAS databases. Subsequently, a clumping procedure was applied to identify independent genetic variants with a linkage disequilibrium threshold of $r^2<0.01$ within a 10,000 kb window. Furthermore, efforts were made to harmonize the effects of SNPs on exposure, ensuring that β values were consistently aligned with the same alleles. Palindromic SNPs with incompatible alleles were thoughtfully removed, thus enabling MR analysis to proceed with SNPs that met these stringent criteria [29].

Statistical analyses

Univariable MR analyses

The primary MR analysis was conducted using the inverse variance weighted (IVW) method, which aggregates Wald ratio estimates of the causal effect for each SNP, assuming the validity of all selected SNPs [30]. To enhance the robustness of our conclusions, additional analytical approaches were implemented: the MR-Egger, weighted median, and weighted model procedures. In cases where Cochran's Q test revealed significant heterogeneity, a random effects model was applied [31]. The MR-Egger method was instrumental in estimating the intercept term as a pleiotropic indicator, which, in turn, was used to identify and rectify potential directional pleiotropic bias [32]. The weighted median method selected the MR median estimate as the causal estimate, signifying a consistent estimate if more than 50% of the weights during analysis were derived from valid IVs [33]. To assess the power of our analysis, a power calculation was performed using an online tool (http://cnsgenomics.com/shiny/mRnd/). Moreover, the simple mode and weighted mode methods clustered SNPs according to the similarity of causal effects and estimated causal effects based on the largest SNP cluster [34]. The strength of the instrumental variables was gauged through the calculation of the F statistic, testing the strength of the association between instrumental variables and their corresponding exposures. The F statistic was computed using the formula: $F=\beta^2_{exposure}/SE^2_{exposure}$ [35].

Multivariable MR analysis

Multivariable MR (MVMR) represented an extension of univariable MR [36]. This analysis was underpinned by robust evidence of strong genetic associations between various stages of life course body size and MASLD. In this endeavor, we selected significant SNPs ($P<5\times10^{-8}$) from the relevant GWAS databases and integrated them with the existing IVs. After diligent curation, which included the removal of duplicate and palindromic SNPs, we obtained the effect size of each SNP and its corresponding standard error based on exposure and results. Within the framework of MVMR, the weighted linear regression-based IVW method was employed to infer causal effects [37].

Pleiotropy and sensitivity analysis

The MR-Egger regression provided insight into the average pleiotropic effect of all IVs through the assessment of the intercept. A notably different intercept from zero, as determined by the MR-Egger test, signified the presence of pleiotropy [38]. To complement this analysis, asymmetry was also scrutinized as an indicator of horizontal pleiotropy through funnel plot visualization [39]. The MR pleiotropy residual sum and outlier (MR-PRESSO) tests were instrumental in identifying and rectifying outliers in IVW linear regression [32]. To ensure the reliability and consistency of our findings, a leave-one-out analysis was performed for each SNP [39]. For the MR analysis, we leveraged the "Two-sample MR version 0.5.7" software application. Additionally, forest plots were generated using the "ggplot2" software package. To mitigate the issue of multiple comparisons, we employed the Bonferroni method in the primary analysis, with a significance threshold set at $P<0.008$ (0.05/6=0.008). All statistical analyses were executed using R version 4.3.1.

Resutls

Univariable MR analyses

Detailed information regarding the instrumental variables used for exposure is available in the supplementary material. Specifically, 42 SNPs were associated with birthweight, 15 SNPs with childhood BMI, 411 SNPs with adult BMI, 59 SNPs with WC, 22 SNPs with WHR, and 7 SNPs with BFP (supplementary Table S1). Importantly, all instrumental variables displayed F-statistic

values exceeding the threshold of 10 (see supplementary Table S1). Univariate MR analysis unveiled a significant Bonferroni-corrected causal relationship between genetically determined body size traits and MASLD. In particular, birthweight (OR_{IVW} = 0.61, 95%CI, 0.52–0.74, $P=2.0\times10^{-7}$), childhood BMI (OR_{IVW} = 1.37, 95%CI, 1.12–1.64, $P=1.6\times10^{-3}$), adult BMI (OR_{IVW} = 1.41, 95%CI, 1.27–1.57, $P=9.2\times10^{-11}$), and WHR (OR_{IVW} = 1.66, 95%CI, 1.21–2.23, $P=2.0\times10^{-3}$) were found to have a harmful effect. However, no causal relationship was observed between BFP (OR_{IVW} = 1.06, 95%CI, 0.69–1.63, $P=7.8\times10^{-1}$), and WC (OR_{IVW} = 1.15, 95%CI, 0.92–1.44, $P=2.1\times10^{-1}$) and MASLD development (Fig. 2). Sensitivity analysis confirmed the reliability of IVW results, and MR-Egger test showed no evidence of pleiotropy (Supplementary Table S2). Following the identification and removal of outlier SNPs by MR-PRESSO (Supplementary Table S3), a leave-one-out analysis was conducted, and no single SNP was found to drive these results (Supplementary Figure S1-S6).

Multivariable MR analyses

Within the context of multivariable MR (MVMR) analysis, the direct causal relationship between birthweight and MASLD remained significant after controlling for T2D (OR=0.46, 95%CI, 0.29–0.74, $P=1.29\times10^{-3}$) and vitamin D (OR=0.61, 95%CI, 0.51–0.73, $P=2.45\times10^{-8}$). However, when adjusting for lipoprotein lipid traits (Triglyceride: OR=0.71, 95%CI, 0.53–0.94, $P=1.78\times10^{-2}$, LDL-C: OR=0.73, 95%CI, 0.56–0.97, $P=2.73\times10^{-2}$, HDL-C: OR=0.70, 95%CI, 0.52–0.94, $P=1.80\times10^{-2}$, ApoB: OR=0.71, 95%CI, 0.55–0.92, $P=1.08\times10^{-2}$, ApoA-1: OR=0.67, 95%CI, 0.46–0.97, $P=3.27\times10^{-2}$) the direct causal relationship disappeared. Furthermore, another model, incorporating childhood BMI and adult BMI, reaffirmed the significant causal effect of birthweight on MASLD (OR=0.68, 95%CI, 0.54–0.86, $P=1.21\times10^{-3}$). Notably, childhood BMI demonstrated a direct causal link to MASLD, remaining significant after adjusting for vitamin D (OR=1.38, 95%CI, 1.14–1.65, $P=7.12\times10^{-4}$) and LDL-C (OR=1.35, 95%CI, 1.13–1.61, $P=8.92\times10^{-4}$).

However, this relationship weakened when T2D (OR=1.16, 95%CI, 0.85–1.58, $P=0.339$) and other lipid levels were considered (HDL-C: OR=1.09, 95%CI, 0.90–1.32, $P=0.378$, triglyceride: OR=1.10, 95%CI, 0.90–1.33, $P=3.54\times10^{-1}$, apoA-1: OR=1.19, 95%CI, 0.94–1.50, $P=0.16$, apoB: OR=1.24, 95%CI, 1.01–1.52, $P=3.55\times10^{-2}$). Additionally, when considering birthweight and adult BMI, the direct causal effect of childhood BMI on MASLD diminished (OR=0.99, 95%CI, 0.85–1.16, $P=9.34\times10^{-1}$). Finally, the direct causal association between adult BMI and MASLD remained robust even after adjustments for several factors (HDL-C: OR=1.41, 95%CI, 1.22–1.63, $P=2.90\times10^{-6}$, LDL-C: OR=1.55, 95%CI, 1.36–1.76, $P=1.23\times10^{-11}$, triglyceride: OR=1.45, 95%CI, 1.26–1.67, $P=3.43\times10^{-7}$, apoA-1: OR=1.43, 95%CI, 1.22–1.69, $P=1.57\times10^{-5}$, apoB: OR=1.60, 95%CI, 1.40–1.82, $P=2.70\times10^{-12}$, T2D: OR=1.57, 95%CI, 1.23–2.00, $P=2.90\times10^{-4}$, vitamin D: OR=1.60, 95%CI, 1.43–1.79, $P=6.66\times10^{-16}$)). In another model after accounting for birthweight and childhood BMI the direct causal effect of adult BMI on MASLD remained significant (OR=1.67, 95%CI, 1.41 to 1.97, $P=1.68\times10^{-9}$), show in Fig. 3 (Supplementary Table S4).

Discussion

This was the first MR study to disentangle the genetically predicted effects of body size on MASLD risk over various stages of life. The study findings demonstrated a causal relationship between life course body size and MASLD. Lower birthweight and duration of obesity were identified as risk factors for MASLD development. Importantly, birthweight and adult BMI were determined

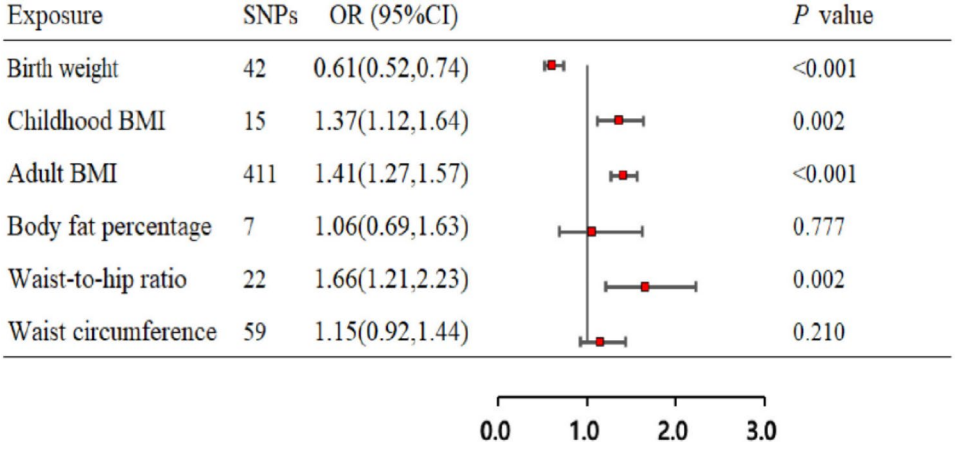

Fig. 2 Univariable MR estimates for the causal Effect of body size traits on MASLD
CI: confidence interval; MR: mendelian randomization; OR: odds ratio; BMI: body mass index; SNPs: single nucleotide polymorphisms

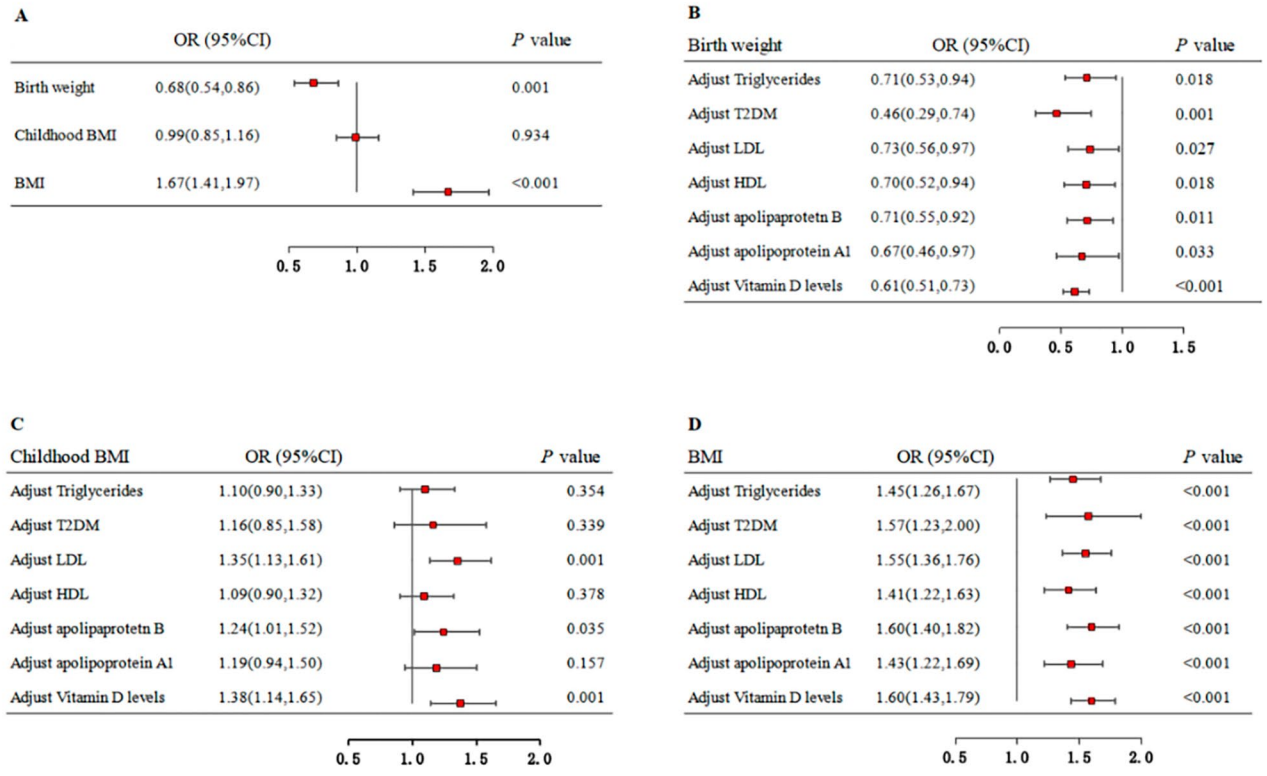

Fig. 3 MVMR results of body size traits on risk of MASLD
(**a**) MVMR results of birthweight, childhood BMI and adult BMI on risk of MASLD
(**b**) Effect of birthweight on MASLD adjusting for vitamin D, T2D and lipoprotein lipid
(**c**) Effect of childhood BMI on MASLD adjusting for vitamin D, T2D and lipoprotein lipid
(**d**) Effect of adult BMI on MASLD adjusting for vitamin D, T2D and lipoprotein lipid
T2DM: type 2 diabetes mellitus; BMI: body mass index; WC: waist circumference; WHR: waist-to-hip ratio; BFP: body fat percentage; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; ApoA-I: apolipoprotein A-I; ApoB: apolipoprotein B

to have direct influences on MASLD development, whereas the direct effect of childhood BMI on MASLD diminished. The findings underscore the importance of monitoring intrauterine fetal development to ensure normal birthweight and reduce the incidence of MASLD. Moreover, we emphasize the significance of early prevention and lifelong treatment of obesity to mitigate the risk of MASLD in adulthood.

The fetus' nutritional environment may result in epigenetic modifications and changes in insulin signaling pathways, thereby disrupting the metabolic system and leading to the development of certain diseases in adulthood, particularly T2D and cardiovascular diseases [40, 41]. Existing observational studies have shown inconsistent results in the relationship between birthweight and MASLD due to differences in diagnostic criteria and confounding variables. Previous studies have shown that both high and low birthweight are risk factors for MASLD. Notably, in the United States, a study encompassing 538 children diagnosed with MASLD through biopsy displayed a notably higher prevalence of low birthweight [42]. Conversely, a cohort study involving white adolescents revealed no significant correlation between birthweight and ultrasonographically diagnosed MASLD [43]. The discrepancy could stem from divergent emphases on the influence of birth weight, which may be skewed by either undernourishment or overnutrition, on the development of MASLD, coupled with the variance in diagnostic techniques employed for MASLD. Leveraging Mendelian randomization (MR) methodologies to minimize potential confounding, recent MR studies have underscored the adverse impact of low birthweight on the prevalence of MASLD, independent of childhood and adult BMI, aligning with the findings of our study. This research has pointed to branched-chain amino acid metabolism as a potential marker of insulin resistance [44]. However, deeper exploration is warranted to comprehensively understand the intricate metabolic associations between birthweight and the development of MASLD.

Gaining insight into the contribution of childhood BMI to the risk of MASLD is challenging, particularly

when birthweight and adult BMI are considered as confounders. Multiple prospective studies have found an association between childhood adiposity and MASLD in late adolescence and maturity, but the results have been inconsistent [43, 45, 46]. After 23 years of follow-up, recent study revealed that adolescents who were identified as overweight or obese between the ages of 6 and 18 were more likely to develop MASLD as adults, but this association can be diminished after adjustment for adult BMI [47]. This is consistent with our study. In the MVMR analysis, the direct effect of childhood BMI on MASLD was generally attenuated by birthweight and adult BMI. Previous research suggests that the duration of childhood overweight or adiposity is a major determinant in the occurrence of adult metabolic outcomes [45–47]. Adiposity in children, frequently persists into adulthood and is difficult to reverse once diagnosed.

Obesity is a well-established risk factor for MASLD in adults. Even among metabolically healthy obese individuals (MHO), prior research has demonstrated the causal role of adiposity in the onset of MASLD [48]. Within our MVMR analysis, we observed that birthweight and childhood BMI were not responsible for the genetic prediction of adult BMI on MASLD risk. This finding further underscores the direct and independent effect of adult BMI on MASLD. Insulin resistance is likely to play a pivotal role in the association between obesity and MASLD. As obesity worsens and insulin resistance intensifies, insulin's ability to inhibit lipolysis diminishes, resulting in an increase in circulating free fatty acids, which are subsequently absorbed and stored by the liver [9]. Simultaneously, there is growing interest in exploring the role of adipose tissue dysfunction and abnormal fat distribution in obese individuals [49].

In the course of this study, we compared the genetic effects of birthweight, childhood BMI, and adult BMI on MASLD to provide a comprehensive assessment of the impact of weight characteristics across individuals' lifespans. Our findings underscore the importance of low birthweight and duration of obesity in the development of MASLD. However, several limitations warrant consideration. Firstly, the datasets pertaining to birthweight, adult BMI, lipoprotein traits, and MASLD were partially derived from the UKB, and some data sources may have overlapped. Precisely estimating the extent of sample overlap presents challenges. To address this, we assessed the F statistic, which confirmed that overlapping samples did not weaken the instrumental variables, as all F statistics exceeded the threshold of 10. Secondly, the birthweight data were restricted to the normal range of 2200–4500 g. Future research should investigate the effects of being underweight or overweight at birth. Thirdly, given that the majority of participants in our MR study were of European descent, our findings should be cautiously extended to other ethnic groups where potential biases may exist.

Conclusion

In summary, this MR study has unraveled distinct causal effects of birthweight, childhood BMI, and adult BMI on the development of MASLD. The relationship between birthweight and duration of obesity and MASLD has been controversial or unclear in previous studies, but the study provides the evidence that lower birthweight and duration of obesity are independent risk factors for MASLD. These findings underscore the importance of interventions that focus on ensuring normal fetal development and early prevention of obesity to reduce the incidence of MASLD in adulthood. Our study provides valuable insights into the intricate interplay between life course body size and MASLD, emphasizing the need for a multifaceted approach to address this burgeoning public health concern.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-024-03383-9.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions

Q.H, L.D. and M.L. conceptualized the research hypothesis and supervised the research process. X.H. undertook data analysis and contributed to the manuscript's composition. S.L, L.N. and Y.G. were responsible for data access and extraction. J.Y. and H.Q. interpreted and verified the results of the analysis. All authors collectively endorsed the final version of the manuscript.

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Data availability

The datasets are available in the MRC Integrative Epidemiology Unit (IEU, https://gwas.mrcieu.ac.uk). Please refer to the supplementary materials for additional data related to this study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Endocrinology and Metabolism, Tianjin Medical University Genaral Hospital, 154 Anshan Road, Heping District, 300052 Tianjin, Tianjin, China

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