Original research

Parental obesity and risk of metabolic dysfunction associated steatotic liver disease in adult offspring: UK birth cohort study

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ABSTRACT

Background Metabolic dysfunction associated steatotic liver disease (MASLD), the most common chronic liver disease globally, may originate early in life. While maternal obesity is linked to offspring MASLD, the roles of paternal obesity and mediation by childhood adiposity remain unclear.

Objectives This study evaluates prospective associations between pre-pregnancy biparental adiposity and offspring MASLD in adulthood.

Design We included 1933 offspring from the UK Avon Longitudinal Study of Parents and Children (ALSPAC) to assess the associations between parental pre-pregnancy body mass index (BMI) and odds of offspring MASLD at age 24 years. MASLD was defined as hepatic steatosis on transient elastography and ≥1 cardiometabolic risk factors. We evaluated causal mediation by childhood adiposity measures.

Results At age 24 years, 10.4% of offspring had MASLD. Pre-pregnancy maternal and paternal obesity were independently associated with an increased odds of offspring MASLD. Each 1 kg/m^2 increase in maternal BMI increased the odds of MASLD by 10% (Odds Ratio [OR] 1.10, 95% CI 1.06 to 1.14), while each 1 kg/m^2 increase in paternal BMI raised the odds by 9% (OR 1.09, 95% CI 1.04 to 1.13). Biparental overweight or obesity was associated with 3.73 times the odds of offspring MASLD (OR 3.73, 95% CI 2.43 to 5.73) compared with parents with a normal BMI, with 67% of this association mediated by cumulative excess childhood BMI, a defined area under the curve for BMI Z score >1 for ages 7–17 years.

Conclusions Excess parental adiposity pre-pregnancy was associated with a higher odds of offspring MASLD, mediated by cumulative excess childhood BMI, highlighting the potential of life course interventions to reduce the risk of MASLD in future generations.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Early life exposures may critically shape the risk of metabolic dysfunction associated steatotic liver disease (MASLD), the most common chronic liver disease worldwide.
⇒ Animal models suggest a transgenerational predisposition to hepatic steatosis in offspring of parents with obesity.
⇒ While population based cohort studies underscore the importance of maternal obesity for offspring MASLD risk, the role of paternal obesity and the potential mediating role of childhood adiposity remain unclear.

WHAT THIS STUDY ADDS

⇒ Using data from a prospective UK birth cohort with over two decades of follow-up, we assessed the independent and joint associations of maternal and paternal obesity pre-pregnancy with offspring MASLD in adulthood.
⇒ Elevations in both maternal and paternal adiposity were associated with increasing odds of MASLD in offspring.
⇒ Offspring with two parents who had overweight or obesity before pregnancy had 3.73 times the odds of MASLD, largely mediated by cumulative excess childhood body mass index (BMI).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings highlight a developmental risk of MASLD associated with biparental obesity and partly mediated by cumulative excess childhood BMI, suggesting a potential of life course interventions aimed at reducing the risk of MASLD later in life and for future generations.

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INTRODUCTION

Metabolic dysfunction associated steatotic liver disease (MASLD), formerly termed non-alcoholic fatty liver disease (NAFLD),[1] is estimated to affect 15% of children and >30% of adults globally.[2–4] MASLD is a spectrum of diseases with a subset having a more fibroinflammatory phenotype associated with cirrhosis and hepatocellular carcinoma and is a rapidly increasing indication for liver transplantation in adults.[5] The new classification of MASLD requires the coexistence of hepatic steatosis and cardiometabolic risk factors,[1] which may help in identifying younger individuals at greater risk of metabolic dysfunction associated morbidity and mortality throughout the lifespan[6] and facilitate the possibility for earlier public health interventions. Rising obesity rates[7] and the increasing

prevalence of MASLD across all age groups, combined with the lack of approved preventive therapies, have prompted research into whether modifiable developmental factors, such as parental obesity, drive the risk of disease.

As the prevalence of obesity continues to increase among younger generations[7] and in those of reproductive age, the influence of biparental obesity on the risk of offspring MASLD should be investigated. Epidemiological studies have revealed an association between maternal obesity[8 9] and risk of offspring MASLD.[10 11] Previous work using murine models has implicated maternal obesity[12] in the programming of offspring metabolism[13 14] and predisposition for MASLD development, driven by an early life diet and modulation of the gut microbiome composition.[15 16] Paternal obesity has also been implicated in offspring metabolic function, possibly through epigenetic changes transmitted by sperm at conception.[17] While observational studies have also demonstrated independent associations between paternal obesity and offspring obesity,[18] how paternal obesity influences offspring susceptibility to MASLD is less understood. Further, it is not known whether excess adiposity among offspring in childhood causally mediates[19] the association between developmental exposures to parental obesity and MASLD risk. A deeper understanding of such biological processes and mediators could provide insight and open new avenues for early detection and timely interventions to mitigate the later burden of MASLD in adulthood.

Here we studied the association between maternal and paternal body mass index (BMI) before pregnancy and the odds of MASLD development in their young adult offspring, accounting for developmental and early life factors using prospective longitudinal data from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort. We further examined how offspring growth and weight status measures causally mediate these associations throughout childhood and adolescence.

METHODS

Study design and population

ALSPAC is a prospective birth cohort study from the University of Bristol, UK, ultimately including 15 447 pregnancies (expected delivery 1 April 1991 to 31 December 1992)[20] of which 14 901 offspring were alive at 1 year.[21] Offspring follow-up clinics were conducted approximately every 2 years from ages 7–17 years and at age 24 years (Focus@24) for repeated anthropometric, biological and lifestyle assessments[20 22] (figure 1).

A total of 4019 ALSPAC offspring attended Focus@24 (5 June 2015 to 31 October 2017). The study website contains details of all of the available data through a fully searchable data dictionary and variable search tool (http://www.bristol.ac.uk/alspac/researchers/our-data). Our study included offspring from singleton pregnancies with valid assessments of liver steatosis and fibrosis via transient elastography (TE). We excluded those with missing cardiometabolic data, missing parental pre-pregnancy height and weight data, or with parental pre-pregnancy BMI <18.5 kg/m^2. We also excluded participants with alcohol use above MetALD (spectrum of steatotic liver disease with overlap of metabolic dysfunction and alcohol related liver disease) thresholds[1] (derived average alcohol consumption >17.5 units/week for women and >26 units/week for men; figure 1). The characteristics of included and excluded offspring with valid assessments for determination of MASLD are presented in online supplemental table 1.

Ascertainment of offspring MASLD at age 24 years

The primary outcome, offspring MASLD at age 24 years, was defined as hepatic steatosis and presence of ≥1 cardiometabolic risk factor.[1] TE (FibroScan Echosens 502 Touch) measured controlled attenuated parameter (CAP) score and stiffness (kPa).[23] Hepatic steatosis was defined as a CAP score ≥275 dB/m, corresponding to ≥5% steatosis.[24] Valid assessments required 10 readings for reliability, CAP score of 100–400 dB/m and IQR/median ratio of <30%.[25] The M probe was used on all participants unless the machine prompted for use of the XL probe.[9] All Focus@24 participants were required to fast for at least 6 hours before TE and phlebotomy for lipid profile and blood glucose.[26 27] Height, weight, waist circumference and seated blood pressure measurements were collected. BMI was calculated as weight in kilograms divided by height in square metres. Cardiometabolic risk factors were defined as an elevated BMI (≥25 kg/m^2) or waist circumference (women >80 cm, men >94 cm); elevated fasting glucose levels (>5.6 mmol/L) or known diabetes (based on questionnaire report of taking metformin or insulin); hypertension (blood pressure >130/85 mm Hg); elevated triglycerides (>1.7 mmol/L); and/or low high density lipoprotein (women HDL <1.3 mmol/L, men HDL <1 mmol/L).[2]

Assessment of parental adiposity before pregnancy

Mothers and fathers received regular questionnaires on health and lifestyle throughout pregnancy and postpartum. Our primary exposure was self-reported parental anthropometrics before pregnancy: height, weight and calculated BMI.[22 28] We also included waist circumference in secondary analyses.

Assessment of covariates

For both parents, age at delivery, smoking during the first 3 months of pregnancy, pre-pregnancy typical alcohol consumption (drinks/week), employment status (full time, part time or unemployed) and highest education attainment were assessed. Mothers also reported whether they had ever been diagnosed with diabetes mellitus or hypertension at the time of study enrolment. Mothers completed a questionnaire assessment on physical activity during pregnancy from which a weighted activity score (MET hours/week) was previously derived[29] by multiplying the reported hours per week of activity with published average metabolic equivalent (MET) scores for leisure time physical activities.[30]

For offspring, sex, mode of delivery (caesarean section or vaginal birth), gestational age and birth weight were abstracted from clinical records and questionnaires. We also included data on antibiotics exposure within the first 6 months of life and breastfeeding duration based on questionnaires completed by mothers at 6 and 15 months postpartum. Additional offspring variables abstracted from Focus@24 clinic questionnaires included smoking (current, former or never) and alcohol consumption. We derived average weekly alcohol consumption in units/week by calculating the average number of days per week the participant reported drinking over the preceding year multiplied by the reported typical number of units of alcohol consumed in a day when drinking. To capture socioeconomic status, offspring postcodes at age 24 years were used to derive the Townsend deprivation scores coded in quintiles to preserve participant privacy according to the ALSPAC policy, with higher quintiles indicating lower socioeconomic status.[31]

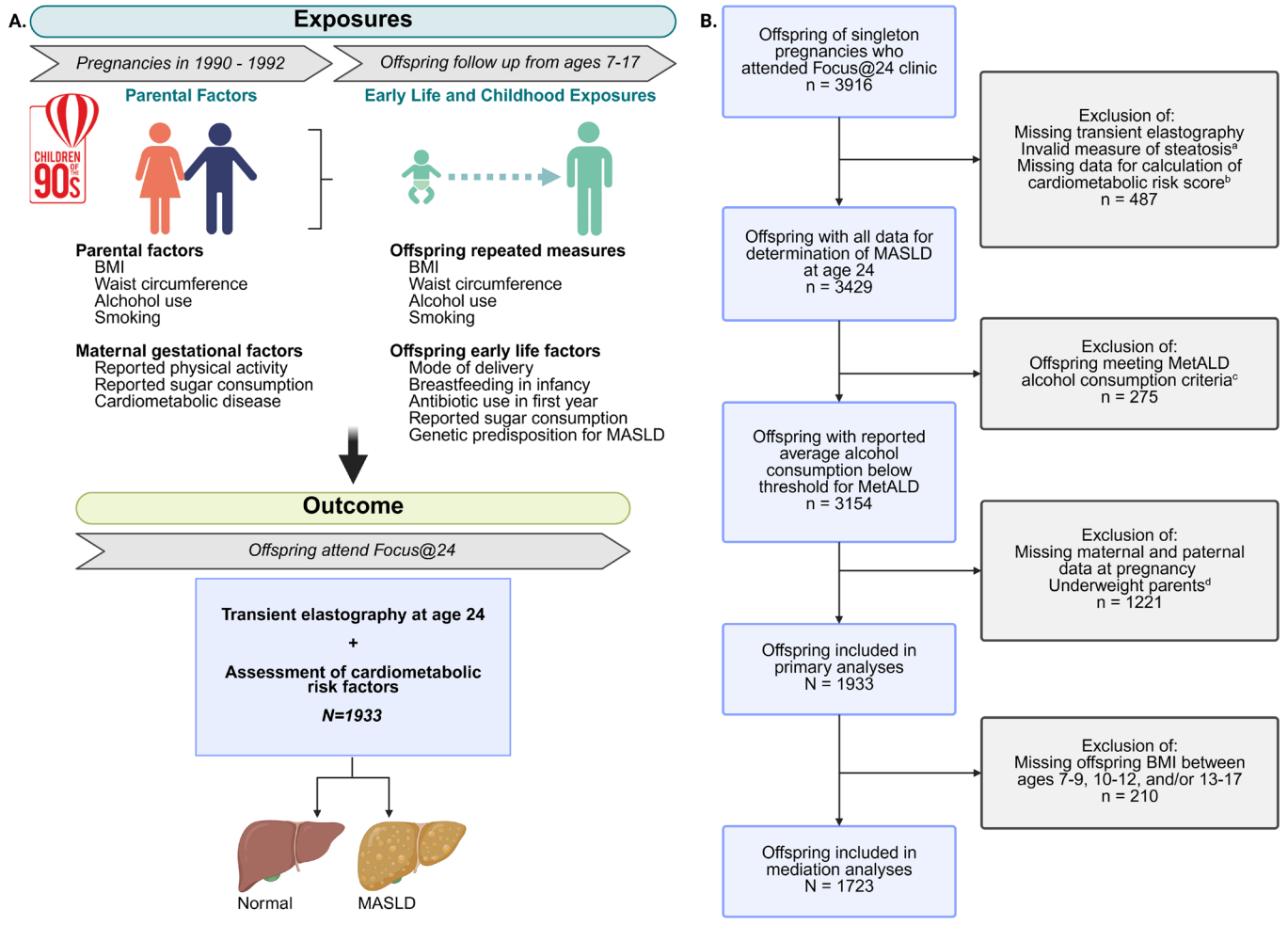

Figure 1 (A) Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort data were used to investigate the association of parental factors and early life exposures on the odds of offspring metabolic dysfunction associated steatotic liver disease (MASLD) at age 24 years. Parental exposures assessed by questionnaires during pregnancy, 1990–92. Offspring were then followed up in research clinics from ages 7 to 17 years, and at 24 years. Offspring MASLD was determined at the follow-up clinic at age 24 years (Focus@24). (B) Flowchart of study inclusion and exclusion criteria. [a]We excluded those with a median (IQR) ratio >30%, a standard cut-off for validity of transient elastography. [b]Cardiometabolic risk was calculated based on MASLD criteria. [c]MetALD thresholds of alcohol use are 140–350 g/week or 17.5–44 units/week for women and 210–420 g/week or 26–52 units/week for men. We excluded participants based on average alcohol consumption in units/week derived from self-reported questionnaires at age 24 years. [d]Defined as body mass index (BMI) <18.5. MetALD, spectrum of steatotic liver disease with overlap of metabolic dysfunction and alcohol related liver disease.

Assessment of offspring childhood adiposity exposures

We leveraged longitudinal assessment of height and weight at ages 7–9, 10–12 and 13–17 years to derive age specific BMI Z scores, based on the 1990 British Growth Reference Charts.[32] We then derived two variables to characterise longitudinal childhood adiposity exposures for ages 7–17 years: BMI trajectory and cumulative excess childhood BMI. For BMI trajectory, BMI Z scores were modelled as a cubic spline of age and grouped into four distinct trajectories using latent class growth mixture models[33] and the lcmm package[34] (online supplemental figure 1). The number of trajectory clusters was determined by the bayesian information criterion. To account for the duration and intensity of excess adiposity, cumulative excess childhood BMI was calculated as the area under the curve for BMI Z scores >1 for ages 7–17 years. This area under the curve is a composite BMI-year measure of cumulative excess childhood BMI.[35 36] A BMI Z score >1 aligns with defined paediatric risk factor criteria for BMI and MASLD.[1]

Secondary analyses of additional parental and offspring exposures

We assessed maternal and offspring dietary patterns, focusing specifically on sugar intake based on previous literature.[37] Mothers completed validated food frequency questionnaires[38] at 32 weeks' gestation from which an average daily sugar intake (g/day) was derived.[39] Offspring dietary assessments were completed at ages 7 and 13 years using 3 day diet diaries[40] from which average daily sugar intake (g/day) was derived.

We additionally examined offspring genetic variants associated with a risk of MASLD using 1000G imputed genome wide data for the cohort, which had been previously collected and described.[41] Following previous work,[42] we selected three single nucleotide polymorphisms: rs738409 (*PNPLA3*), rs58542926 (*TM6SF2*) and rs13130041 (*HSD17B13*), which were used as a proxy for rs72613567, $r^2=0.95$, because rs72613567 was not available in the ALSPAC genotype data. Genotype data were obtained from the 1000 Genomes imputed dataset and analysed

as allele dosages (range 0–2), representing the expected number of effect alleles per individual.

Statistical analysis

For descriptive statistics according to offspring MASLD status at age 24 years, we used mean (SD) and median (IQR) values where appropriate. Logistic regression models were used to estimate the associations between pre-pregnancy maternal and paternal BMI and odds of offspring MASLD by calculating ORs and 95% CIs. Parental BMI was analysed both categorically (normal 18.5–24.9, overweight 25.0–29.9 and obese ≥30.0 kg/m^2) and continuously per 1 kg/m^2 and per SD. To characterise the dose–response relationship between parental BMI and odds of offspring MASLD, we fitted restricted cubic spline models with three knots positioned at the 10th, 50th and 90th percentiles of the parental BMI, using a BMI of 25 kg/m^2 as the reference value. Tests for non-linearity were performed by comparing models with and without the non-linear spline terms. Parental BMI categories were paired for each pregnancy to examine how biparental overweight and obesity jointly affected the odds of MASLD in their offspring.

Multivariable models were adjusted for offspring characteristics including sex (female or male), smoking status (current, former or never) and average alcohol consumption at age 24 years (units/week), Townsend deprivation score at age 24 years (quintile) as well as parental factors, including parental age at delivery, parental smoking status (current within first 3 months of pregnancy, former or never) and maternal history of diabetes mellitus. We used multiple imputation[43] to impute the missing covariates. Specifically, covariates including offspring sex, offspring smoking status at age 24 years, offspring alcohol intake at age 24 years, offspring Townsend deprivation score at age 24 years, offspring breastfeeding exposure, offspring sugar intake at ages 7 and 13 years, parental age at offspring delivery, parental pre-pregnancy BMI, parental pre-pregnancy waist circumference, parental smoking status in first 3 months of pregnancy, maternal sugar intake at 32 weeks' gestation and maternal history of diabetes mellitus were jointly imputed 10 times and the multivariable regression results were combined by Rubin's rule.

We performed sensitivity analyses to assess the association between pre-pregnancy parental waist circumference (cm) and offspring MASLD, assessing waist circumference categorically (normal vs elevated; elevated defined as >80 cm for mothers and >94 cm for fathers) and continuously per 5 cm. In secondary analyses, we assessed for potential confounding through the addition of offspring sugar intake at ages 7 and 13 years, and maternal sugar intake at 32 weeks' gestation in multivariable models. A secondary genetic sensitivity multivariable analysis was completed to account for known single nucleotide polymorphisms associated with fatty liver disease[44] (*PNPLA3* rs738409, *TM6SF2* rs58542926 and *HSD17B13* rs13130041). We additionally performed a sensitivity analysis to assess selection bias based on exclusion criteria by applying multiple imputation for missing parental BMI data.

We investigated whether the pattern of BMI change (childhood BMI trajectory) and cumulative excess BMI from ages 7 to 17 years causally mediated the association between biparental BMI and offspring MASLD, after adjusting for several confounders. A causal mediation analysis estimated two effects: a direct effect and an indirect effect. For our analysis, the direct effect estimated the impact of biparental BMI on the odds of offspring MASLD without any changes in the mediators, childhood BMI trajectory and childhood cumulative excess BMI. The indirect effect estimated the impact on offspring MASLD odds that occurred through changes in the mediators while keeping the biparental BMI constant. We performed causal mediation using an imputation method to estimate direct and indirect effects in multiple regression models with robust standard errors obtained using the sandwich estimator.[45–47] These estimates were derived from previously collected data and combined through Rubin's rule.[45] We determined the proportion of the overall effect that was due to indirect effects of the mediators, childhood BMI trajectory and childhood cumulative excess BMI. All mediation analyses were conducted using the R package medflex (V.0.6–10).[46]

Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Bristol.[48] Analyses were performed using R (V.4.4.0) and all statistical tests were two sided with p values <0.05 considered statistically significant. Figures were created using GraphPad Prism (V.10.1.2) and BioRender.

Patient and public involvement

No patients or members of the public were directly involved in the design, conduct, reporting and dissemination plans of this study. There are patients and members of the public who sit on an advisory committee which meets regularly to provide advice, guidance and feedback for the general ALSPAC study.

RESULTS

A total of 1933 offspring were included in the study; 201 had MASLD and 1732 had a normal liver at age 24 years (figure 1 and table 1). Overall, the prevalence of offspring MASLD was 10.4% and all cases were also defined as NAFLD (ie, presence of hepatic steatosis on TE; online supplemental table 2). At age 24 years, compared with those without MASLD, offspring with MASLD were more likely to be male, had a greater BMI and a lower Townsend deprivation score (table 1). In addition, both maternal and paternal anthropometric measures were larger, parental smoking was more common and parental education levels were lower for offspring with MASLD versus those without MASLD. Current drinking among offspring, smoking, early life factors, childhood sugar consumption as well as other parental factors were similar (table 1 and online supplemental table 3). Offspring at age 24 years have not previously been reported to have identified cases of viral hepatitis or use of antiviral medications,[9] and the use of obesogenic and hepatotoxic medications was rare among both cases and controls (online supplemental table 3).

Parental adiposity status before pregnancy and offspring MASLD risk

We evaluated the association between pre-pregnancy maternal and paternal BMI and odds of MASLD among their offspring at age 24 years (table 2). Both pre-pregnancy maternal and paternal excess adiposity were associated with an increased odds of MASLD among their adult offspring. Maternal pre-pregnancy overweight status (OR 1.79, 95% CI 1.22 to 2.62) and obese status (OR 2.97, 95% CI 1.72 to 5.12) were associated with increasing odds of offspring MASLD. Paternal overweight status (OR 1.53, 95% CI 1.11 to 2.10) and obese status (OR 1.71, 95% CI 1.00 to 2.93) were also associated with increased odds of offspring MASLD. For each 1 kg/m^2 increase in maternal BMI, the odds of development of offspring MASLD increased by 10% (OR 1.10, 95% CI 1.06 to 1.14; p_{trend}<0.001). For each 1 kg/m^2 increase in paternal BMI, the odds of development

Table 1 Characteristics of offspring, mothers and fathers stratified by metabolic dysfunction associated steatotic liver disease (MASLD) in offspring at age 24 years

	Normal liver (n=1732)	MASLD (n=201)
Offspring characteristics at age 24 years		
Women (n (%))	1072 (62)	87 (43)
BMI (kg/m^2)	23.9 (3.93)	31.8 (5.57)
Current smoker (n (%))	255 (15)	30 (15)
Missing (n (%))	208 (12)	17 (9)
Alcohol consumption (units/week)*	5.3 (4.6)	5.3 (4.9)
Missing (n (%))	100 (6)	23 (11)
Townsend deprivation score, quintiles (n (%))		
1 (lowest)	553 (32)	62 (31)
2	246 (14)	39 (19)
3	290 (17)	45 (22)
4	326 (19)	35 (17)
5 (highest)	274 (16)	16 (8)
Missing (n (%))	43 (3)	<5 (<2)
Offspring early life factors		
Birth weight (g) (median (IQR))	3458 (3120–3760)	3500 (3200–3800)
Estimated gestational age (weeks)	39.5 (1.7)	39.6 (1.7)
Vaginal birth (n (%))	1507 (87)	174 (87)
Breastfed for at least 6 months (n (%))	751 (43)	92 (46)
Exposed to antibiotics in first 6 months (n (%))	1182 (68)	128 (64)
Maternal characteristics around pregnancy		
Age (years)	29.7 (4.35)	28.9 (4.29)
Pre-pregnancy BMI (kg/m^2)	22.6 (3.18)	24.2 (4.20)
Waist circumference (cm) (median (IQR))	66.0 (63.5–71.1)	68.6 (66.0–73.7)
Missing (n (%))	507 (29)	76 (38)
Maternal history of diabetes mellitus (n (%))	12 (0.7)	7 (3.5)
Missing (n (%))	<5 (<1)	<5 (<2)
Current smoker (n (%))†	188 (11.9)	52 (14.9)
Missing (n (%))	15 (1)	<5 (<2)
Pregnancy physical activity score (MET hours/week) (median (IQR))	15.9 (4.0–25.9)	15.2 (2.9–24.4)
Missing (n (%))	96 (6)	19 (10)
Employed full time (n (%))	679 (43.1)	154 (44.0)
Some college education or degree (n (%))	356 (22.6)	65 (18.6)
Ethnicity (n (%))		
White	1679 (97)	195 (97)
Black	13 (0.8)	<5 (<2)
South Asian	<5 (<1)	<5 (<2)
Chinese	<5 (<1)	<5 (<2)
Other	13 (0.8)	<5 (<2)
Paternal characteristics around pregnancy		
Age (years)	31.5 (5.33)	30.7 (5.14)
BMI (kg/m^2)	24.9 (3.03)	26.0 (3.75)
Waist circumference (cm) (median (IQR))	83.8 (81.3–86.4)	86.4 (81.3–91.4)
Missing (n (%))	132 (8)	17 (9)
Current smoker (n (%))†	303 (19.3)	90 (25.7)
Missing (n (%))	106 (6)	13 (7)
Employed full time (n (%))	1409 (89.5)	312 (89.1)
Some college education or degree (n (%))	485 (30.8)	72 (20.6)
Ethnicity (n (%))		
White	1677 (97)	197 (98)
Black	11 (0.7)	<5 (<2)
South Asian	<5 (<1)	<5 (<2)
Chinese	<5 (<1)	<5 (<2)
Other	14 (0.8)	<5 (<2)

Values are mean (SD) unless otherwise indicated.
*Average derived by self-reported frequency of alcohol consumption and number of units of alcohol consumed on a typical day when drinking over the past 1 year.
†As of 18 weeks' gestation.
BMI, body mass index; MET, metabolic equivalent of task.

of offspring MASLD increased by 9% (OR 1.09, 95% CI 1.04 to 1.13; $p_{trend}<0.001$). Multivariable restricted cubic splines demonstrated a significant linear dosage response relationship for both maternal and paternal BMI ($p_{linear}<0.001$ for maternal BMI and $p_{linear}<0.001$ for paternal BMI) and offspring odds of MASLD at age 24 years (online supplemental figure 2).

As sensitivity analyses, we assessed the association between maternal and paternal pre-pregnancy waist circumference and odds of offspring MASLD. For every 5 cm increase in pre-pregnancy maternal waist circumference, we observed an association with higher odds of offspring MASLD (OR 1.13, 95% CI 1.03 to 1.24; p_{trend} 0.013). We observed a similar independent association between increasing paternal waist circumference and increased odds of offspring MASLD (OR 1.27, 95% CI 1.14 to 1.41; $p_{trend}<0.001$) (online supplemental table 4).

When considering the relationship between pre-pregnancy adiposity of parent pairs and their offspring, offspring of parent pairs with overweight or obesity had 3.73 times the odds of MASLD at age 24 years (OR 3.73, 95% CI 2.43 to 5.73; figure 2) compared with offspring of both parents with a normal BMI. We also performed a sex stratified analysis and observed no strong sexual dimorphism in the association between biparental overweight or obesity and odds of offspring MASLD (figure 2).

Causal mediation by offspring childhood adiposity

We performed causal mediation analyses to investigate whether the positive association between biparental overweight or obesity and odds of offspring MASLD was mediated by childhood adiposity exposures, as indicated by (1) childhood BMI trajectories and (2) childhood cumulative excess BMI across ages 7–17 years (online supplemental table 5). In our analysis, the direct effect estimates the association between biparental adiposity and odds of offspring MASLD independent of offspring childhood adiposity exposures. The indirect effect estimates the impact on the odds of offspring MASLD caused by changes in the offspring childhood adiposity exposures when biparental adiposity is held constant. Childhood BMI trajectory accounted for 9% of the total observed effect of the association between biparental overweight or obesity and increased odds of offspring MASLD (indirect effect OR 1.22, 95% CI 1.09 to 1.36; direct effect OR 2.75, 95% CI 1.73 to 4.38; table 3). In contrast, childhood cumulative excess BMI mediated substantially more of the association, contributing to 67% of the total effect (indirect effect OR 2.60, 95% CI 2.02 to 3.36; direct effect OR 1.30, 95% CI 0.76 to 2.22; table 3).

Secondary analyses

We additionally adjusted for maternal and offspring sugar consumption and genetic predispositions associated with fatty liver disease (PNPLA3 rs738409, TM6SF2 rs58542926 and HSD17B13 rs13130041). The observed association between biparental overweight or obesity and increased odds of offspring MASLD was similar (OR 3.90, 95% CI 2.43 to 6.25; online supplemental table 6).

We further conducted a sensitivity analysis applying multiple imputation for missing parental BMI data to assess whether selection bias and attrition drive our findings (online supplemental table 7). This expanded cohort included 3031 offspring with imputed parental BMI. For offspring born to parents who had both overweight and obesity versus parents with a normal BMI, the odds of MASLD was 3.70 (95% CI 2.58 to 5.29) in the expanded cohort compared with 3.73 (95% CI 2.43 to 5.73) in the primary analysis restricted to offspring with complete

Table 2 Association between parental adiposity before pregnancy and offspring metabolic dysfunction associated steatotic liver disease (MASLD) at age 24 years

	Parental adiposity					
	Normal*	Overweight*	Obese*	BMI per 1 kg/m^2	BMI per SD†	p_{trend}‡
Maternal						
No of cases/non-cases	134/1432	44/235	23/65			
Unadjusted OR (95% CI)	1 (reference)	2.00 (1.39–2.89)	3.78 (2.28–6.28)	1.12 (1.08–1.16)	1.48 (1.32–1.67)	<0.001
Adjusted OR (95% CI)§	1 (reference)	1.79 (1.22–2.62)	2.97 (1.72–5.12)	1.10 (1.06–1.14)	1.39 (1.23–1.58)	<0.001
Paternal						
No of cases/ non-cases	86/966	92/654	23/112			
Unadjusted OR (95% CI)	1 (reference)	1.58 (1.16–2.15)	2.31 (1.40–3.80)	1.10 (1.06–1.15)	1.37 (1.21–1.56)	<0.001
Adjusted OR (95% CI)§	1 (reference)	1.53 (1.11–2.10)	1.71 (1.00–2.93)	1.09 (1.04–1.13)	1.31 (1.14–1.49)	<0.001

*BMI categories were defined as: normal=18.5–24.9 kg/m^2, overweight=25–29.9 kg/m^2, obese ≥30 kg/m^2.
†SD defined as 3.44 for maternal BMI and 3.20 for paternal BMI.
‡p_{trend} was calculated using BMI as a continuous variable.
§Multivariable models were adjusted for offspring sex, offspring smoking status at age 24 years, offspring average alcohol consumption at age 24 years (units/week), offspring Townsend deprivation score (quintile) at age 24 years, maternal history of diabetes mellitus, parental ages at delivery, parental smoking status during pregnancy, with maternal BMI analyses additionally adjusted for paternal BMI, and paternal BMI analyses additionally adjusted for maternal BMI.
BMI, body mass index.

parental BMI (n=1933). These consistent results suggest that selection bias did not substantially influence our findings.

DISCUSSION

Our prospective birth cohort analyses showed independent associations between pre-pregnancy maternal and paternal obesity and increased odds of MASLD in adult offspring, accounting for several covariates throughout the life course. The odds of offspring MASLD development more than tripled when both parents had overweight or obesity before pregnancy compared with offspring of parents with a normal BMI. Importantly, childhood cumulative excess adiposity causally mediated 67% of the association between biparental overweight or obesity and offspring MASLD. Our findings highlight biparental obesity as an emerging developmental risk factor for MASLD in offspring, mainly mediated by the accumulation of excess adiposity during childhood. These associations remained robust in secondary analyses accounting for maternal and offspring sugar consumption and offspring genetic predisposition for fatty liver disease.

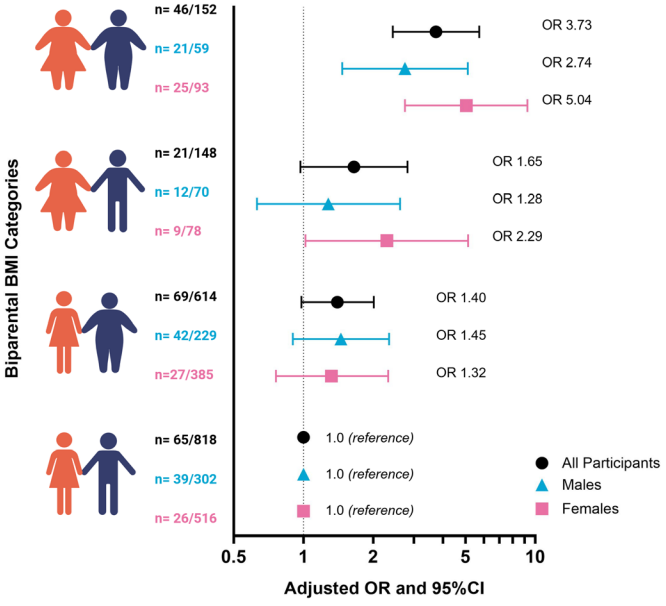

Figure 2 Adjusted ORs (95% CIs) for categories of biparental body mass index (BMI) and the odds of offspring metabolic dysfunction associated steatotic liver disease (MASLD) at age 24 years. Numbers of offspring cases/non-cases are reported next to each parent pair category. Table 2 lists the variables adjusted in the model.

To our knowledge, this is among the first studies to apply the current case definition of MASLD and examine biparental anthropometrics before pregnancy in relation to adult offspring MASLD risk in a large birth cohort. The MASLD definition requires evidence of metabolic dysfunction in addition to hepatic steatosis, offering a clinically relevant classification that is not exclusion based like the former NAFLD criteria. While previous studies focused mainly on maternal obesity and the link to NAFLD or hepatic steatosis,[8 10 49–51] little is known on the independent impact of paternal obesity and joint influence of biparental obesity, of which the burden is increasing globally among men and women of reproductive age.[7] In a study of the Raine cohort in Australia, Ayonrinde *et al* assessed the relationship between parental anthropometrics and offspring hepatic steatosis, finding a positive association between maternal pre-pregnancy obesity and steatosis in female offspring only.[52] Differences between our findings and those from the Raine cohort likely reflect their use of a potentially less objective ultrasound measure of steatosis, younger age at liver assessment and lower steatosis prevalence among men, highlighting the strength of our study in capturing clinically relevant MASLD among adult offspring using TE for assessment of steatosis.

Our work has extended previous analyses by Abeysekera *et al* that similarly used the ALSPAC cohort to assess associations between maternal obesity and offspring hepatic steatosis at age 24 years.[49] Using a negative parental control model, the authors described similar independent associations between maternal and paternal BMI and offspring NAFLD risk, with an emphasis on the association of maternal obesity. In our study, we further contextualised the relationship between excess parental adiposity and offspring MASLD risk by assessing paired parental BMI, illustrating a notably heightened odds of offspring MASLD when both parents had overweight or obesity before pregnancy. These results lend support to an early life influence of biparental obesity on offspring metabolic health,[53] suggesting efforts to mitigate excess adiposity of both mothers and fathers before

Table 3 Causal mediation analyses for pre-pregnancy biparental adiposity with risk of offspring metabolic dysfunction associated steatotic liver disease (MASLD) at age 24 years, according to offspring childhood adiposity exposures

	Biparental adiposity *			
	Mother and father with normal BMI	Mother with normal BMI and father with overweight or obesity	Mother with overweight or obesity and father with normal BMI	Mother and father with overweight or obesity
Childhood BMI trajectory†				
Direct effect (OR (95% CI))‡	1 (reference)	1.22 (0.84 to 1.79)	1.65 (0.95 to 2.86)	2.75 (1.73 to 4.38)
Indirect effect (OR (95% CI))§	1 (reference)	1.10 (1.03 to 1.18)	1.08 (0.96 to 1.21)	1.22 (1.09 to 1.36)
% Total effect mediated	—	30	10	9
Childhood cumulative excess BMI†¶				
Direct effect (OR (95% CI))‡	1 (reference)	1.17 (0.83 to 1.66)	1.16 (0.67 to 2.01)	1.30 (0.76 to 2.22)
Indirect effect (OR (95% CI))§	1 (reference)	1.14 (1.02 to 1.26)	1.53 (1.21 to 1.92)	2.60 (2.02 to 3.36)
% Total effect mediated	—	41	69	67

*Normal BMI was defined as 18.5–24.9 kg/m^2 and overweight or obesity as ≥25 kg/m^2.
†Multivariable models were adjusted for offspring sex, offspring smoking status at age 24 years, offspring average alcohol consumption at age 24 years (units/week), offspring Townsend deprivation score (quintile) at age 24 years, maternal history of diabetes mellitus, parental ages at delivery, and parental smoking status during pregnancy.
‡Direct effect is an estimate of the portion of the total effect that still occurs if there is no response in the mediator with changes in the exposure; this is the direct effect of biparental adiposity on the odds of offspring MASLD.
§Indirect effect is an estimate of the portion of the total effect that still occurs if the exposure remains constant with changes in the mediator; this is the indirect effect of offspring childhood adiposity exposures in the causal pathway between biparental adiposity and the odds of offspring MASLD.
¶Childhood cumulative excess BMI was derived as an area under the curve composite of offspring BMI Z score >1 through childhood (7–17 years).
BMI, body mass index.

conceiving may confer longitudinal benefits to the metabolic outcomes of their future offspring.

The mechanisms underlying the influence of parental obesity on the risk of hepatic steatosis in offspring are incompletely elucidated, and previous preclinical models have implicated both maternal factors on the gestational environment and paternal and maternal characteristics associated with epigenetic changes. Murine models of maternal obesity show that maternal nutrition during gestation can prime offspring hepatic metabolism and function via epigenetic mechanisms, increasing the risk of offspring steatosis and fibrosis in response to post-weaning obesogenic diet exposure.[13] Soderborg *et al* illustrated how differences between the early infant gut microbiomes of offspring born to mothers with and without obesity may have causal roles in offspring MASLD risk in a preclinical model, finding increased periportal inflammation, impaired immune function and excessive weight gain with exposure to a western style diet among mice with maternal obesity associated dysbiosis.[16] Maternal and paternal exposure to an obesogenic diet was independently shown to influence offspring hepatic mass, steatosis and triacylglycerol content, with more severe findings among offspring of parent pairs with obesity.[53] Paternal and maternal metabolic syndrome models have been shown to jointly downregulate offspring hepatocyte neuronal regeneration related protein through epigenetic reprogramming, altering hepatic lipid metabolism and insulin resistance.[14]

There is more limited understanding of mechanisms of paternal obesity influencing offspring metabolic outcomes. Previous work has shown histone modification and DNA methylation alterations in response to paternal obesity and obesogenic diets,[54] which are transmitted through sperm and associated with altered gene expression in the placenta, embryo and later metabolic dysfunction in offspring.[55 56] In a rat model of a paternal obesogenic diet, only female offspring of male rats exposed to an unhealthy diet showed altered hepatic expression of the genes *Ppara*, *Lcn2* and *Tmcc2* attributed to changes in DNA methylation and leading to a phenotypic expression of impaired glucose tolerance.[57] Future studies are necessary to better characterise mechanisms of intergenerational risks of MASLD in response to maternal and paternal factors.

We comprehensively evaluated the mediating role of childhood adiposity exposures in the association between parental obesity and offspring MASLD risk. While previous research has shown that including offspring BMI in regression models attenuates the relationship between maternal obesity and offspring hepatic steatosis[10 58] and childhood adiposity is associated with NAFLD risk, formal causal mediation analyses leveraging longitudinal offspring adiposity measurement are limited.[59 60] We leveraged repeated measures of BMI and a causal mediation analytical framework to better contextualise the relationship between biparental obesity and odds of offspring MASLD. We found that higher cumulative excess childhood BMI mediated a substantial portion of the increased odds of MASLD associated with biparental obesity. If validated, this suggests two critical windows in need of further investigation as potential modifiers for generational MASLD risk: pre-gestationally among future parents and early in childhood for individuals with excess adiposity. Our findings highlight the potential of life course interventions aimed at reducing the risk of MASLD later in life and for future generations. However, a deeper understanding of the influence of behavioural and social factors, as well as their interplay with genetic, epigenetic and dysbiosis mechanisms, is critically needed for the design of feasible and scalable interventions.

Our study had multiple strengths, including the use of a large, thoroughly phenotyped birth cohort of offspring followed for more than 20 years with available prospectively collected parental data from pregnancy and repeated clinical, biological and behavioural measures throughout childhood. We applied the current case definition for MASLD, which determines steatosis based on TE, applying validated cut-off values derived from adults with histologically proven liver disease.[23 24] We also used a causal mediation framework to contextualise the generational MASLD risk, finding that much of the association between biparental obesity and odds of offspring MASLD was mediated by cumulative excess childhood BMI.

We recognise several study limitations. Parental anthropometric measures pre-pregnancy were self-reported; however, previous work from this cohort showed a high correlation between maternal reported weight and clinical measurements at the first prenatal visit.[51] Further, data were lacking to assess parental MASLD status, paternal comorbidities at the time of pregnancy and offspring physical inactivity in early adulthood. Growth parameters before age 7 years were not available for all offspring, limiting our ability to assess the mediation role of very early childhood weight gain[61 62]; however, we leveraged all repeated measurements obtained throughout childhood and adolescence to capture cumulative excess BMI for offspring. Importantly, validation in prospective and more diverse cohorts is needed to further explore relationships between parental adiposity, genetic risk, epigenetic changes and socio-environmental exposures.[63]

CONCLUSIONS

In this large prospective birth cohort study, we identified and quantified the independent associations between maternal and paternal pre-pregnancy adiposity and the odds of offspring MASLD. We found that not only maternal but also paternal obesity increased the risk of offspring MASLD. Although the mechanisms behind this association are complex, our study suggests a window where early intervention on excess adiposity may decrease the burden of MASLD among future generations. Further studies are needed to explore whether the risk of offspring MASLD may be mitigated by parental weight loss, in the context of genetic, epigenetic and environmental factors.

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Ethics approval This study involves human participants. Ethical approval for the study was obtained from the Avon Longitudinal Study of Parents and Children (ALSPAC) Ethics and Law Committee and the local research ethics committees. Precise details on specific ethics approvals are available on the study website (http://www.bristol.ac.uk/alspac/researchers/research-ethics/). All work was conducted in accordance with the Declaration of Helsinki and the Declaration of Istanbul. Informed consent was collected for the use of biological samples following the Human Tissue Act (2004), and for the use of data collected from questionnaires and clinics following the recommendations of the ALSPAC Ethics and Law Committee at the time. The study was exempt from review by the institutional review board at Washington University, St Louis. Participants gave informed consent to participate in the study before taking part.

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