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Maternal Macronutrient Intake at Pregnancy and Offspring Growth Trajectory through Childhood: A Prospective Analysis in the Growing Up Today Study 2 Cohort

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Abstract

Background—Childhood obesity has become a public health challenge globally. Existing studies have indicated a potential link between maternal dietary macronutrient compositions and subsequent weight changes in their offspring during early childhood, although few studies have been conducted through early adulthood.

Objective—We aim to investigate the relationship between maternal macronutrient intake before or during pregnancy and offspring body weight from late childhood till early adulthood.

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Disclaimers

The authors declare that they have no conflicts of interest related to this study.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Methods—We included 5,715 children from the Growing Up Today Study 2 (GUTS2; mean 11.8 years old at baseline in 2004) born to 4,731 mothers who participated in the Nurses' Health Study II (NHSII) during 1989-1995. Diet during or before pregnancy was assessed using a validated food frequency questionnaire (FFQ) in 1991 and 1995. Age- and sex-specific body mass index (BMI) were used to define overweight and obesity in childhood and adolescence. Multivariable linear and log-binomial regression models with generalized estimating equations were used to evaluate the associations of interest.

Results—The mean (SD) maternal macronutrients percent energy intake during pregnancy were 19.3% (3.1) for protein, 51.2% (6.6) for carbohydrates, and 30.8% (5.0) for total fat. For diet during pregnancy, after multivariate adjustment for maternal and offspring risk factors, compared with the lowest quartile, the highest quartile of *trans* fatty acid consumption was associated with a 0.20 unit (95% CI: 0.00, 0.40) increase in BMI z-score without a significant linear trend (P-trend = 0.06). A positive association with BMI z-score was also observed for total fat intake (β : 0.21; 95% CI: 0.05, 0.36; P-trend = 0.02) when replacing total carbohydrate, and vice versa (β : -0.24; 95% CI: -0.40, -0.08; P-trend = 0.02 for total carbohydrate intake). For diet before pregnancy, none of the macronutrients were associated with offspring BMI z-score or the risk of overweight or obesity.

Conclusions—Higher fat, especially *trans* fat intake, during pregnancy was positively associated with higher body weight among offspring. Other macronutrients from various food sources were not associated with the offspring weight. Overall, these data suggest that, apart from *trans* fatty acids, other macronutrient composition of maternal diet may have minimal impact on offspring body weight in this well-nourished population.

Keywords

macronutrient; *trans* fatty acid; pregnancy; childhood obesity; prospective cohort study

Introduction

Childhood obesity has become a public health challenge globally, with increasing prevalence in the US[1]. Compared with normal weight, overweight or obesity during childhood and adolescence increases the risk of adverse cardiometabolic outcomes, including elevated blood pressure, dyslipidemia and insulin resistance before adulthood[2]. Childhood overweight or obesity is also strongly associated with adverse health outcomes in adulthood, contributing to the development of cardiovascular disease[3,4], metabolic syndrome[5,6] and cancer[7]. Preventive strategies are essential in addressing the rising incidence of childhood overweight and obesity, thereby mitigating the long-term chronic disease outcomes.

Growing evidence has indicated a potential link between maternal diet during pregnancy and subsequent weight changes in their offspring during childhood[8-10]. Observational studies have explored the association between maternal macronutrient intake and offspring body composition, and the results were inconsistent. Some studies showed that higher animal protein, sugar and saturated fatty acids intake during pregnancy was associated with increased adiposity during early childhood through age 6[11,12], while others reported no or inverse associations [9,13]. No research has yet been conducted to explore maternal

intake of macronutrients and by various food sources in relation to long-term weight gain of offspring through early adulthood.

To fill this knowledge gap, we investigated prospective associations between maternal macronutrient intake, including macronutrients from various food sources during peri-pregnancy period and body mass index (BMI) z-score in offspring from middle-childhood into early adulthood. We hypothesized that animal proteins, refined carbohydrates, and saturated and *trans* fats are associated with higher body weight, whereas the opposite associations exist for plant proteins, whole grain carbohydrates, and *cis* unsaturated fats. We also examined the risk of developing childhood overweight and obesity as a secondary outcome.

Method

Design and study population

In 1989, 116,430 registered female nurses aged 25 to 42 years, were enrolled into the Nurses' Health Study II (NHSII) through returning a questionnaire assessing medical history, lifestyle, etc [14]. Similar, biennial questionnaires were administered to update participants' characteristics. In 1991 and every four years thereafter, diet was assessed in the NHSII by a validated food frequency questionnaire (FFQ) [15,16].

In 2004, 17,280 children of NHSII female participants between the ages of 8 and 15 (year of birth in 1989-1996) were invited to participate in the Growing Up Today Study 2 (GUTS2) study. Of these, baseline questionnaires were completed for 10,918 children in 2004, and follow-up questionnaires were administered in 2006, 2008 and 2011. Since there were no offspring BMI or BMI z-score data in the GUTS2 2013 cycle, the end of follow-up was set to be 2011 in this study. For the current analysis, we examined the association of NHSII mothers' macronutrients intake before and during pregnancy with offspring body weight outcomes trajectory, respectively. The inclusion and exclusion criteria for participants before and during pregnancy were presented in Supplementary Figures 1-2. Finally, the "during-pregnancy analysis" included 2,868 mothers and 3,049 children, while the "pre-pregnancy analysis" included 2,697 mothers and 2,903 children. The sample size for this study was determined based on the availability of data within the study period. Of note, since the current analyses were restricted to participants largely free of chronic diseases at baseline, the findings from the current study may not be generalized to populations with the diseases. The baseline characteristics for participants during and before pregnancy were shown in Table 1 and Supplementary Table 1, respectively.

NHSII and GUTS2 studies were approved by the Human Subjects Committee of the Harvard T.H. Chan School of Public Health, and the Institutional Review Board of Brigham and Women's Hospital. Return of the NHSII and GUTS2 questionnaires implied informed consent.

Assessment of macronutrients intake during peri-pregnancy period

The assessment of maternal macronutrient intake during peri-pregnancy period was conducted with a validated semiquantitative FFQ. This FFQ, administered in 1991 and 1995,

collected detailed information on the frequency and portion sizes of over 130 different food items consumed in the preceding year. Nutrient intakes were then calculated by multiplying the frequency of each food item consumption by its nutrient content, and the nutritional contributions from all items were summed to provide an overall intake assessment [15-17]. The amount of macronutrient intake was computed by multiplying the relative frequency that each food item consumed by the macronutrient content of the specific portion size, using United States Department of Agriculture and Harvard University Food Composition Database[18,19]. We computed the percentage of energy intake from each macronutrient by multiplying the amount of the macronutrient (grams) by its energy content per gram (calories/gram), and then dividing this by the total energy intake (calories) reported in the FFQ. We further derived participants' intake of total protein, animal protein, vegetable protein, dairy protein, total carbohydrate, carbohydrate from whole grains, carbohydrate from refined grains, total fat, saturated fatty acids (SFA), monounsaturated fatty acids (MUFA), *trans* fatty acids (TFA), and polyunsaturated fatty acids (PUFA).

Determination of diet during versus before pregnancy

To align the dietary assessments with the pregnancy at issue, we used FFQ return date and the child's date of birth to determine whether the diet was relevant to the period before pregnancy or during pregnancy. Specifically, we subtracted 38 weeks or roughly 9.5 months, from the offspring's birth date to determine the date of conception. We subtracted the FFQ return date by 12 months to determine the beginning of the time window of dietary reporting. If the conception date occurred after the start of the dietary assessment and the child's birthday fell after the FFQ was returned, the dietary assessment was considered to include the early stage of pregnancy. Conversely, if conception occurred after the start of the dietary assessment but the birthday preceded the FFQ return, the dietary assessment reflected the full pregnancy period. Finally, if conception occurred before the dietary assessment began, but the birthday was after this start date and before the FFQ return, then the assessment was viewed as capturing the latter part of pregnancy. Details are shown in Supplementary Figure 3. To determine diet before pregnancy, if the conception date was after the 1991 FFQ return date and before the diet start date of 1995 FFQ, and the children's birthday was between the 1991 and 1995 return dates, we used 1991 FFQ for diet before pregnancy. If the conception date and children's birthday were both after 1995 FFQ return date, we used 1995 FFQ for diet before pregnancy.

Assessment of maternal and offspring covariates

Data on maternal covariates and risk factors for childhood obesity were obtained from the NHSII biennial questionnaires in 1989, 1991, 1993 and 1995[19], and 2009 NHSII pregnancy[20] questionnaires, and included: age at delivery, race/ethnicity, spouse educational attainment, BMI before pregnancy, alcohol intake before pregnancy (0 g/day, 0-5 g/day, 5-15 g/day, >15 g/day), smoking status (never smoke, past smoker, current smoker), physical activity (0-9 MET- hours/week, 9-27 MET hours/week, >27 MET hours/week), parity (0, 1, 2, 3, 4+ children, missing), pregnancy complications (gestational diabetes mellitus, pre-eclampsia, gestational hypertension, cesarean delivery), and diet quality as assessed by the Alternative Healthy Eating Index (AHEI) score. The categorization of smoking, alcohol intake, and parity was consistent with approaches

commonly used in previous studies [10,21,22]. The physical activity levels were categorized into tertiles of MET-hours per week. Data on offspring covariates were obtained from the 2004 GUTS2 baseline questionnaire and included sex, birth weight, gestational age, and cumulative average AHEI score during follow-up. These covariates were considered because they are important maternal predictors of childhood body weight status and may also correlate with mothers' dietary preferences.

Assessment of offspring overweight/obesity

BMI of offspring was computed as self-reported weight (kg) divided by self-reported height (m^2). Self-reported weight and height have been shown to be reasonably accurate in children and adolescents, as described in previous studies [23,24]. We computed BMI z-scores by using the Centers for Disease Control (CDC) growth charts, as described previously[25]. Multiple imputation was performed to impute missing BMI data in the GUTS2 cohort using the SAS PROC MI procedure and five imputation datasets were generated using the same imputation method[22]. The predictor variables included the offspring's valid body mass index assessments at baseline and during follow-up, as well as age and sex. Validity of the imputations has been demonstrated previously, and the measured and imputed BMI values were strongly correlated[22]. Overweight and obesity status in childhood and adolescence (<18 years), as a secondary outcome, was defined using age- and sex- specific BMI thresholds described by the International Obesity Task Force[26].

Statistical analysis

We used data from GUTS2 questionnaires from 2004 through 2011. In the current study, offspring were followed up from return of the 2004 GUTS2 questionnaire to the end of follow-up in 2011. To evaluate the association between maternal macronutrients intake before and during pregnancy and offspring BMI z-scores trajectory, multivariable linear regression models with generalized estimating equations (GEE) were used to compute mean BMI z-score change and its 95% confidence intervals (95% CIs). The GEE approach, utilizing an unstructured correlation matrix, accounted for the pattern of dependence between repeated BMI z-scores measured from the same child. The models also accounted for the clustering of offspring from the same mother. Multivariable log-binomial regression models with GEE were used to examine the relationship between maternal macronutrients intake and the risk of offspring overweight or obesity during follow-up, with the specification of an exchangeable correlation structure. We also examined interaction terms between each macronutrient and time scale, which was modeled as 1 to 4 to represent the four time points of outcome measurements. Since the interaction terms were not significant, we subsequently focused on the regression coefficients of macronutrient terms, which reflected the impact of macronutrient intake on the overall, long-term trajectory of offspring weight.

The multivariable linear and log-binomial regression were adjusted for maternal age at delivery, offspring age, offspring sex, pregnancy complications (gestational diabetes, preeclampsia, gestational hypertension, cesarean delivery), maternal race, maternal AHEI score, maternal physical activity, highest level of education completed by spouse, gestational age of offspring, parity, maternal alcohol intake, and maternal smoking status. In addition,

each macronutrient model was mutually adjusted for other macronutrients and maternal total caloric energy intake. Median values of each macronutrient intake category were modeled as a continuous variable to examine the linear trend.

We built isocaloric models so that the regression coefficient of a macronutrient represents the association of substituting the macronutrient for another macronutrient. For example, when we evaluated total protein intake in relation to the BMI z score, we considered total energy intake and total carbohydrate intake but left total fat intake out of the model so that the coefficient of total protein reflected the association of substituting total protein for the same energy from fat intake. Similarly, we used isocaloric substitution models to assess the impact on offspring BMI z-score trajectories when substituting MUFA from plants for MUFA from animals, vegetable protein for animal protein, PUFA for SFA, and carbohydrates from whole grains for carbohydrates from refined grains. The selection of reference macronutrients for the substitution models was based on practical and clinically relevant considerations. For the analysis of birthweight, we used the isocaloric multivariable generalized linear model to assess the association between each macronutrient and offspring birthweight change. In a sensitivity analysis, based on the multivariable models described above, we further adjusted for offspring cumulative average AHEI score during follow-up to describe the relationship between maternal macronutrients during pregnancy and offspring BMI z-score trajectory. Several secondary analyses were performed to assess the robustness of our primary findings. Stratified analyses were based on maternal weight status before pregnancy (lean ($<25\text{kg/m}^2$); overweight or obese ($\geq 25\text{kg/m}^2$)) and offspring sex (male/female).

All analyses were performed separately in the five imputation datasets, and results were aggregated using the SAS PROC MIANALYZE procedure to derive composite estimates of associations and their 95% CIs. Statistical analyses were performed with the use of SAS version 9 for UNIX (SAS Institute Inc, Cary, NC) and R version 3.5.2. All statistical tests were 2-sided and significance was defined as $P < 0.05$.

Results

Baseline characteristics of the 3049 offspring and their 2868 mothers considered for the analysis of associations of diet during pregnancy were described in Table 1. Participants were on average 32.4 years old at the delivery, largely lean before pregnancy (68.0% BMI < 25), and mostly never smoked (67.8%) before pregnancy. More female participants were overweight or obese before pregnancy if their total protein and fat intake were in the highest quartile (21.1% for total protein; 19.6% for total fat) during pregnancy. More individuals smoked in the group with the lowest quartile of energy intake from total carbohydrate compared to the highest quartile (29.9% compared with 21.1%). The offspring population included more female offspring (52.8%) than male. The mean (SD) maternal macronutrients percent energy intake during pregnancy were 19.3% (3.1) for protein, 51.2% (6.6) for carbohydrates, and 30.8% (5.0) for total fat. (Table 1).

Table 2 shows the association between maternal macronutrients intake during pregnancy and offspring BMI z-score trajectory during childhood till adulthood. In the multivariable

analysis, in substitution of carbohydrate intake, comparing to the lowest quartile, the highest quartile of *trans* fatty acid consumption during pregnancy was associated with a 0.20 unit (95% CI: 0.00, 0.40; P-trend = 0.06) increase in BMI z-score. A similar relationship was observed for total fat intake [β : 0.21 (95% CI: 0.05, 0.36; P-trend = 0.02)], but not for other fatty acid consumption. Replacing total fat, the highest quartile energy from total carbohydrate take was associated with a 0.24 unit decrease (95% CI: -0.40, -0.08; P-trend = 0.02) of BMI z-score. The relationship was attenuated for carbohydrate from refined grains [β : -0.17 (95% CI: -0.34, 0.00; P-trend = 0.05)]. Other macronutrients, including total protein, protein from animals, vegetables or dairy products were not associated with the outcome, either. Additionally, none of the macronutrients before pregnancy was associated with childhood BMI z-score trajectory (Table 3).

Supplementary Figure 4 presents the intake of each macronutrient before and during pregnancy, respectively, in relation to the risk of overweight or obesity in offspring. Of note, the highest quartile energy intake from *trans* fatty acids during pregnancy was associated with 59% increase (95% CI: 4%, 143%; P-trend = 0.048) in the risk of offspring overweight or obesity. Intakes from other macronutrients, before or during pregnancy, was not associated with the risk of overweight or obesity from middle childhood till adulthood.

Subgroup analyses were performed to investigate whether the associations between maternal macronutrients intake during pregnancy and offspring BMI z-score trajectory differed by overweight status before pregnancy and offspring sex. The relationship between maternal *trans* fatty acid intake during pregnancy and offspring BMI z-score remained significant among female offspring (β : 0.26; 95% CI: 0.00, 0.51; P-trend = 0.06). The pattern of associations for *trans* fat was similar, although none of the associations achieved statistical significance by overweight status before pregnancy, which was probably due to reduced power in subgroup analyses (Supplementary Figure 5-6). Other macronutrient subgroups were not significantly associated with BMI Z-score trajectory across offspring sex or overweight status before pregnancy and the association were not modified by these two subgroups, either.

For birthweight analysis, in substitution of total fat, the highest quartile of dairy protein intake before pregnancy was associated with 0.07 kg (95% CI: 0.01, 0.12; P-trend = 0.01) increase in birthweight. Similarly, the 4th quartile total fat energy intake was associated with 0.05 kg increment in offspring birthweight [β : 0.05 (95% CI: 0.00, 0.11; P-trend = 0.13)]. While in substitution of total fat, the association reversed for the highest quartile carbohydrates from refined grain and birthweight [β : -0.09 (95% CI: -0.16, -0.02; P-trend < 0.01)] (Supplementary Table 2). No macronutrients consumed during pregnancy was associated with birthweight (Supplementary Table 3).

No significant associations were observed for substituting carbohydrate from whole grains for carbohydrate from refined grains, MUFA from plants for MUFA from animals, PUFA for SFA or protein from vegetables for protein from animals either before or during pregnancy (Supplementary Table 4). In the sensitivity analysis, based on the multivariable model, the relationship between top quartile *trans* fatty acid intake during pregnancy and offspring BMI

z-score persisted (β : 0.20 (95% CI: 0.00, 0.40; P-trend = 0.06) after we further adjusted for offspring AHEI score during follow-up (Supplementary Table 5).

Discussion

In our study, we prospectively examined the association between maternal macronutrients intake before and during pregnancy and offspring BMI z-score and overweight/obese risk during childhood through early adulthood. The primary findings are that, in substitution of carbohydrate intake, total and *trans* fatty acid intake during pregnancy was associated with higher offspring BMI z-score and higher risk of offspring overweight/obesity. Intake of other macronutrients before pregnancy, including the macronutrients from different food sources, was not significantly associated with offspring BMI z-score or overweight/obesity risk. Notably, higher intake of dairy protein and total fat before pregnancy was associated with increased birthweight, while the intake of carbohydrates from refined grains showed an inverse association. These associations were independent of established and potential risk factors of childhood obesity. The findings also largely persisted by offspring sex although the associations for boys were weaker.

Previous studies have evaluated the association between maternal fat intake during pregnancy and offspring weight change. Concordant to our study, a prospective cohort study in Spain showed that, the highest quartile of *trans* fatty acid intake was associated with 1.13 – 2.21 fold increased risk of offspring overweight or obesity at age 4 to 5[27]. Ekaterina et al. found that high maternal total fat intake during pregnancy was associated with 0.9 kg/m² increase in BMI and 4.0 cm increase in waist circumferences among male offspring at age 20 [28]. These studies evaluated offspring weight at a specific age. In contrast, our study incorporated four-time outcome measurements, spanning from age 12 till 18 years old, to capture the overall trajectory of offspring weight change over the late childhood period. In contrast to Ekaterina et al., we found that the positive association between *trans* fatty acid intake during pregnancy and BMI z-score in offspring was significant among female offspring. Animal studies on prenatal programming have also shown that female offspring's weight and metabolism are more significantly impacted by a maternal high-fat diet [29,30], possibly due to differences in sex hormones or insulin regulation[31]. Our study also found a marginally-significant inverse association between refined grain carbohydrate intake and offspring BMI z-score trajectory, which is contrary to our hypothesis. A study by Zhu et al. reported that higher refined grain intake during pregnancies among mothers with gestational diabetes mellitus (GDM) was associated with increased BMI z-scores and higher obesity risk among offspring at age 7 [32]. In contrast, Meinila et al.[33] found that higher carbohydrate intake during pregnancy was associated with lower offspring body fat mass or percentage at 5 years. The reasons underlying the discrepancy between the current and previous studies are unknown, although GDM may interact with carbohydrate intake on modulating the offspring body weight[34]. Our study is also among the first to comprehensively examine other macronutrients from different food sources during peri-pregnancy period, and long-term weight change trajectories in offspring. Clearly, more evidence is needed to further substantiate the body of evidence regarding macronutrient compositions of maternal diet in relation to childhood weight change.

In the current study, we did not observe associations between *trans* fat intake and birthweight, although it is worth noting that an analysis in the Project Viva showed that each 1% increment in energy from total *trans* fatty acid consumption during the second trimester was associated with 0.29 unit increase in fetal growth measured by birthweight-for-gestational age z score (BWGAZ) [35]. We used the direct birthweight measurement, which is a familiar measure and commonly used in clinical practice, making it easier for clinicians and policy makers to understand the clinical significance the association found in this study. We nevertheless found positive associations between dairy protein, total fat intake and birthweight. Concordant with our findings, a Danish cohort study showed that higher protein from dairy products is associated with 65g increment in mean birthweight[36]. A prospective cohort study embedded in the Generation R showed the highest quintile dairy protein intake is associated with 115g birthweight increase, with significant linear trend[37]. In accordance to our findings for total fat intake, a population study conducted in Minnesota and Oklahoma revealed that each standard deviation (SD) increase in maternal total fat intake was positively associated with 0.84% increment of infant body fat [38]. Maternal dietary pattern with higher total fat proportion was also associated with higher birthweight in Norwegian mother-child dyads [39]. However, in our study, we found that the pre-pregnancy dietary macronutrient composition was associated more strongly with birthweight than macronutrient composition during pregnancy. Potential reasons underlying the different findings between previous and the current study are unknown, although it is likely that long-term dietary practices may have stronger impact on maternal metabolic health, which may lead to differential placenta development[40] and fetal growth in early gestation[41]. The rapid development of early embryo largely relies on maternal nutrient status, which may have a significant impact on birthweight[42,43]. Nevertheless, more data are needed to further elucidate these associations.

It is still unclear about the exact mechanisms through which *trans* fatty acids intake during pregnancy may impact long-term children's growth. *Trans* fatty acid has shown to be associated with dyslipidemia, endothelial dysfunction, insulin resistance, all-cause mortality and coronary heart disease[44,45]. Both human and animal studies showed that excessive *trans* fatty acid intake during pregnancy may result in greater fetal growth. The association may be explained by that *trans* fatty acid may impair the placental transfer of n-3 fatty acids and disrupt of their metabolism, thereby increasing the risk of overweight and diabetes in offspring[46]. Feeding studies in mice demonstrated that higher and prolonged *trans* fatty acid intake during gestation led to increased tumor necrosis factor- α (TNF- α) and resistin gene expression in offspring adipose tissue, as well as compromised mitochondrial bioenergetics and lipid metabolism in the liver, which were associated with reduced insulin sensitivity and a higher risk of obesity[47,48]. In summary, *trans* fatty acid intake during pregnancy has been linked to impaired fetal growth, insulin resistance, and increased risk of obesity in offspring, potentially due to disruptions in placental fatty acid transfer and metabolism.

Our study had several strengths. This is the first study to comprehensively investigate the association between macronutrient intake from various food sources during the peri-pregnancy period and its impact on birthweight, long-term offspring weight changes, and the risk of overweight/obesity. The large sample size increased the power of our analyses.

We also extended the offspring follow-up beyond early childhood into late-childhood and adolescence, providing new insight into how maternal macronutrient intake affected long-term offspring growth trajectory till adulthood. Besides, the detailed pregnancy and nutrition intake information were acquired by using validated questionnaires, and the information on maternal and offspring lifestyle allowed us to conduct comprehensive analyses. We used four-time outcome measurements and accounted for the correlation between each measurement, which enabled us to better interpret the average weight change trajectory of offspring during late childhood. Additionally, we employed a percentage energy substitution model, which helped mitigate confounding by total energy intake and facilitated the translation of our findings into future macronutrient composition recommendations for females of reproductive age.

There are also some limitations. The FFQ did not specifically inquire about diet during pregnancy, and we used questionnaire return date and offspring birthday to distinguish the diet intake time frame to approximate the maternal intake during or before pregnancy. These may introduce misclassifications of diet at different periods surrounding pregnancy, although it was suggested that dietary patterns change little from before to during pregnancy[49]. Since the NHSII participants were mostly Caucasians and registered nurses, our results may not be generalizable to other race/ethnic groups and people with inadequate health literacy. Another limitation was that we used self-reported weight and height to estimate the overweight or obesity status among offspring, while there was a slight tendency of underreporting weight and height in US young adolescents[24]. Although self-reported measurements were reliable to predict obesity-related outcomes as reported before[50], given the prospective study design, such non-differential misclassification will likely lead to the attenuation of the association of interest. Furthermore, we lacked more detailed information about offspring body composition measures. Lastly, we cannot exclude the role of residual or unmeasured confounding in our findings.

Conclusions

In this well-nourished mother-child cohort, we found that *trans* fatty acid intake during pregnancy was positively associated with higher offspring BMI z-score and the risk of developing overweight or obesity from middle childhood to adulthood, independent of child's diet. Other macronutrients were not significantly associated with higher body weight or the risk of overweight or obesity. Further research is needed to replicate our findings and examine other dietary components that may have significant impact on offspring growth.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors' responsibilities were as follows –CS and QS: designed research; CS: analyzed data and performed statistical analysis; JC, JEH, CZ, BL and MW curated and managed data; CS: wrote the paper; QS: have primary responsibility for final content; and all authors: read, edited, and approved the final manuscript.

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Data sharing

Data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval by the authors.

List of abbreviations

BMI	Body mass index
NHSII	Nurses' Health Study II
GUTS 2	Growing Up Today Study 2
FFQ	Food frequency questionnaire
SFA	Saturated fatty acids
MUFA	Monounsaturated fatty acids
TFA	<i>Trans</i> fatty acids
PUFA	Polyunsaturated fatty acids
GEE	Generalized estimating equations
AHEI	Alternative Healthy Eating Index

References

1. Hales CM, Fryar CD, Carroll MD, et al. Trends in Obesity and Severe Obesity Prevalence in US Youth and Adults by Sex and Age, 2007-2008 to 2015-2016. *JAMA*. 2018;319:1723–5. doi: 10.1001/jama.2018.3060 [PubMed: 29570750]
2. Friedemann C, Heneghan C, Mahtani K, et al. Cardiovascular disease risk in healthy children and its association with body mass index: systematic review and meta-analysis. *BMJ*. 2012;345:e4759. doi: 10.1136/bmj.e4759 [PubMed: 23015032]
3. Freedman DS, Dietz WH, Tang R, et al. The relation of obesity throughout life to carotid intima-media thickness in adulthood: the Bogalusa Heart Study. *Int J Obes Relat Metab Disord*. 2004;28:159–66. doi: 10.1038/sj.ijo.0802515 [PubMed: 14581934]
4. Umer A, Kelley GA, Cottrell LE, et al. Childhood obesity and adult cardiovascular disease risk factors: a systematic review with meta-analysis. *BMC Public Health*. 2017;17:683. doi: 10.1186/s12889-017-4691-z [PubMed: 28851330]
5. Lloyd LJ, Langley-Evans SC, McMullen S. Childhood obesity and risk of the adult metabolic syndrome: a systematic review. *Int J Obes*. 2012;36:1–11. doi: 10.1038/ijo.2011.186
6. Hudda MT, Aarestrup J, Owen CG, et al. Association of Childhood Fat Mass and Weight With Adult-Onset Type 2 Diabetes in Denmark. *JAMA Netw Open*. 2021;4:e218524. doi: 10.1001/jamanetworkopen.2021.8524 [PubMed: 33929520]
7. Mohammadian Khonsari N, Shahrestanaki E, Ehsani A, et al. Association of childhood and adolescence obesity with incidence and mortality of adulthood cancers. A systematic review and

- meta-analysis. *Front Endocrinol Lausanne*. 2023;14:1069164. doi: 10.3389/fendo.2023.1069164 [PubMed: 36742402]
8. Wang Y, Wang K, Du M, et al. Maternal consumption of ultra-processed foods and subsequent risk of offspring overweight or obesity: results from three prospective cohort studies. *BMJ*. 2022;379:e071767. doi: 10.1136/bmj-2022-071767 [PubMed: 36198411]
 9. Brion MJ, Ness AR, Rogers I, et al. Maternal macronutrient and energy intakes in pregnancy and offspring intake at 10 y: exploring parental comparisons and prenatal effects. *Am J Clin Nutr*. 2010;91:748–56. doi: 10.3945/ajcn.2009.28623 [PubMed: 20053880]
 10. Strohmaier S, Bogl LH, Eliassen AH, et al. Maternal healthful dietary patterns during peripregnancy and long-term overweight risk in their offspring. *Eur J Epidemiol*. 2020;35:283–93. doi: 10.1007/s10654-020-00621-8 [PubMed: 32185575]
 11. Murrin C, Shrivastava A, Kelleher CC, et al. Maternal macronutrient intake during pregnancy and 5 years postpartum and associations with child weight status aged five. *Eur J Clin Nutr*. 2013;67:670–9. doi: 10.1038/ejcn.2013.76 [PubMed: 23612514]
 12. Tielemans MJ, Steegers EAP, Voortman T, et al. Protein intake during pregnancy and offspring body composition at 6 years: the Generation R Study. *Eur J Nutr*. 2017;56:2151–60. doi: 10.1007/s00394-016-1255-4 [PubMed: 27376355]
 13. Brei C, Stecher L, Meyer DM, et al. Impact of Dietary Macronutrient Intake during Early and Late Gestation on Offspring Body Composition at Birth, 1, 3, and 5 Years of Age. *Nutrients*. 2018;10. doi: 10.3390/nu10050579
 14. Colditz GA, Manson JE, Hankinson SE. The Nurses' Health Study: 20-year contribution to the understanding of health among women. *J Womens Health*. 1997;6:49–62. doi: 10.1089/jwh.1997.6.49 [PubMed: 9065374]
 15. Willett WC, Sampson L, Browne ML, et al. The use of a self-administered questionnaire to assess diet four years in the past. *Am J Epidemiol*. 1988;127:188–99. doi: 10.1093/oxfordjournals.aje.a114780 [PubMed: 3337073]
 16. Salvini S, Hunter DJ, Sampson L, et al. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. *Int J Epidemiol*. 1989;18:858–67. doi: 10.1093/ije/18.4.858 [PubMed: 2621022]
 17. Gu X, Wang DD, Sampson L, et al. Validity and Reproducibility of a Semiquantitative Food Frequency Questionnaire for Measuring Intakes of Foods and Food Groups. *Am J Epidemiol*. 2024;193:170–9. doi: 10.1093/aje/kwad170 [PubMed: 37552965]
 18. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol*. 1985;122:51–65. doi: 10.1093/oxfordjournals.aje.a114086 [PubMed: 4014201]
 19. Bao Y, Bertoia ML, Lenart EB, et al. Origin, Methods, and Evolution of the Three Nurses' Health Studies. *Am J Public Health*. 2016;106:1573–81. doi: 10.2105/AJPH.2016.303338 [PubMed: 27459450]
 20. Michels KB, Willett WC, Graubard BI, et al. A longitudinal study of infant feeding and obesity throughout life course. *Int J Obes*. 2007;31:1078–85. doi: 10.1038/sj.ijo.0803622
 21. Dhana K, Zong G, Yuan C, et al. Lifestyle of women before pregnancy and the risk of offspring obesity during childhood through early adulthood. *Int J Obes*. 2018;42:1275–84.
 22. Dhana K, Haines J, Liu G, et al. Association between maternal adherence to healthy lifestyle practices and risk of obesity in offspring: results from two prospective cohort studies of mother-child pairs in the United States. *BMJ*. 2018;362:k2486. doi: 10.1136/bmj.k2486 [PubMed: 29973352]
 23. Goodman E, Hinden BR, Khandelwal S. Accuracy of teen and parental reports of obesity and body mass index. *Pediatrics*. 2000;106:52–8. doi: 10.1542/peds.106.1.52 [PubMed: 10878149]
 24. Himes JH, Faricy A. Validity and reliability of self-reported stature and weight of US adolescents. *Am J Hum Biol*. 2001;13:255–60. doi: 10.1002/1520-6300(200102/03)13:2<255::AID-AJHB1036>3.0.CO;2-E [PubMed: 11460871]
 25. Freedman DS, Berenson GS. Tracking of BMI z Scores for Severe Obesity. *Pediatrics*. 2017;140. doi: 10.1542/peds.2017-1072

26. Cole TJ, Bellizzi MC, Flegal KM, et al. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ*. 2000;320:1240–3. doi: 10.1136/bmj.320.7244.1240 [PubMed: 10797032]
27. Scholz A, Navarrete-Muñoz EM, García-de-la-Hera M, et al. Association between trans fatty acid intake and overweight including obesity in 4 to 5-year-old children from the INMA study. *Pediatr Obes*. 2019;14:e12528. doi: 10.1111/ijpo.12528 [PubMed: 30957427]
28. Maslova E, Rytter D, Bech BH, et al. Maternal intake of fat in pregnancy and offspring metabolic health - A prospective study with 20 years of follow-up. *Clin Nutr*. 2016;35:475–83. doi: 10.1016/j.clnu.2015.03.018 [PubMed: 25933442]
29. Yokomizo H, Inoguchi T, Sonoda N, et al. Maternal high-fat diet induces insulin resistance and deterioration of pancreatic β -cell function in adult offspring with sex differences in mice. *Am J Physiol-Endocrinol Metab*. 2014;306:E1163–75. doi: 10.1152/ajpendo.00688.2013 [PubMed: 24691028]
30. Akhaphong B, Gregg B, Kumusoglu D, et al. Maternal High-Fat Diet During Pre-Conception and Gestation Predisposes Adult Female Offspring to Metabolic Dysfunction in Mice. *Front Endocrinol*. 2022;12. doi: 10.3389/fendo.2021.780300
31. Han J, Xu J, Epstein PN, et al. Long-term effect of maternal obesity on pancreatic beta cells of offspring: reduced beta cell adaptation to high glucose and high-fat diet challenges in adult female mouse offspring. *Diabetologia*. 2005;48:1810–8. doi: 10.1007/s00125-005-1854-8 [PubMed: 16010523]
32. Zhu Y, Olsen SF, Mendola P, et al. Maternal dietary intakes of refined grains during pregnancy and growth through the first 7 y of life among children born to women with gestational diabetes. *Am J Clin Nutr*. 2017;106:96–104. doi: 10.3945/ajcn.116.136291 [PubMed: 28592607]
33. Meinilä J, Klemetti MM, Huvinen E, et al. Macronutrient intake during pregnancy in women with a history of obesity or gestational diabetes and offspring adiposity at 5 years of age. *Int J Obes*. 2021;45:1030–43. doi: 10.1038/s41366-021-00762-0
34. Renault KM, Carlsen EM, Nørgaard K, et al. Intake of carbohydrates during pregnancy in obese women is associated with fat mass in the newborn offspring. *Am J Clin Nutr*. 2015;102:1475–81. doi: 10.3945/ajcn.115.110551 [PubMed: 26561621]
35. Cohen JF, Rifas-Shiman SL, Rimm EB, et al. Maternal trans fatty acid intake and fetal growth. *Am J Clin Nutr*. 2011;94:1241–7. doi: 10.3945/ajcn.111.014530 [PubMed: 21918217]
36. Olsen SF, Halldorsson TI, Willett WC, et al. Milk consumption during pregnancy is associated with increased infant size at birth: prospective cohort study. *Am J Clin Nutr*. 2007;86:1104–10. doi: 10.1093/ajcn/86.4.1104 [PubMed: 17921389]
37. Heppe DH, van Dam RM, Willemsen SP, et al. Maternal milk consumption, fetal growth, and the risks of neonatal complications: the Generation R Study. *Am J Clin Nutr*. 2011;94:501–9. doi: 10.3945/ajcn.111.013854 [PubMed: 21697074]
38. Nagel EM, Jacobs D, Johnson KE, et al. Maternal Dietary Intake of Total Fat, Saturated Fat, and Added Sugar Is Associated with Infant Adiposity and Weight Status at 6 mo of Age. *J Nutr*. 2021;151:2353–60. doi: 10.1093/jn/nxab101 [PubMed: 33982119]
39. Englund-Ogge L, Brantsaeter AL, Juodakis J, et al. Associations between maternal dietary patterns and infant birth weight, small and large for gestational age in the Norwegian Mother and Child Cohort Study. *Eur J Clin Nutr*. 2019;73:1270–82. doi: 10.1038/s41430-018-0356-y [PubMed: 30459338]
40. Teo SM, Murrin CM, Mehegan J, et al. Associations between the maternal healthy lifestyle score and its individual components during early pregnancy with placental outcomes. *Placenta*. 2023;139:75–84. doi: 10.1016/j.placenta.2023.06.001 [PubMed: 37336158]
41. Chavatte-Palmer P, Tarrade A, Rousseau-Ralliard D. Diet before and during Pregnancy and Offspring Health: The Importance of Animal Models and What Can Be Learned from Them. *Int J Environ Res Public Health*. 2016;13:586. doi: 10.3390/ijerph13060586 [PubMed: 27314367]
42. Marshall NE, Abrams B, Barbour LA, et al. The importance of nutrition in pregnancy and lactation: lifelong consequences. *Am J Obstet Gynecol*. 2022;226:607–32. doi: 10.1016/j.ajog.2021.12.035 [PubMed: 34968458]

43. Stephenson J, Heslehurst N, Hall J, et al. Before the beginning: nutrition and lifestyle in the preconception period and its importance for future health. *Lancet*. 2018;391:1830–41. doi: 10.1016/S0140-6736(18)30311-8 [PubMed: 29673873]
44. de Souza RJ, Mente A, Maroleanu A, et al. Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. *BMJ*. 2015;351:h3978. doi: 10.1136/bmj.h3978 [PubMed: 26268692]
45. Remig V, Franklin B, Margolis S, et al. Trans Fats in America: A Review of Their Use, Consumption, Health Implications, and Regulation. *J Am Diet Assoc*. 2010;110:585–92. doi: 10.1016/j.jada.2009.12.024 [PubMed: 20338284]
46. Mennitti LV, Oliveira JL, Morais CA, et al. Type of fatty acids in maternal diets during pregnancy and/or lactation and metabolic consequences of the offspring. *J Nutr Biochem*. 2015;26:99–111. doi: 10.1016/j.jnutbio.2014.10.001 [PubMed: 25459884]
47. de Velasco PC, Chicaybam G, Ramos-Filho DM, et al. Maternal intake of trans-unsaturated or interesterified fatty acids during pregnancy and lactation modifies mitochondrial bioenergetics in the liver of adult offspring in mice. *Br J Nutr*. 2017;118:41–52. doi: 10.1017/S0007114517001817 [PubMed: 28797310]
48. Duque-Guimarães DE, de Castro J, Martinez-Botas J, et al. Early and prolonged intake of partially hydrogenated fat alters the expression of genes in rat adipose tissue. *Nutrition*. 2009;25:782–9. doi: 10.1016/j.nut.2008.12.004 [PubMed: 19251397]
49. Crozier SR, Robinson SM, Godfrey KM, et al. Women's dietary patterns change little from before to during pregnancy. *J Nutr*. 2009;139:1956–63. doi: 10.3945/jn.109.109579 [PubMed: 19710161]
50. Strauss RS. Comparison of measured and self-reported weight and height in a cross-sectional sample of young adolescents. *Int J Obes Relat Metab Disord*. 1999;23:904–8. doi: 10.1038/sj.ijo.0800971 [PubMed: 10490794]

Table 1

Baseline characteristics of participants during pregnancy

Maternal Characteristics	Total Protein Energy		Total Carbohydrate		Total Fat		Total
	Quartile 1 (n=719)	Quartile 4 (n=717)	Quartile 1 (n=720)	Quartile 4 (n=707)	Quartile 1 (n=707)	Quartile 4 (n=720)	
Age, mean (SD)	32.3 (3.5)	32.5 (3.7)	32.3 (3.7)	32.7 (3.6)	32.9 (3.6)	32.3 (3.7)	32.4 (3.6)
Smoking status, %							
Never	67.6	66.0	60.7	72.1	69.7	64.6	67.8
Past smoker	18.4	20.8	21.7	16.3	18.7	18.1	18.9
Current smoker	7.1	5.6	8.2	4.8	5.1	8.3	6.3
Missing	7.0	7.7	9.4	6.8	6.5	9.0	7.0
Alcohol intake (g/d), %							
0	42.6	51.0	40.7	51.2	47.8	44.2	45.3
0-5	34.2	31.9	33.5	32.5	30.1	36.4	35.1
5-15	13.2	8.1	13.3	8.3	11.9	9.0	10.5
> 15	2.5	0.7	2.6	0.3	2.7	0.8	1.5
Missing	7.5	8.2	9.9	7.6	7.5	9.6	7.5
AHEI, mean (SD)	40.0 (10.5)	45.3 (9.3)	40.3 (9.1)	44.6 (10.9)	46.5 (10.4)	38.7 (9.1)	42.1 (9.9)
Physical activity (MET-hours/week), %							
0-9	31.8	28.9	37.2	24.0	22.6	41.1	31.9
9-27	33.7	35.7	31.4	33.2	32.4	29.4	32.8
27	27.3	27.3	21.5	35.5	37.9	19.9	27.9
Missing	7.2	8.1	9.9	7.2	7.1	9.6	7.4
BMI (kg/m ²), %							
< 18.5	4.3	3.5	2.5	6.1	5.8	3.3	4.0
18.5 - 25	68.0	58.2	57.9	68.7	67.9	58.9	64.0
25 - 30	8.9	14.5	14.9	8.3	9.3	13.2	11.9
30	3.6	6.6	6.3	2.7	2.8	6.4	4.7
Missing	15.2	17.3	18.5	14.1	14.1	18.2	15.4
Pregnancy complications, %							
GDM	26.6	31.9	31.1	25.2	26.2	29.2	27.8
	3.6	7.3	6.4	3.0	3.8	6.1	5.1
Preeclampsia	3.1	3.8	3.6	2.7	2.3	2.4	3.0

Gestational hypertension	3.8	5.0	6.0	3.0	3.0	5.4	4.4
Caesarean delivery	20.7	22.5	22.9	20.5	20.5	21.3	20.9
Caucasian, %	97.2	97.2	98.1	96.3	95.9	97.6	97.3
Parity, %							
Nulliparous	28.7	32.5	27.8	32.5	33.5	25.8	30.4
1	33.5	31.9	33.1	32.5	31.7	33.9	32.5
2	18.5	14.4	15.6	17.4	17.3	16.1	16.6
3	3.2	3.2	4.2	2.8	2.5	5.3	4.2
4+	1.5	1.3	1.3	1.0	1.0	1.0	1.3
Missing	14.6	16.7	18.2	13.7	14.0	17.9	15.0
Husband education, %							
Highschool	16.7	13.7	16.1	13.4	11.6	17.9	14.9
College	46.5	47.3	50.6	44.7	45.3	50.0	47.5
Graduate school	31.7	33.9	28.3	34.4	36.5	27.2	32.3
Missing	5.1	5.2	5.0	7.5	6.6	4.9	5.4
Macronutrients % energy, mean (SD)							
Total protein	15.6 (1.4)	23.3 (1.8)	21.3 (3.0)	17.2 (2.6)	19.0 (3.4)	19.5 (2.9)	19.3 (3.1)
Animal protein	10.6 (1.9)	18.6 (2.2)	17.0 (3.2)	11.9 (2.8)	13.7 (3.6)	15.0 (3.2)	14.5 (3.4)
Vegetable protein	5.0 (1.2)	4.7 (1.0)	4.4 (0.8)	5.3 (1.4)	5.3 (1.3)	4.5 (0.9)	4.9 (1.1)
Dairy protein	3.9 (1.6)	6.1 (2.6)	5.1 (2.4)	4.7 (2.1)	5.2 (2.4)	4.6 (2.1)	5.1 (2.2)
Total carbohydrate	55.8 (6.4)	46.7 (5.8)	42.9 (3.4)	59.6 (3.7)	58.1 (5.4)	44.3 (4.3)	51.2 (6.6)
Carbohydrates from Whole Grain	3.1 (2.4)	3.2 (2.2)	2.4 (1.7)	4.0 (3.1)	4.1 (3.1)	2.5 (1.7)	3.2 (2.4)
Carbohydrates from Refined Grain	31.8 (7.1)	21.7 (4.6)	22.7 (4.8)	30.6 (7.9)	28.3 (8.1)	24.7 (5.4)	26.4 (6.6)
Total fat	30.1 (5.5)	30.9 (4.9)	36.0 (3.9)	25.4 (3.4)	24.4 (2.5)	37.2 (2.8)	30.8 (5.0)
SFA	10.9 (2.4)	11.4 (2.2)	13.3 (2.1)	9.2 (1.7)	8.8 (1.4)	13.7 (1.8)	11.2 (2.3)
MUFA	11.5 (2.3)	11.5 (2.1)	13.7 (1.8)	9.4 (1.5)	9.0 (1.1)	14.2 (1.4)	11.6 (2.2)
MUFA from plants	6.2 (2)	4.7 (1.3)	6.0 (1.9)	4.9 (1.6)	4.3 (1.2)	6.6 (1.9)	5.5 (1.7)
MUFA from animals	5.0 (1.5)	6.5 (1.6)	7.3 (1.4)	4.4 (1.1)	4.4 (1.0)	7.2 (1.5)	5.8 (1.6)
PUFA	5.3 (1.4)	5.2 (1.1)	5.9 (1.3)	4.6 (1.0)	4.4 (0.9)	6.2 (1.4)	5.3 (1.2)
Trans fat	1.6 (0.6)	1.4 (0.5)	1.8 (0.6)	1.2 (0.4)	1.1 (0.3)	2.0 (0.6)	1.5 (0.5)
Offspring Characteristics	Quartile 1 (n=762)	Quartile 4 (n=762)	Quartile 1 (n=762)	Quartile 4 (n=762)	Quartile 1 (n=762)	Quartile 4 (n=762)	Quartile 4 (n=3049)
Age at baseline, year, mean (SD)	12.4 (1.2)	12.5 (1.1)	12.5 (1.1)	12.3 (1.3)	12.2 (1.3)	12.5 (1.1)	12.4 (1.1)

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Birthweight, kg, mean (SD)	3.5 (0.6)	3.5 (0.6)	3.6 (0.6)	3.5 (0.6)	3.5 (0.6)	3.6 (0.6)	3.5 (0.6)	3.5 (0.6)	3.5 (0.6)
Gestational age, week, %									
Missing	13.5	13.1	14.8	11.5	12.3	13.0	13.3		
<37	6.3	8.4	6.2	6.8	7.5	6.3	7.2		
37-39	23.5	24.3	23.8	24.9	24.4	24.5	23.7		
39-42	52.5	51.4	52.0	52.2	51.8	52.0	52.0		
43+	4.2	2.8	3.3	4.5	3.9	4.2	3.9		
Female, %	52.5	49.9	52.4	50.4	52.0	52.9	52.8		

BMI, body mass index; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; AHEI, alternative healthy eating index; GDM, gestational diabetes mellitus.

Table 2

Offspring BMI z-score trajectory and 95% confidence intervals (95% CI) during follow-up across quartiles of maternal macronutrients intake during pregnancy.

	Macronutrients, Quartile Energy %				P-Trend
	Q1	Q2	Q3	Q4	
Total Protein					
Median (IQR)	15.9 (14.8, 16.7)	18.4 (17.8, 18.8)	20.1 (19.7, 20.7)	22.9 (21.9, 24.1)	
Model 1 [†]	0 (reference)	0.10 (−0.03, 0.23)	0.12 (−0.03, 0.26)	0.15 (0.01, 0.29)	0.05
Model 2 [‡]	0 (reference)	0.05 (−0.09, 0.18)	0.03 (−0.12, 0.18)	0.00 (−0.16, 0.17)	0.95
Animal Protein					
Median (IQR)	10.7 (9.5, 11.6)	13.4 (12.9, 13.8)	15.4 (14.8, 16.0)	18.2 (17.2, 19.6)	
Model 1	0 (reference)	0.09 (−0.05, 0.22)	0.09 (−0.05, 0.23)	0.14 (−0.00, 0.28)	0.06
Model 2	0 (reference)	0.03 (−0.11, 0.17)	0.00 (−0.15, 0.15)	−0.01 (−0.19, 0.17)	0.80
Dairy Protein					
Median(IQR)	2.6 (2.0, 3.0)	4.1 (3.7, 4.4)	5.6 (5.2, 6.0)	7.6 (6.9, 8.6)	
Model 1	0 (reference)	0.02 (−0.13, 0.17)	0.03 (−0.12, 0.17)	0.03 (−0.12, 0.18)	0.55
Model 2	0 (reference)	0.02 (−0.13, 0.18)	0.04 (−0.11, 0.18)	0.02 (−0.13, 0.18)	0.65
Vegetable Protein					
Median (IQR)	3.8 (3.5, 4.0)	4.5 (4.4, 4.6)	5.1 (4.9, 5.3)	6.0 (5.7, 6.4)	
Model 1	0 (reference)	−0.05 (−0.20, 0.09)	0.04 (−0.11, 0.18)	−0.03 (−0.19, 0.12)	0.88
Model 2	0 (reference)	−0.04 (−0.19, 0.11)	0.07 (−0.08, 0.22)	0.04 (−0.15, 0.22)	0.35
Total Carbohydrate					
Median (IQR)	43.7 (41.1, 45.4)	49.1 (48.1 50.1)	53.2 (52.2, 54.3)	58.5 (56.9, 61.2)	
Model 1	0 (reference)	−0.12 (−0.26, 0.03)	−0.09 (−0.25, 0.07)	−0.25 (−0.40, −0.10)	0.01
Model 2	0 (reference)	−0.11 (−0.26, 0.03)	−0.08 (−0.24, 0.08)	−0.24 (−0.40, −0.08)	0.02
Carbohydrates from Whole Grain					
Median (IQR)	1.0 (0.6, 1.2)	2.0 (1.8, 2.3)	3.4 (3.0, 3.8)	5.7 (4.8, 7.0)	
Model 1	0 (reference)	−0.02 (−0.16, 0.13)	−0.03 (−0.19, 0.13)	−0.09 (−0.24, 0.07)	0.16
Model 2	0 (reference)	−0.02 (−0.16, 0.13)	−0.03 (−0.20, 0.13)	−0.09 (−0.25, 0.06)	0.14
Carbohydrates from Refined Grain					
Median (IQR)	19.5 (17.4, 20.9)	24.0 (23.0, 25.0)	27.8 (26.9, 29.0)	33.8 (31.8, 37.0)	

Macronutrients, Quartile Energy %					
	Q1	Q2	Q3	Q4	P-Trend
Model 1	0 (reference)	-0.05 (-0.19, 0.10)	-0.07 (-0.20, 0.07)	-0.19 (-0.34, -0.04)	0.02
Model 2	0 (reference)	-0.04 (-0.19, 0.11)	-0.06 (-0.20, 0.09)	-0.17 (-0.34, 0.00)	0.05
Total Fat					
Median (IQR)	25.1 (23.2, 26.4)	29.0 (28.3, 29.9)	32.3 (31.4, 33.0)	36.4 (35.0, 38.5)	
Model 1	0 (reference)	0.11 (-0.02, 0.25)	0.18 (0.04, 0.32)	0.22 (0.07, 0.38)	0.02
Model 2	0 (reference)	0.11 (-0.03, 0.24)	0.17 (0.02, 0.31)	0.21 (0.05, 0.36)	0.02
SFA					
Median (IQR)	8.7 (8.0, 9.3)	10.5 (10.1, 10.8)	11.8 (11.4, 12.1)	13.7 (13.1, 14.7)	
Model 1	0 (reference)	0.07 (-0.07, 0.21)	0.16 (0.02, 0.30)	0.16 (0.01, 0.30)	0.04
Model 2	0 (reference)	0.01 (-0.13, 0.16)	0.07 (-0.09, 0.23)	0.03 (-0.17, 0.23)	0.63
MUFA					
Median (IQR)	9.1 (8.3, 9.7)	10.8 (10.4, 11.2)	12.2 (11.9, 12.5)	14.0 (13.4, 15.0)	
Model 1	0 (reference)	0.14 (-0.02, 0.29)	0.12 (-0.02, 0.27)	0.24 (0.09, 0.38)	0.02
Model 2	0 (reference)	0.07 (-0.10, 0.24)	0.01 (-0.16, 0.19)	0.06 (-0.16, 0.29)	0.67
PUFA					
Median (IQR)	4.0 (3.6, 4.2)	4.8 (4.6, 5.0)	5.5 (5.3, 5.7)	6.6 (6.3, 7.2)	
Model 1	0 (reference)	0.04 (-0.10, 0.18)	0.10 (-0.04, 0.25)	0.17 (0.04, 0.31)	0.02
Model 2	0 (reference)	0.00 (-0.14, 0.15)	0.05 (-0.11, 0.21)	0.10 (-0.07, 0.27)	0.13
Trans Fat					
Median (IQR)	1.0 (0.8, 1.1)	1.3 (1.2, 1.4)	1.6 (1.5, 1.7)	2.2 (2.0, 2.4)	
Model 1	0 (reference)	0.16 (0.02, 0.30)	0.19 (0.04, 0.33)	0.26 (0.11, 0.42)	0.01
Model 2	0 (reference)	0.12 (-0.03, 0.27)	0.14 (-0.02, 0.30)	0.20 (0.00, 0.40)	0.06

BMI z-score, body mass index z-score; 95%CI, 95% confidence interval; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; AHEI, alternative healthy eating index.

¹ Adjusted for maternal age at pregnancy (continuous), race (Caucasian, not Caucasian), smoking status at pregnancy (never, current, past), alcohol intake at pregnancy (0, 0-5, 5-15, 15+, missing), AHEI (continuous), physical activity (0-9 MET-hours/week, 9-27 MET-hours/week, 27+ MET-hour/week), gestational complications (yes, no), parity (nulliparous, 1, 2, 3, 4 + previous pregnancies, missing), gestational age (37, 37-39, 40-42, ≥ 43 weeks), husband's education (high school, college, graduate school, missing), offspring sex (boy/girl), offspring age (continuous).

² Further adjusted for maternal total energy intake (continuous). Protein models further adjusted for percentage of energy from total carbohydrate intake. Animal protein models were further adjusted for vegetable protein energy, and vice versa. Carbohydrate models further adjusted for percentage of energy from total protein intake. Carbohydrates from Whole Grain models were further adjusted for Carbohydrates from Refined Grain energy, and vice versa. Fat models further adjusted for percentage of energy from total protein intake. Each of the SFA, MUFA, and PUFA models were further adjusted

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for trans-fatty acid, with the SFA model also accounting for PUFA and MUFA, the MUFA model for SFA and PUFA, and the PUFA model for SFA and MUFA. The *Trans* Fat model further adjusted for total energy intake, total protein energy intake, SFA, PUFA, MUFA.

Table 3

Offspring BMI z-score trajectory and 95% confidence intervals (95% CI) during follow-up across quartiles of maternal macronutrients intake before pregnancy.

	Macronutrients, Quartile Energy %				P- Trend
	Q1	Q2	Q3	Q4	
Total Protein					
Median (IQR)	15.7 (14.5, 16.5)	18.2 (17.7, 18.8)	20.2 (19.7, 20.7)	22.9 (22.0, 24.1)	
Model 1 ¹	0 (reference)	0.08 (-0.06, 0.22)	0.13 (-0.01, 0.28)	0.15 (0.01, 0.30)	0.04
Model 2 ²	0 (reference)	0.06 (-0.09, 0.20)	0.09 (-0.06, 0.25)	0.09 (-0.08, 0.26)	0.19
Animal Protein					
Median (IQR)	10.6 (9.1, 11.3)	13.2 (12.6, 13.8)	15.4 (14.8, 16.0)	18.2 (17.3, 19.5)	
Model 1	0 (reference)	0.10 (-0.04, 0.24)	0.14 (-0.00, 0.28)	0.15 (0.00, 0.29)	0.04
Model 2	0 (reference)	0.06 (-0.09, 0.21)	0.08 (-0.09, 0.24)	0.06 (-0.14, 0.25)	0.46
Vegetable Protein					
Median (IQR)	3.8 (3.5, 4.1)	4.6 (4.4, 4.7)	5.1 (5.0, 5.3)	6.1 (5.8, 6.6)	
Model 1	0 (reference)	-0.04 (-0.19, 0.10)	-0.03 (-0.19, 0.12)	-0.15 (-0.32, 0.03)	0.09
Model 2	0 (reference)	-0.03 (-0.17, 0.11)	-0.00 (-0.16, 0.16)	-0.08 (-0.27, 0.10)	0.32
Dairy Protein					
Median (IQR)	2.4 (1.9, 2.7)	3.8 (3.5, 4.1)	5.2 (4.8, 5.5)	7.2 (6.6, 8.1)	
Model 1	0 (reference)	0.00 (-0.15, 0.15)	-0.02 (-0.16, 0.13)	0.05 (-0.12, 0.21)	0.47
Model 2	0 (reference)	-0.01 (-0.17, 0.14)	-0.04 (-0.18, 0.11)	0.01 (-0.16, 0.17)	0.91
Total Carbohydrate					
Median (IQR)	43.1 (40.5, 44.9)	48.6 (47.6, 49.5)	52.7 (51.6, 53.8)	58.6 (56.9, 61.8)	
Model 1	0 (reference)	-0.02 (-0.14, 0.10)	-0.06 (-0.17, 0.05)	-0.15 (-0.27, -0.03)	0.05
Model 2	0 (reference)	0.00 (-0.15, 0.16)	-0.02 (-0.18, 0.15)	-0.13 (-0.32, 0.05)	0.12
Carbohydrates from Whole Grain					
Median (IQR)	0.9 (0.6, 1.2)	2.0 (1.7, 2.3)	3.4 (3.0, 3.8)	5.8 (4.9, 7.3)	
Model 1	0 (reference)	0.04 (-0.11, 0.18)	0.03 (-0.14, 0.19)	-0.07 (-0.24, 0.10)	0.23
Model 2	0 (reference)	0.03 (-0.12, 0.18)	0.03 (-0.13, 0.19)	-0.05 (-0.22, 0.11)	0.31
Carbohydrates from Refined Grain					
Median (IQR)	19.3 (17.4, 20.6)	24.0 (23.0, 25.0)	28.2 (27.2, 29.4)	34.0 (32.0, 37.5)	

Macronutrients, Quartile Energy %					
	Q1	Q2	Q3	Q4	P- Trend
Model 1	0 (reference)	0.01 (-0.14, 0.16)	-0.07 (-0.21, 0.08)	-0.03 (-0.18, 0.12)	0.40
Model 2	0 (reference)	0.03 (-0.13, 0.18)	-0.03 (-0.18, 0.13)	0.04 (-0.14, 0.22)	0.76
Total Fat					
Median (IQR)	24.7 (22.8, 26.0)	28.8 (28.1, 29.6)	32.0 (31.2, 32.9)	36.2 (34.9, 38.2)	
Model 1	0 (reference)	0.11 (-0.04, 0.27)	0.16 (0.01, 0.31)	0.11 (-0.04, 0.27)	0.09
Model 2	0 (reference)	0.10 (-0.06, 0.25)	0.14 (-0.01, 0.30)	0.10 (-0.05, 0.25)	0.12
SFA					
Median (IQR)	8.6 (7.7, 9.1)	10.4 (10.1, 10.7)	11.7 (11.4, 12.2)	13.7 (13.1, 14.8)	
Model 1	0 (reference)	0.08 (-0.07, 0.22)	0.13 (-0.03, 0.28)	0.10 (-0.05, 0.26)	0.12
Model 2	0 (reference)	0.05 (-0.10, 0.21)	0.09 (-0.11, 0.28)	0.06 (-0.16, 0.28)	0.48
MUFA					
Median (IQR)	9.1 (8.3, 9.6)	10.8 (10.5, 11.2)	12.2 (11.9, 12.6)	14.2 (13.6, 15.2)	
Model 1	0 (reference)	0.07 (-0.07, 0.22)	0.07 (-0.08, 0.21)	0.12 (-0.03, 0.27)	0.11
Model 2	0 (reference)	0.04 (-0.12, 0.20)	0.02 (-0.17, 0.20)	0.04 (-0.20, 0.28)	0.77
PUFA					
Median (IQR)	4.1 (3.7, 4.3)	4.9 (4.7, 5.1)	5.7 (5.5, 5.9)	6.8 (6.4, 7.5)	
Model 1	0 (reference)	0.06 (-0.08, 0.21)	0.03 (-0.11, 0.17)	0.11 (-0.03, 0.25)	0.12
Model 2	0 (reference)	0.05 (-0.11, 0.20)	0.01 (-0.15, 0.17)	0.09 (-0.09, 0.26)	0.30
Trans Fat					
Median (IQR)	0.9 (0.8, 1.0)	1.3 (1.2, 1.4)	1.6 (1.5, 1.8)	2.2 (2.0, 2.5)	
Model 1	0 (reference)	0.12 (-0.03, 0.26)	0.10 (-0.06, 0.25)	0.10 (-0.06, 0.26)	0.25
Model 2	0 (reference)	0.10 (-0.05, 0.25)	0.07 (-0.10, 0.24)	0.07 (-0.13, 0.27)	0.58

BMI z-score, body mass index z-score; 95%CI, 95% confidence interval; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; AHEI, alternative healthy eating index.

¹ Adjusted for maternal age at pregnancy (continuous), race (Caucasian, not Caucasian), smoking status at pregnancy (never, current, past), alcohol intake at pregnancy (0, 0-5, 5-15, 15+, missing), AHEI (continuous), physical activity (0-9 MET-hours/week, 9-27 MET-hours/week, 27+ MET-hour/week), gestational complications (yes, no), parity (nulliparous, 1, 2, 3, 4 + previous pregnancies, missing), gestational age (37, 37-39, 40-42, ≥ 43 weeks), husband's education (high school, college, graduate school, missing), offspring sex (boy/girl), offspring age (continuous).

² Further adjusted for maternal total energy intake (continuous). Protein models further adjusted for percentage of energy from total carbohydrate intake. Animal protein models were further adjusted for vegetable protein energy, and vice versa. Carbohydrate models further adjusted for percentage of energy from total protein intake. Carbohydrates from Whole Grain models were further adjusted for Carbohydrates from Refined Grain energy, and vice versa. Fat models further adjusted for percentage of energy from total protein intake. Each of the SFA, MUFA, and PUFA models were further adjusted

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