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Nutritional Epidemiology

Maternal Diet Quality During Pregnancy and Offspring Hepatic Fat in Early Childhood: The Healthy Start Study

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A B S T R A C T

Background: Overnutrition in utero may increase offspring risk of nonalcoholic fatty liver disease (NAFLD), but the specific contribution of maternal diet quality during pregnancy to this association remains understudied in humans.

Objectives: This study aimed to examine the associations of maternal diet quality during pregnancy with offspring hepatic fat in early childhood (median: 5 y old, range: 4–8 y old).

Methods: Data were from 278 mother–child pairs in the longitudinal, Colorado-based Healthy Start Study. Multiple 24-h recalls were collected from mothers during pregnancy on a monthly basis (median: 3 recalls, range: 1–8 recalls starting after enrollment), and used to estimate maternal usual nutrient intakes and dietary pattern scores [Healthy Eating Index-2010 (HEI-2010), Dietary Inflammatory Index (DII), and Relative Mediterranean Diet Score (rMED)]. Offspring hepatic fat was measured in early childhood by MRI. Associations of maternal dietary predictors during pregnancy with offspring log-transformed hepatic fat were assessed using linear regression models adjusted for offspring demographics, maternal/perinatal confounders, and maternal total energy intake.

Results: Higher maternal fiber intake and rMED scores during pregnancy were associated with lower offspring hepatic fat in early childhood in fully adjusted models [Back-transformed β (95% CI): 0.82 (0.72, 0.94) per 5 g/1000 kcal fiber; 0.93 (0.88, 0.99) per 1 SD for rMED]. In contrast, higher maternal total sugar and added sugar intakes, and DII scores were associated with higher offspring hepatic fat [Back-transformed β (95% CI): 1.18 (1.05, 1.32) per 5% kcal/d added sugar; 1.08 (0.99, 1.18) per 1 SD for DII]. Analyses of dietary pattern subcomponents also revealed that lower maternal intakes of green vegetables and legumes and higher intake of "empty calories" were associated with higher offspring hepatic fat in early childhood.

Conclusions: Poorer maternal diet quality during pregnancy was associated with greater offspring susceptibility to hepatic fat in early childhood. Our findings provide insights into potential perinatal targets for the primordial prevention of pediatric NAFLD.

Keywords: developmental origins, diet quality, maternal–child health, fatty liver, pediatrics

Abbreviations: ASA24, automated self-administered 24-h recall; DII, Dietary Inflammation Index; HEI-2010, Healthy Eating Index-2010; METs, metabolic equivalents; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; rMED, Relative Mediterranean Diet Score.

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Introduction

The increasing incidence of pediatric nonalcoholic fatty liver disease (NAFLD) is a concerning public health issue [1,2]. Pediatric NAFLD is closely associated with obesity, insulin resistance, and other metabolic syndrome components [3]. NAFLD in youth also can progress to more severe forms of the disease, including nonalcoholic steatohepatitis (NASH) and liver fibrosis [4–6], which may contribute to a greater burden of disease in adulthood. Notably, data from the United Network for Organ Sharing database support that NASH was the most rapidly growing indication for liver transplantation among young adults from 2002 to 2012 [7]. Together, this supports the need for more pediatric-specific research aiming to understand potential risk factors for youth-onset NAFLD.

The Developmental Origins of Health and Disease theory posits that suboptimal exposures during vulnerable developmental life stages, including the in utero period, can induce persistent metabolic and physiological disturbances that contribute to susceptibility to chronic diseases, including NAFLD [8], later in life [9]. Indeed, studies have shown that fetal exposure to markers of an obesogenic environment in utero, including maternal obesity [10,11] or specific maternal metabolic markers, such as glucose and/or lipids [12,13], is predictive of higher offspring hepatic fat in childhood. Maternal lifestyle during pregnancy, including both diet and physical activity patterns, may also play a critical role in influencing offspring NAFLD risk. Specifically, with regard to the maternal diet, animal models support an association of maternal high-sucrose and/or high-fat intake during pregnancy with hepatic steatosis in offspring [14–19]. Understanding the contribution of maternal diet quality during pregnancy to offspring NAFLD risk is important, but challenging, because of the complexity of dietary nutrients and the multiple ways in which these nutrients interact within the diet as a whole. However, limited evidence exists in humans on the link between maternal diet quality during pregnancy and later hepatic fat accrual among offspring.

The overall objective of this study was to examine associations between maternal diet quality during pregnancy and offspring hepatic fat in early childhood (~5 y) using data from the longitudinal Healthy Start Study in Colorado. Specifically, we assessed maternal diet quality using two distinct but complementary metrics: *1*) *maternal usual nutrient intakes* (that is, for energy, carbohydrates, protein, and fat), which provide insight into the effects of maternal macronutrient distribution during pregnancy; and *2*) *maternal dietary pattern scores* for three *a priori* indices [Healthy Eating Index-2010 (HEI-2010), Dietary Inflammation Index (DII)®, and Relative Mediterranean Diet (rMED) Scores], which provide insight into the synergistic effects of multiple foods and beverages consumed together during pregnancy. We hypothesized that poorer maternal diet quality during pregnancy, characterized by higher intakes of sugar and fat and lower adherence to "healthy" dietary patterns, would be associated with greater offspring hepatic fat accrual in early childhood.

Methods

Study population

The Healthy Start Study is an observational, prebirth cohort based in Colorado. A total of 1410 pregnant women were initially enrolled in the study from obstetric clinics at the University of Colorado Hospital from 2010 to 2014. Participant inclusion criteria were >15 y old, no prior stillbirths, <24 weeks of gestation, singleton pregnancy, and no pre-existing serious chronic disease (cancer, psychiatric disease, steroid-dependent asthma, or diabetes). In-person study visits with mother–child dyads were completed in early pregnancy (median: 17 wk) and midpregnancy (median: 27 wk), delivery (median postnatal age: 1 d), infancy (2 visits; median age: 5 mo and 22 mo), and early childhood (median age: 5 y; referred hereafter as the "early childhood visit"). All participants provided written informed consent and offspring ≥7 y at the early childhood visit provided oral assent for all study procedures. The study was approved by the Colorado Multiple Institutional Review Board. The Healthy Start Study is voluntarily registered as an observational study at clinicaltrials.gov (NCT02273297).

A flow chart summarizing the selection of participants for this study is shown in Figure 1. A total of 1311 of the 1410 mother–child dyads who were initially enrolled in early pregnancy had valid data for the maternal diet during pregnancy ($n = 44$ missing dietary data, $n = 47$ missing key dietary covariate information, and $n = 8$ with extreme energy intake for all recalls, which we defined as <500 or >5000 kcal/d similar to prior studies in pregnant women [20]). All other preprocessing steps performed on the maternal dietary data are described in detail next under "Maternal Dietary Assessment." Subsequently, 911 dyads returned for an in-person visit during early childhood. Among those dyads, a subset of 278 children underwent abdominal MRI in early childhood to assess hepatic fat (the outcome of interest), which comprised the analytical sample included in regression analyses to examine the associations between maternal diet during pregnancy and hepatic fat of the offspring in early childhood.

Maternal dietary assessment

The maternal diet during pregnancy was assessed by monthly, 24-h dietary recalls using the NCI Automated Self-Administered 24-h recall (ASA24) system [21]. The Nutrition Obesity Research Center at the University of North Carolina at Chapel Hill assisted both with data collection by ASA24 and dietary data analysis/processing. Intake of macronutrients and micronutrients were calculated per participant per recall. MyPyramid Food Equivalents were also derived using the United States Department of Agriculture's MyPyramid Equivalents Database (versions 1.0 and 2.0). Up to eight recalls were completed per participant, starting from the first study visit in early pregnancy through the end of pregnancy, resulting in a total of 3957 recalls completed by 1366 participants in pregnancy (23% with one recall, 27% with two recalls, 18% with three recalls, 13% with four recalls, 10% with five recalls, and 10% with six or more recalls). Among these, we excluded 59 recalls that were missing intake day of the week or gestational age at intake (key covariates for estimating usual intake; corresponding to $n = 47$ participants excluded) and 68 recalls with extreme energy intake (defined as <500 or >5000 kcal/d; corresponding to $n = 8$ participants excluded). The remaining 3830 recalls completed by 1311 participants across pregnancy were then used to calculate maternal usual nutrient intakes and dietary pattern scores.

Calculation of maternal usual nutrient intakes

The NCI method was used to estimate usual macronutrient intakes during pregnancy from the repeated ASA24 dietary

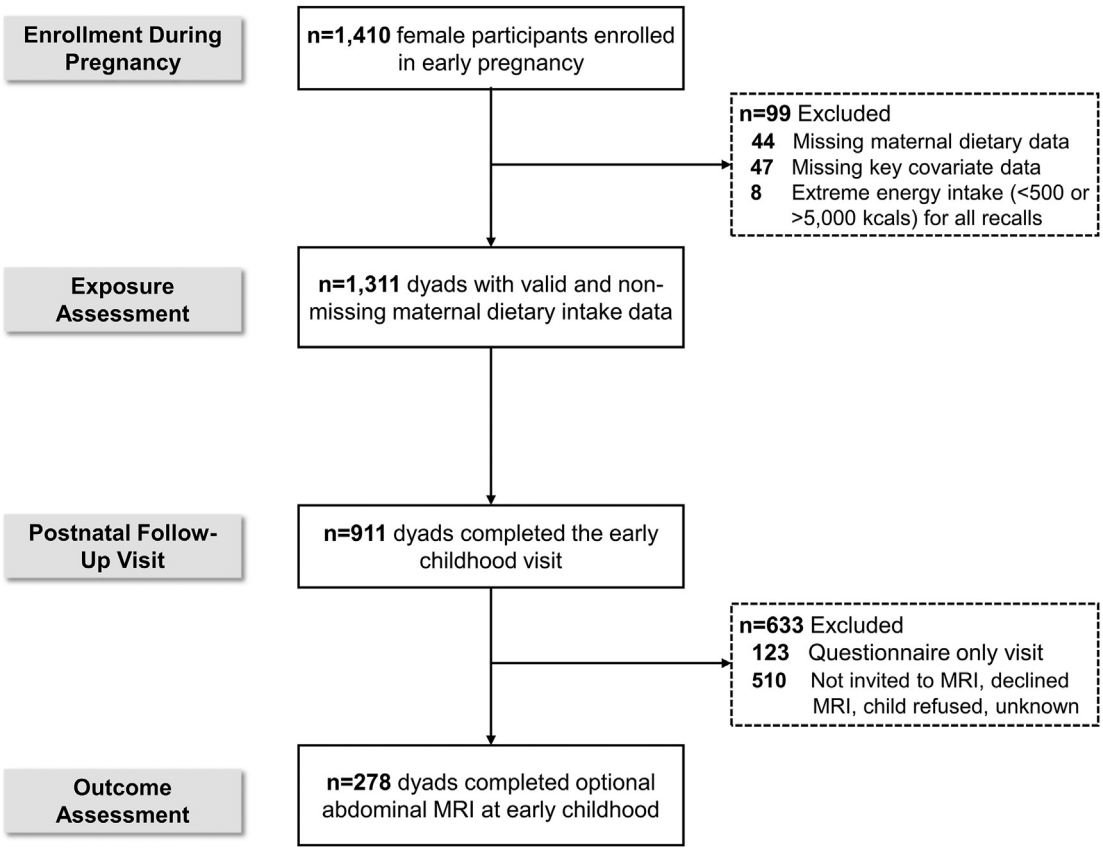

FIGURE 1. Flowchart summarizing the selection of participants.

recalls [22–26]. The macronutrients of interest were total energy, total carbohydrates, total sugar, added sugar, total protein, total fat, SFA, MUFA, and PUFA intake. Because all nutrients of interest were consumed by everyone on an almost daily basis, we used a 1-part, "amount only" model to predict usual intake. The exception was for added sugar, which was not consumed in 20 recalls (equating to <1% of all recalls); thus, prior to modeling, any zero intake values were replaced with a half of the minimum intake for added sugar among consumers [27]. We used the NCI macros NLMIXED_UNIVARIATE, NLMIXED_BIVARIATE, DISTRIB_BIVARIATE, and PREDICT_INTAKE_DENSITY (v1.2 for all) in SAS (v9.4) to model the usual intake for each nutrient as a nutrient density relative to energy intake (that is, % kcal/d, except for fiber, which was calculated as g/1000 kcal/d). All available recalls per participant across pregnancy were used for modeling, and all models were adjusted for covariates known to impact dietary intake when calculating usual intake, including recall sequence, day of the week (weekend compared with weekday), and gestational age at intake. The output was then used in downstream regression analyses to examine measurement error-corrected associations of maternal usual nutrient intake densities with offspring hepatic fat in early childhood. All SAS macros can be downloaded from the NCI website: https://prevention.cancer.gov/research-groups/biometry/measurement-error-impact/.

Calculation of maternal dietary pattern scores

We also calculated maternal scores for three a priori dietary pattern indices (HEI-2010, DII, and rMED) during pregnancy. Our goal in calculating three indices was to assess maternal adherence to different dietary patterns that are each defined by a unique combination of foods and/or nutrient intakes that relate to specific mechanisms of action (for example, inflammation), helping us to understand whether one dietary pattern is more beneficial than another in relation to offspring hepatic fat concentrations. In addition, all three dietary pattern indices have been associated with markers of altered neonatal development among offspring in the Healthy Start Study (that is, neonatal adiposity for HEI-2010 and DII [28,29] and cord blood DNA methylation for rMED [30]).

Healthy Eating Index-2010 (HEI-2010)

The HEI-2010 was developed to assess the diet quality based on adherence to the 2010 Dietary Guidelines for Americans, which would have been the current dietary guidelines at the time that maternal dietary intake was assessed in this study. Specifically, HEI-2010 consists of nine adequacy components (total fruit, whole fruit, total vegetables, greens and beans, whole grains, dairy, total protein, seafood and plant proteins, and fatty acids) and three moderation components (refined grains, sodium, and empty calories) [31,32]. As previously described [28], we calculated the average intake of each component across multiple recalls during pregnancy, and then converted intake to densities per 1000 kcal/d, except for the FA ratio subcomponent, which was calculated as the ratio of PUFA + MUFA intake (g/d) divided by SFA intake (g/d). Alcohol was not included in the "empty calories" component because consumption during pregnancy was minimal (<13 g alcohol/1000 kcal per recall).

Subcomponents were then scored from 0 to 5, 0 to 10, or 0 to 20 using published criteria [32], resulting in total scores that ranged from 0 (lowest adherence) to 100 (highest adherence). This was performed using SAS macros from the NCI website (https://epi.grants.cancer.gov/hei/sas-code.html).

Dietary Inflammation Index (DII)

The DII was developed as an indicator of the inflammatory potential of an individual's diet based on intake of dietary components shown to be associated with increased or decreased concentrations of circulating inflammatory markers [33]. DII scores were calculated based on average intake across multiple recalls during pregnancy for 28 nutrient intakes, as previously described [29]: energy, total fat, SFA, MUFA, PUFA, ω-3 PUFAs, ω-6 PUFAs, *trans*-fat, total carbohydrates, fiber, protein, cholesterol, iron, Vitamin A, Vitamin C, Vitamin D, Vitamin E, niacin, thiamine, riboflavin, Vitamin B6, Vitamin B12, folic acid, magnesium, zinc, selenium, alcohol, and caffeine. Inflammatory effect scores, which indicate the relative contribution of each nutrient to the final II score, were computed based on 1943 peer-reviewed articles, as described by Shivappa et al. [33]. Specifically, scores were first assigned as "+1" for anti-inflammatory nutrients and "−1" for proinflammatory nutrients and then adjusted based on the total number of articles that cited its pro- or anti-inflammatory effects. DII scores were calculated by standardizing nutrient intakes to global means, multiplying by their inflammatory effect scores, and taking the sum across nutrients [33].

Relative Mediterranean Diet Score (rMED)

The rMED score was developed to assess adherence to a Mediterranean-style diet based on nine key food groups (vegetables (excluding potatoes), legumes, fruits/nuts/seeds, fish and seafood, cereals, meat, dairy, olive oil, and alcohol) [34]. For this study, we used an adjusted rMED score that *excluded* alcohol due to the recommendation of no alcohol consumption during pregnancy, similar to others [35]. As previously described [30], for each food group, we calculated the average intake for each food group across multiple recalls during pregnancy, converted average intake to densities (per 1000 kcal/d), and then assigned a score of 0, 1, or 2 to the first, second, or third tertile of intake, respectively. For meat and dairy, tertile scoring was reversed (that is, higher consumption = lower score). For legumes, fish/seafood, and olive oil, intake had a skewed distribution due to a high prevalence of nonconsumers, which made it difficult to calculate tertiles. Instead, we set the first category to 0, which included >33% of the participants, and then defined the second and third categories by splitting the rest of the participants based on the median intake among those who consumed each food group. Total scores were calculated by summing subscores for all food groups and ranged from 0 (lowest) and 16 (highest adherence).

Offspring hepatic fat assessment

At the early childhood visit (when offspring were ~5 y of age), an abdominal MRI was performed on offspring participants to measure hepatic fat content, as previously described [36]. Briefly, a series of T1-weighted coronal images were acquired by trained technicians using a 3T HDx imager scanner (General Electric) or a 3T Skyra scanner (Siemens AG) while participants were awake and laying in the supine position. Hepatic fat was measured using a validated, multi-inference, 6-point MRI–proton density fat fraction technique and the Lipoquant plug-in for OsiriX [37], as previously described [36].

Covariate assessment

Maternal assessments performed during pregnancy have been described in detail [38–40]. Maternal sociodemographic variables, including race and ethnicity, education, household income, and maternal smoking during pregnancy were assessed by self-reported questionnaires during pregnancy. Prepregnancy BMI was calculated using maternal height measured at the first research visit and prepregnancy weight obtained from medical records at the first prenatal visit (91%) or self-reported at the first research visit [40]. Physical activity in pregnancy was assessed using the Pregnancy Physical Activity Questionnaire [41] as average metabolic equivalents (METs) in hours per week. All women were screened for gestational diabetes mellitus at 24–28 wk and results were abstracted from medical records. At both visits during pregnancy, fasting blood draws were also performed and used to measure maternal triglycerides [assessed using an AU400e Chemistry Analyzer (Olympus America Inc.)], as well as other metabolic markers, by the Clinical and Translational Research Center Core Laboratory at University of Colorado Hospital. Offspring sex was abstracted from medical records, and offspring race and ethnicity were determined by maternal self-report. At the early childhood visit, offspring height (cm) and weight (kg) were measured and BMI z-scores and percentiles were calculated using CDC 2000 growth charts [42]. Offspring fat mass, fat-free mass, and percent body fat were assessed by air displacement plethysmography [BODPOD (COSMED Inc.) with the pediatric option].

Statistical analyses

We tested associations of each maternal dietary predictor during pregnancy, the independent variable, with offspring hepatic fat in early childhood, and the dependent variable, using multivariable-adjusted linear regression models. Hepatic fat data were natural log-transformed prior to analyses to ensure normally distributed residuals in regression. We examined the effect of potential confounders on associations by adjusting models for covariates as follows: *model 1* = unadjusted; *model 2* = adjusted for offspring sex, offspring race and ethnicity, and offspring age in early childhood (y), maternal age at enrollment (y), maternal education (<12th grade, high school diploma, some college or associate degree, college degree, or graduate degree), parity (0, 1, or 2+ prior live births), prepregnancy BMI (kg/m^2), smoking during pregnancy (any/none), and physical activity (METs-h/wk) during pregnancy; *model 3* = adjusted for model 2 covariates plus maternal total energy intake (kcal/d) during pregnancy. In base models (model 1), we tested for effect modification by child sex using product interaction terms but found no evidence of a significant interaction (all P >0.05). Therefore, all results were reported for both sexes combined. To enhance the interpretability of estimates due to log transformation of the outcome, all regression estimates and 95% CIs were back transformed and, therefore, reflect the percentage change in offspring hepatic fat associated with each maternal dietary predictor (per 5 unit increase for maternal usual nutrient intakes and per 1 SD increase for maternal dietary pattern scores). We also reported whether P

values were below Bonferroni-corrected thresholds adjusted for multiple testing [$P < 0.005$ for maternal nutrient intakes ($\alpha = 0.05/10$ nutrients) and $P < 0.0167$ for dietary pattern scores ($\alpha = 0.05/3$ dietary pattern scores)]. All analyses were performed in SAS (version 9.4).

Post hoc analyses

After estimating the associations of maternal dietary pattern total scores with offspring hepatic fat, we further explored the associations of maternal dietary pattern subcomponents with offspring hepatic fat using similar linear regression models as above. This was performed for the 12 HEI-2010 subcomponents and 8 rMED subcomponents, using maternal intake density for each subcomponent as the independent variable in models. We did not explore the associations of the 28 DII subcomponents due to multiple testing concerns and because the DII was designed as a global measure of diet-associated inflammation.

Sensitivity analyses

We conducted sensitivity analyses to assess whether associations were robust to adjustment for other covariates of interest that were only available in a subset of participants. First, given our prior finding that maternal triglycerides were also associated with offspring hepatic fat in early childhood in this same cohort [12] and may mediate our findings, we compared results if we also adjusted for maternal triglycerides during pregnancy (assessed as average triglycerides across visits during pregnancy). Second, given other studies have shown that offspring adiposity may mediate associations of maternal overnutrition with offspring hepatic fat [10,43], we also compared results if we adjusted for offspring adiposity in early childhood (assessed as percent body fat). Across the sensitivity analyses, we compared the direction, magnitude, and precision of estimates before compared with after adjustment for the above covariates.

Results

Characteristics of participants

Characteristics of the mother–child dyads included in this study are shown in Table 1. The mean (SD) age of offspring at the early childhood visit was 4.8 ± 0.8 y. Approximately half of the children were non-Hispanic White (53%), followed by 27% Hispanic and 21% non-Hispanic Black or other, and most children were normal weight (79%) according to age- and sex-specific BMI percentiles (Table 1). The characteristics of this analytical sample were similar to the full sample of 1410 mother–child dyads enrolled in early pregnancy in terms of key sociodemographic and maternal/perinatal variables (Supplemental Table 1), except that our analytical sample had a higher percentage of mothers with a college or graduate degree (51%) and less gestational smoking (5%) compared with the full sample (44% with college or graduate degree and 9% gestational smoking). Correlations among the maternal dietary predictors of interest are reported in Supplemental Table 2.

Associations of maternal usual nutrient intakes in pregnancy with offspring hepatic fat

Estimates for the association of maternal usual nutrient intakes during pregnancy with offspring hepatic fat in early childhood from multivariable-adjusted linear regression models are shown in Table 2. Higher maternal fiber intake during pregnancy was associated with *lower* offspring log-hepatic fat in early childhood, and higher maternal total sugar and added sugar intakes during pregnancy were associated with *higher* offspring log-hepatic in early childhood in all three models (Table 2, all $P < 0.05$).

TABLE 1
Characteristics of mother–child dyads ($n = 278$)

Maternal characteristics in pregnancy	*n*	Mean (SD) or *n* (%)
Age at enrollment (y), mean (SD)	278	28.6 (5.8)
Maternal education, *n* (%)	278	
<12th Grade		32 (11%)
High school diploma		33 (12%)
Some college or associate degree		71 (26%)
College degree		74 (27%)
Graduate degree		68 (24%)
Household income, *n* (%)	278	
<$40,000		78 (28%)
$40,000–$70,000		52 (19%)
>$70,000		104 (37%)
Missing/do not know		44 (16%)
Parity, *n* (%)	278	
0 Prior live births		136 (49%)
1 Prior live births		91 (33%)
2+ Prior live births		51 (18%)
Prepregnancy BMI (kg/m^2), mean (SD)	278	26.9 (7.2)
Physical activity (MET-h/wk), mean (SD)	278	191.1 (94.1)
Reported energy intake (kcal/d), mean (SD)	278	2080 (664)
Gestational smoking, *n* (%)	278	15 (5%)
Offspring characteristics in early childhood	*n*	Mean (SD) or *n* (%)
Age (y), mean (SD)	278	4.8 (0.8)
Male sex, *n* (%)	278	134 (48%)
Race/ethnicity, *n* (%)	278	
Hispanic		75 (27%)
Non-Hispanic White		147 (53%)
Non-Hispanic Black		32 (12%)
Non-Hispanic Other		24 (9%)
BMI category, *n* (%)[1]	277	
Underweight (<5th percentile)		22 (8%)
Normal (5th to <85th percentile)		219 (79%)
Overweight (85th to <95th percentile)		22 (8%)
Obesity (≥95th percentile)		14 (5%)
Hepatic fat (%), median (IQR)	278	1.7 (1.2, 2.2)

MET, metabolic equivalents.

Associations of maternal dietary pattern scores in pregnancy with offspring hepatic fat

The mean (SD) for each maternal dietary pattern score were 56.2 (14.0) for HEI-2010 (range: 20.3–89.5); 0.32 (1.53) for DII (range: −3.8, 4.0); and 6.4 (2.4) for rMED (range: 0–15). Estimates for associations of each maternal dietary pattern score during pregnancy with offspring hepatic fat in early childhood from multivariable-adjusted linear regression models are shown in Table 3. Maternal HEI-2010 score during pregnancy was not associated with offspring hepatic fat in any of the models (Table 3). However, higher maternal DII score was associated with *higher* offspring hepatic fat in model 1 ($P = 0.03$;

TABLE 2
Associations of maternal usual nutrient intake with offspring log-hepatic fat in early childhood ($n = 278$)

Nutrient	Mean (SD)	Model 1[1]		Model 2[2]		Model 3[3]	
		β (95% CI)[4]	P	β (95% CI)[4]	P	β (95% CI)[4]	P
Energy (kcal/d)	2080 (664)	1.00 (0.97, 1.02)	0.76	0.99 (0.97, 1.02)	0.66	1.02 (0.98, 1.08)	0.33
CHO (% kcal/d)	50.4 (7.6)	1.02 (0.93, 1.12)	0.69	1.03 (0.94, 1.13)	0.52	1.04 (0.94, 1.14)	0.44
Fiber (g/1000 kcal)	9.4 (3.8)	0.89 (0.79, 0.99)	0.035	0.86 (0.75, 0.98)	0.021	0.82 (0.72, 0.94)	0.005*
Total sugar (% kcal/d)	23.3 (6.8)	1.11 (1.01, 1.21)	0.023	1.13 (1.03, 1.23)	0.010	1.15 (1.05, 1.26)	0.004*
Added sugar (% kcal/d)	11.9 (5.8)	1.12 (1.01, 1.25)	0.032	1.16 (1.03, 1.29)	0.011	1.18 (1.05, 1.32)	0.004*
Protein (% kcal/d)	16.1 (3.7)	1.01 (0.87, 1.17)	0.92	1.03 (0.88, 1.21)	0.68	0.98 (0.82, 1.17)	0.83
Total fat (% kcal/d)	35.1 (6.1)	0.97 (0.86, 1.09)	0.60	0.95 (0.84, 1.08)	0.43	0.95 (0.84, 1.08)	0.42
Saturated fat (% kcal/d)	12.2 (3.0)	1.04 (0.82, 1.32)	0.73	1.07 (0.84, 1.36)	0.59	0.99 (0.75, 1.31)	0.96
Monounsaturated fat (% kcal/d)	12.6 (2.5)	1.10 (0.84, 1.43)	0.49	1.06 (0.81, 1.38)	0.68	0.92 (0.66, 1.30)	0.65
Polyunsaturated fat (% kcal/d)	7.3 (2.4)	1.02 (0.74, 1.41)	0.91	1.01 (0.72, 1.41)	0.96	0.82 (0.54, 1.25)	0.35

[1] Model 1: Unadjusted.
[2] Model 2: Adjusted for offspring sex, race/ethnicity, and age in early childhood, maternal age at enrollment, maternal education, parity, pre-pregnancy BMI, smoking during pregnancy, and physical activity during pregnancy.
[3] Model 3: Adjusted for model 2 covariates plus maternal energy intake (kcal/d) during pregnancy.
[4] Coefficients are back transformed and represent the ratio of geometric means for the dependent variable (that is, the percentage change in offspring hepatic fat) per 5 unit increase in each maternal usual nutrient intake during pregnancy; except for energy intake (+100 kcal/d). Asterisk (*) indicates Bonferroni-corrected $P < 0.005$ ($\alpha = 0.05/10$ nutrients).

unadjusted) and model 2 ($P = 0.03$; adjusted for offspring and maternal confounders) (Table 3). After adjusting for maternal energy intake during pregnancy in model 3, the magnitude of the association between maternal DII scores and offspring hepatic fat was unchanged, but the association was no longer significant ($P = 0.07$) (Table 3). In contrast, a higher maternal rMED score was associated with *lower* offspring hepatic fat, although the association was significant only in model 3 (adjusted for offspring and maternal confounders and maternal energy intake during pregnancy; $P = 0.036$) (Table 3).

Post hoc analyses of dietary pattern subcomponents

Associations of the subcomponents for maternal HEI-2010 and rMED scores during pregnancy with offspring hepatic fat from linear regression models are shown in Figures 2 and 3, respectively, and summarized in Supplemental Table 3. Among the HEI-2010 subcomponents, maternal "greens and beans" intake (in cup equivalents/1000 kcal) was associated with lower offspring hepatic fat in early childhood, and maternal "empty calories" intake (in % kcal/d) was associated with higher offspring hepatic fat in fully adjusted linear regression models (model 3) (Figure 2, Supplemental Table 3). Among the rMED subcomponents, we found marginal inverse associations of maternal legume intake (in cup equivalents/1000 kcal) and offspring hepatic fat, and marginal positive associations of maternal meat intake (in oz equivalents/1000 kcal) with offspring hepatic fat; however, none of these associations were significant (Figure 3, Supplemental Table 3).

Sensitivity analyses

In sensitivity analyses, we found that most associations of maternal nutrient intakes and dietary pattern scores with offspring hepatic fat were unchanged in terms of directionality, effect size, and significance when additionally adjusted for average maternal triglycerides during pregnancy or offspring percentage of body fat in early childhood (Supplemental Table 4).

Discussion

In this study, we comprehensively examined the associations of maternal diet quality during pregnancy, assessed both in terms of individual nutrient intakes and *a priori* dietary patterns, with

TABLE 3
Associations of maternal dietary pattern scores with offspring log-hepatic fat in early childhood ($n = 278$)

Dietary pattern:	Mean (SD)[4]	Model 1[1]		Model 2[2]		Model 3[3]	
		β (95% CI)[5]	P	β (95% CI)[5]	P	β (95% CI)[5]	P
HEI-2010 Score	56.1 (14.0)	0.97 (0.92, 1.03)	0.32	0.97 (0.91, 1.04)	0.36	0.97 (0.90, 1.03)	0.30
DII Score	0.32 (1.53)	1.07 (1.01, 1.13)	0.030	1.08 (1.01, 1.15)	0.030	1.08 (0.99, 1.18)	0.07
rMED Score	6.4 (2.4)	0.95 (0.90, 1.01)	0.09	0.94 (0.88, 1.00)	0.05	0.93 (0.88, 0.99)	0.036

DII, dietary inflammatory index; HEI-2010, Healthy Eating Index-2010; rMED, Relative Mediterranean Diet Score.
[1] Model 1: Unadjusted.
[2] Model 2: Adjusted for offspring sex, race/ethnicity, and age in early childhood, maternal age at enrollment, maternal education, parity, pre-pregnancy BMI, smoking during pregnancy, and physical activity during pregnancy.
[3] Model 3: Adjusted for model 2 covariates plus maternal energy intake (kcal/d) during pregnancy.
[4] The ranges for each score among participants in this sample were as follows: HEI-2010, 20.3 to 89.5; rMED, 0 to 15; and DII, −3.8 to 4.0.
[5] Coefficients are back transformed and represent the ratio of geometric means for the dependent variable (that is. the percent change in offspring hepatic fat) per 1 SD increase in each dietary pattern score during pregnancy. Asterisk (*) indicates Bonferroni-corrected $P < 0.017$ ($\alpha = 0.05/3$ dietary pattern scores).

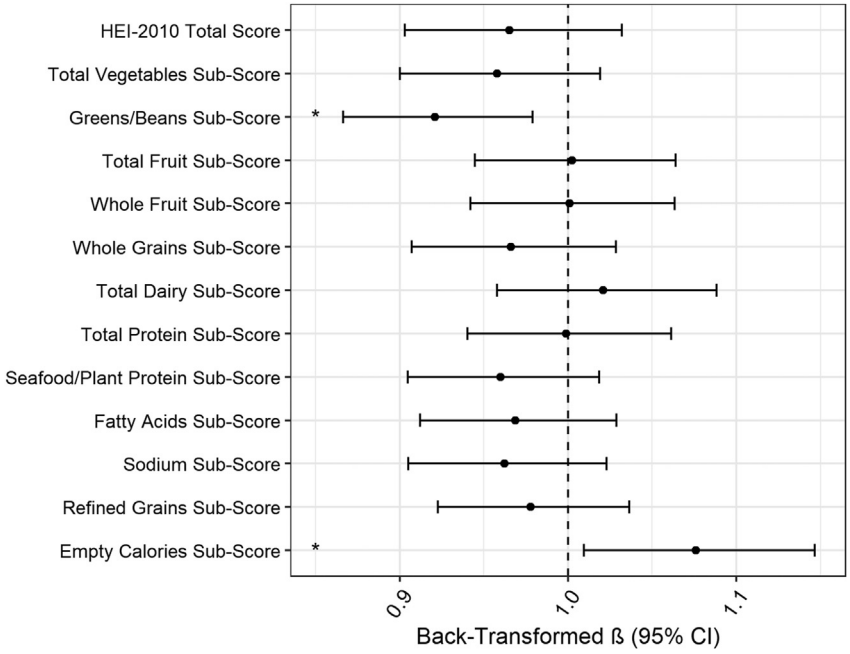

FIGURE 2. Associations of HEI-2010 subcomponents with offspring hepatic fat in early childhood ($n = 278$). Points and error bars are back-transformed regression estimates and 95% CIs, respectively, and represent the ratio of geometric means for the dependent variable (that is, the percent change in offspring hepatic fat) per 1 SD increase in each dietary pattern subcomponent. Asterisk (*) indicates associations with $P < 0.05$. All estimates are from linear regression models adjusted for offspring sex, race, ethnicity, age in early childhood, maternal age at enrollment, maternal education, parity, prepregnancy BMI, smoking during pregnancy, physical activity during pregnancy, and maternal energy intake (kcal/d) during pregnancy. HEI-2010, Healthy Eating Index-2010.

offspring hepatic fat measured by MRI in early childhood. Lower maternal fiber intake and higher maternal sugar intake, particularly as *added* sugar, were associated with higher offspring hepatic fat, pointing to a potential involvement of carbohydrate *quality* during pregnancy as a risk factor. In addition, lower adherence to a Mediterranean diet pattern and higher adherence to a proinflammatory diet pattern were associated with higher offspring hepatic fat in early childhood. These findings remained unchanged after adjusting for potential confounders like prepregnancy BMI and total energy intake during pregnancy, suggesting that the effects were independent of maternal energy balance. Additional studies are needed to confirm these initial findings; however, overall, our results suggest that maternal diet quality during pregnancy may be a lifecourse exposure associated with offspring risk of NAFLD.

Our findings underscore the value of considering both individual dietary components and holistic dietary patterns when assessing diet quality, an approach that also aligns with studies showing that both single- and multicomponent dietary interventions can be effective in improving health outcomes in adults [44,45]. With respect to maternal nutrient intakes during pregnancy, we observed opposing associations of maternal fiber intake (protective) and maternal added sugar intake (detrimental) with offspring hepatic fat. Consistent with these findings, our analyses evaluating the effects of dietary pattern subcomponents also showed that intake of fiber-rich food groups such as green vegetables and legumes (subcomponents of HEI-2010 and rMED scores) were associated with lower offspring hepatic fat, whereas the intake of energy-dense "empty calories" (a subcomponent of HEI-2010 that includes added sugar from

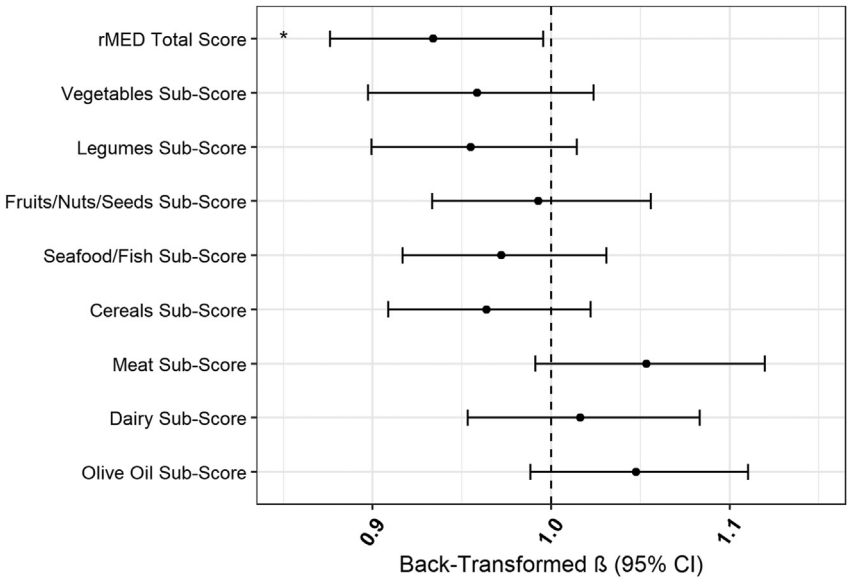

FIGURE 3. Associations of rMED subcomponents with offspring hepatic fat in early childhood ($n = 278$). Points and error bars are back-transformed regression estimates and 95% CIs, respectively, and represent the ratio of geometric means for the dependent variable (that is, the percent change in offspring hepatic fat) per 1 SD increase in each dietary pattern subcomponent. Asterisk (*) indicates associations with $P < 0.05$. All estimates are from linear regression models adjusted for offspring sex, race, ethnicity, age in early childhood, maternal age at enrollment, maternal education, parity, prepregnancy BMI, smoking during pregnancy, physical activity during pregnancy, and maternal energy intake (kcal/d) during pregnancy. rMED, Relative Mediterranean Diet Score.

sugar-sweetened beverages) was associated with higher offspring hepatic fat.

Different mechanisms may explain the associations we found between these maternal nutrient intakes and offspring NAFLD susceptibility. For example, our findings are consistent with evidence that higher intake of dietary fiber and low-GI carbohydrates during pregnancy are associated with better maternal weight control and improved metabolic homeostasis [46–49], which may be mediating factors underlying our findings. Our results, however, were relatively unchanged in sensitivity analyses adjusted for maternal triglycerides during pregnancy, a metabolic marker previously associated with offspring hepatic fat in early childhood in this same mother–child cohort [12]. This suggests that maternal triglyceride concentrations do not mediate the associations observed in this analysis. Alternatively, maternal fiber or sugar intake during pregnancy have been associated with gut microbiota alterations in mothers and/or offspring [50–53], which may, in turn, predispose offspring to fatty liver via metabolic and inflammatory pathways [19]. Such microbiome changes [54], as well as other in utero metabolic alterations related to placental inflammation, oxidative stress, and/or fetal adipose tissue physiology [55–57], represent biological pathways that may be linking maternal diet quality with offspring risk of NAFLD and will need to be explored as a future direction.

We also examined associations of a priori maternal dietary patterns during pregnancy, which capture the synergistic effects of foods and beverages consumed together, with offspring hepatic fat. This analysis showed that higher scores for a proinflammatory diet pattern and lower scores for a Mediterranean-style diet pattern predicted higher offspring hepatic fat in early childhood. To our knowledge, no other human studies of these dietary pattern indices during pregnancy have focused on offspring hepatic fat specifically as an outcome, although studies have assessed associations with other measures of offspring size. Notably, higher DII scores during pregnancy (reflecting a more inflammatory diet) have been associated with smaller size at birth (both in terms of weight and length) [58–60], whereas higher Mediterranean diet scores during pregnancy have been associated with increased placental weight and fetal size [61], and lower risk of fetal growth restriction [62] and low birth weight [63]. Related to these findings, we recently showed that body composition trajectories characterized by smaller birth size followed by faster rates of adiposity accretion in the first 5 y were a risk factor for higher hepatic fat in early childhood among offspring in the Healthy Start Study [64]. Taken together, these findings suggest that offspring size and/or body composition early in life should be investigated in the future as mediating factors that may link maternal dietary patterns with offspring hepatic fat later in childhood.

Limitations of this study include using a self-reported method (24-h dietary recalls) to assess maternal dietary intake, which may be prone to recall and social desirability biases. We did, however, take several steps to limit the measurement error, such as performing multiple, repeated 24-h dietary recalls [65], calculating usual nutrient intakes using the NCI method [22,24], and assessing energy-adjusted associations [66]. We also evaluated maternal diet quality using 2 approaches (based on usual nutrient intakes and dietary pattern adherence) and, although this provided a comprehensive assessment of the exposure of interest, only a few maternal diet–offspring hepatic fat associations survived multiple testing corrections. As such, our work will need to be replicated in other studies. In this study, we did not assess trimester-specific associations of maternal diet with offspring hepatic fat and instead focused on average diet across multiple dietary recalls that spanned from mid-to-late pregnancy. We also did not explore whether postnatal dietary exposures, such as breastfeeding during infancy or diet quality during childhood, have mediating or modifying effects on the observed associations. Both of these research questions will be important future research directions. Strengths of this study include the use of a sophisticated MRI–proton density fat fraction technique to assess offspring hepatic fat in early childhood, which is more sensitive and specific than other methods of detecting hepatic fat, such as ultrasound [67], increasing the reproducibility and rigor of our findings. The longitudinal study design, starting with comprehensive assessments of mothers in early pregnancy and continuing on offspring through infancy and childhood, allowed us to assess the temporality of associations and adjust for a variety of covariates.

In conclusion, poorer maternal diet quality during pregnancy, particularly characterized by lower carbohydrate quality (lower fiber and higher sugar), lower adherence to a Mediterranean diet pattern, and higher adherence to a proinflammatory diet pattern, was associated with offspring hepatic fat in early childhood (~5 y old) independent of child adiposity. Although additional research is needed to validate these findings in other populations and determine the underlying mechanisms at play, our findings may help to inform prenatal dietary interventions aimed at improving metabolic health and reducing NAFLD risk among offspring.

Data availability statement

The datasets analysed during the current study may be requested pending application to and approval by the Healthy Start Study.

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Author contribution

The authors' responsibilities were as follows—CCC, KS, and DD: conceived and designed the study; CCC: performed data analyses and wrote the first draft of the manuscript; KAS, ALBS, APS, CF, JFF, LKK, BFM, JRH, and NS: assisted with data cleaning, calculation of dietary pattern scores, and writing the manuscript; AS: oversaw MRI acquisition and analyses; WP and SSS: assisted with data interpretation and writing the manuscript; and all authors: read, contributed to, and approved the final manuscript.

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Author disclosures

JRH owns a controlling interest in Connecting Health Innovations LLC (CHI), a company that has licensed the right to his invention of the dietary inflammatory index (DII) from the University of South Carolina to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. NS is an employee of CHI. The subject matter of this article will not have any direct bearing on that work, nor has that activity exerted any influence on this project.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tjnut.2023.01.039.

References

[1] A.K. Sahota, W.L. Shapiro, K.P. Newton, S.T. Kim, J. Chung, J.B. Schwimmer, The incidence of nonalcoholic fatty liver disease in children: 2009–2018, Pediatrics 146 (6) (2020), e20200771, https://doi.org/10.1542/peds.2020-0771.

[2] E.L. Anderson, L.D. Howe, H.E. Jones, J.P. Higgins, D.A. Lawlor, A. Fraser, The prevalence of non-alcoholic fatty liver disease in children and adolescents: a systematic review and meta-analysis, PLOS ONE 10 (10) (2015), e0140908, https://doi.org/10.1371/journal.pone.0140908.

[3] D. Tricò, S. Caprio, G. Rosaria Umano, B. Pierpont, J. Nouws, A. Galderisi, et al., Metabolic features of non-alcoholic fatty liver (NAFL) in obese adolescents: findings from a multiethnic cohort, Hepatology 68 (4) (2018) 1376–1390, https://doi.org/10.1002/hep.30035.

[4] A.E. Feldstein, P. Charatcharoenwitthaya, S. Treeprasertuk, J.T. Benson, F.B. Enders, P. Angulo, The natural history of nonalcoholic fatty liver disease in children: follow-up study for up to 20-years, Gut 58 (11) (2009) 1538–1544, https://doi.org/10.1136/gut.2008.171280.

[5] C.E. Cioffi, J.A. Welsh, R.L. Cleeton, S.A. Caltharp, R. Romero, M.L. Wulkan, et al., Natural history of NAFLD diagnosed in childhood: a single-center study, Children (Basel). 4 (5) (2017), https://doi.org/10.3390/children4050034.

[6] A.X. Holterman, G. Guzman, G. Fantuzzi, H. Wang, K. Aigner, A. Browne, et al., Nonalcoholic fatty liver disease in severely obese adolescent and adult patients, Obesity (Silver Spring) 21 (3) (2013) 591–597, https://doi.org/10.1002/oby.20174.

[7] I. Doycheva, D. Issa, K.D. Watt, R. Lopez, G. Rifai, N. Alkhouri, Nonalcoholic steatohepatitis is the most rapidly increasing indication for liver transplantation in young adults in the United States, J. Clin. Gastroenterol. 52 (4) (2018) 339–346, https://doi.org/10.1097/mcg.0000000000000925.

[8] J.E. Friedman, Developmental programming of obesity and diabetes in mouse, monkey, and man in 2018: where are we headed? Diabetes 67 (11) (2018) 2137–2151, https://doi.org/10.2337/dbi17-0011.

[9] M.A. Hanson, P.D. Gluckman, Early developmental conditioning of later health and disease: physiology or pathophysiology? Physiol. Rev. 94 (4) (2014) 1027–1076, https://doi.org/10.1152/physrev.00029.2013.

[10] A. Bellatorre, A. Scherzinger, E. Stamm, M. Martinez, B. Ringham, D. Dabelea, Fetal overnutrition and adolescent hepatic fat fraction: the exploring perinatal outcomes in children study, J. Pediatr. 192 (2018) 165–170, https://doi.org/10.1016/j.jpeds.2017.09.008, e1.

[11] S. Patel, D.A. Lawlor, M. Callaway, C. Macdonald-Wallis, N. Sattar, A. Fraser, Association of maternal diabetes/glycosuria and pre-pregnancy body mass index with offspring indicators of non-alcoholic fatty liver disease, BMC Pediatr 16 (2016) 47, https://doi.org/10.1186/s12887-016-0585-y.

[12] C.C. Cohen, E.C. Francis, W. Perng, K.A. Sauder, A. Scherzinger, S.S. Sundaram, et al., Exposure to maternal fuels during pregnancy and offspring hepatic fat in early childhood: the Healthy Start Study, Pediatr. Obes. 17 (7) (2022), e12902, https://doi.org/10.1111/ijpo.12902.

[13] M.L. Geurtsen, R.J. Wahab, J.F. Felix, R. Gaillard, V.W.V. Jaddoe, Maternal early-pregnancy glucose concentrations and liver fat among school-age children, Hepatology 74 (4) (2021) 1902–1913, https://doi.org/10.1002/hep.31910.

[14] B.M. Gregorio, V. Souza-Mello, J.J. Carvalho, C.A. Mandarim-de-Lacerda, M.B. Aguila, Maternal high-fat intake predisposes nonalcoholic fatty liver disease in C57BL/6 offspring, Am. J. Obstet. Gynecol. 203 (5) (2010) 495.e1–495.e8, https://doi.org/10.1016/j.ajog.2010.06.042.

[15] M. Kjaergaard, C. Nilsson, A. Rosendal, M.O. Nielsen, K. Raun, Maternal chocolate and sucrose soft drink intake induces hepatic steatosis in rat offspring associated with altered lipid gene expression profile, Acta Physiol 210 (1) (2014) 142–153, https://doi.org/10.1111/apha.12138.

[16] S.R. Thorn, K.C. Baquero, S.A. Newsom, K.C. El Kasmi, B.C. Bergman, G.I. Shulman, et al., Early life exposure to maternal insulin resistance has persistent effects on hepatic NAFLD in juvenile nonhuman primates, Diabetes 63 (8) (2014) 2702–2713, https://doi.org/10.2337/db14-0276.

[17] C.E. McCurdy, J.M. Bishop, S.M. Williams, B.E. Grayson, M.S. Smith, J.E. Friedman, et al., Maternal high-fat diet triggers lipotoxicity in the fetal livers of nonhuman primates, J. Clin. Invest. 119 (2) (2009) 323–335, https://doi.org/10.1172/JCI32661.

[18] U.D. Wankhade, Y. Zhong, P. Kang, M. Alfaro, S.V. Chintapalli, K.M. Thakali, et al., Enhanced offspring predisposition to steatohepatitis with maternal high-fat diet is associated with epigenetic and microbiome alterations, PLOS ONE 12 (4) (2017), e0175675, https://doi.org/10.1371/journal.pone.0175675.

[19] U.D. Wankhade, Y. Zhong, P. Kang, M. Alfaro, S.V. Chintapalli, B.D. Piccolo, et al., Maternal high-fat diet programs offspring liver steatosis in a sexually dimorphic manner in association with changes in gut microbial ecology in mice, Sci. Rep. 8 (1) (2018) 16502, https://doi.org/10.1038/s41598-018-34453-0.

[20] A.P. Starling, K.A. Sauder, J.L. Kaar, A.L. Shapiro, A.M. Siega-Riz, D. Dabelea, Maternal dietary patterns during pregnancy are associated with newborn body composition, J Nutr 147 (7) (2017) 1334–1339, https://doi.org/10.3945/jn.117.248948.

[21] A.F. Subar, S.I. Kirkpatrick, B. Mittl, T.P. Zimmerman, F.E. Thompson, C. Bingley, et al., The automated self-administered 24-hour dietary recall (ASA24): a resource for researchers, clinicians, and educators from the National Cancer Institute, J. Acad. Nutr. Diet. 112 (8) (2012) 1134–1137, https://doi.org/10.1016/j.jand.2012.04.016.

[22] V. Kipnis, D. Midthune, D.W. Buckman, K.W. Dodd, P.M. Guenther, S.M. Krebs-Smith, et al., Modeling data with excess zeros and measurement error: application to evaluating relationships between episodically consumed foods and health outcomes, Biometrics 65 (4) (2009) 1003–1010, https://doi.org/10.1111/j.1541-0420.2009.01223.x.

[23] J.A. Tooze, V. Kipnis, D.W. Buckman, R.J. Carroll, L.S. Freedman, P.M. Guenther, et al., A mixed-effects model approach for estimating the distribution of usual intake of nutrients: the NCI method, Stat. Med. 29 (27) (2010) 2857–2868, https://doi.org/10.1002/sim.4063.

[24] J.A. Tooze, D. Midthune, K.W. Dodd, L.S. Freedman, S.M. Krebs-Smith, A.F. Subar, et al., A new statistical method for estimating the usual intake of episodically consumed foods with application to their

distribution, J. Am. Diet. Assoc. 106 (10) (2006) 1575–1587, https://doi.org/10.1016/j.jada.2006.07.003.
[25] L.S. Freedman, A. Schatzkin, D. Midthune, V. Kipnis, Dealing with dietary measurement error in nutritional cohort studies, J. Natl. Cancer Inst. 103 (14) (2011) 1086–1092, https://doi.org/10.1093/jnci/djr189.
[26] L.S. Freedman, D. Midthune, R.J. Carroll, N. Tasevska, A. Schatzkin, J. Mares, et al., Using regression calibration equations that combine self-reported intake and biomarker measures to obtain unbiased estimates and more powerful tests of dietary associations, Am. J. Epidemiol. 174 (11) (2011) 1238–1245, https://doi.org/10.1093/aje/kwr248.
[27] K.A. Herrick, L.M. Rossen, R. Parsons, K.W. Dodd, Estimating usual dietary intake from National Health and Nutrition Examination Survey data using the National Cancer Institute method, Vital Health Stat 2 (178) (2018) 1–63. PMID: 29775432.
[28] A.L.B. Shapiro, J.L. Kaar, T.L. Crume, A.P. Starling, A.M. Siega-Riz, B.M. Ringham, et al., Maternal diet quality in pregnancy and neonatal adiposity: the Healthy Start Study, Int. J. Obes (Lond). 40 (7) (2016) 1056–1062, https://doi.org/10.1038/ijo.2016.79.
[29] B.F. Moore, K.A. Sauder, A.P. Starling, J.R. Hébert, N. Shivappa, B.M. Ringham, et al., Proinflammatory diets during pregnancy and neonatal adiposity in the Healthy Start Study, J. Pediatr. 195 (2018) 121–127, https://doi.org/10.1016/j.jpeds.2017.10.030, e2.
[30] L.K. Küpers, S. Fernández-Barrés, A. Nounu, C. Friedman, R. Fore, G. Mancano, et al., Maternal Mediterranean diet in pregnancy and newborn DNA methylation: a meta-analysis in the PACE Consortium, Epigenetics 17 (11) (2022) 1419–1431, https://doi.org/10.1080/15592294.2022.2038412.
[31] P.M. Guenther, S.I. Kirkpatrick, J. Reedy, S.M. Krebs-Smith, D.W. Buckman, K.W. Dodd, et al., The Healthy Eating Index-2010 is a valid and reliable measure of diet quality according to the 2010 Dietary Guidelines for Americans, J. Nutr. 144 (3) (2014) 399–407, https://doi.org/10.3945/jn.113.183079.
[32] P.M. Guenther, K.O. Casavale, J. Reedy, S.I. Kirkpatrick, H.A.B. Hiza, K.J. Kuczynski, et al., Update of the Healthy Eating Index: HEI-2010, J. Acad. Nutr. Diet. 113 (4) (2013) 569–580, https://doi.org/10.1016/j.jand.2012.12.016.
[33] N. Shivappa, S.E. Steck, T.G. Hurley, J.R. Hussey, J.R. Hébert, Designing and developing a literature-derived, population-based dietary inflammatory index, Public Health Nutr 17 (8) (2014) 1689–1696, https://doi.org/10.1017/S1368980013002115.
[34] G. Buckland, A. Agudo, L. Luján, P. Jakszyn, H. B Bueno-de-Mesquita, D. Palli, et al., Adherence to a Mediterranean diet and risk of gastric adenocarcinoma within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study, Am. J. Clin. Nutr. 91 (2) (2010) 381–390, https://doi.org/10.3945/ajcn.2009.28209.
[35] S. Fernández-Barrés, D. Romaguera, D. Valvi, D. Martínez, J. Vioque, E.M. Navarrete-Muñoz, et al., Mediterranean dietary pattern in pregnant women and offspring risk of overweight and abdominal obesity in early childhood: the INMA birth cohort study, Pediatr. Obes. 11 (6) (2016) 491–499, https://doi.org/10.1111/ijpo.12092.
[36] C.C. Cohen, W. Perng, S.S. Sundaram, A. Scherzinger, K. Shankar, D. Dabelea, Hepatic fat in early childhood is independently associated with estimated insulin resistance: the Healthy Start Study, J. Clin. Endocrinol. Metab. 106 (11) (2021) 3140–3150, https://doi.org/10.1210/clinem/dgab541.
[37] L.P. Smits, B.F. Coolen, M.D. Panno, J.H. Runge, W.H. Nijhof, J. Verheij, et al., Noninvasive differentiation between hepatic steatosis and steatohepatitis with MR imaging enhanced with USPIOs in patients with nonalcoholic fatty liver disease: a proof-of-concept study, Radiology 278 (3) (2016) 782–791, https://doi.org/10.1148/radiol.2015150952.
[38] T.L. Crume, A.L. Shapiro, J.T. Brinton, D.H. Glueck, M. Martinez, M. Kohn, et al., Maternal fuels and metabolic measures during pregnancy and neonatal body composition: the Healthy Start Study, J. Clin. Endocrinol. Metab. 100 (4) (2015) 1672–1680, https://doi.org/10.1210/jc.2014-2949.
[39] A.L.B. Shapiro, S.J. Schmiege, J.T. Brinton, D. Glueck, T.L. Crume, J.E. Friedman, et al., Testing the fuel-mediated hypothesis: maternal insulin resistance and glucose mediate the association between maternal and neonatal adiposity, the Healthy Start Study, Diabetologia 58 (5) (2015) 937–941, https://doi.org/10.1007/s00125-015-3505-z.
[40] A.P. Starling, J.T. Brinton, D.H. Glueck, A.L. Shapiro, C.S. Harrod, A.M. Lynch, et al., Associations of maternal BMI and gestational weight gain with neonatal adiposity in the Healthy Start Study, Am. J. Clin. Nutr. 101 (2) (2015) 302–309, https://doi.org/10.3945/ajcn.114.094946.
[41] L. Chasan-Taber, M.D. Schmidt, D.E. Roberts, D. Hosmer, G. Markenson, P.S. Freedson, Development and validation of a Pregnancy Physical Activity Questionnaire, Med. Sci. Sports Exerc. 36 (10) (2004) 1750–1760.
[42] R.J. Kuczmarski, C.L. Ogden, S.S. Guo, L.M. Grummer-Strawn, K.M. Flegal, Z. Mei, et al., 2000 CDC growth charts for the United States: methods and development, Vital Health Stat 11 (246) (2002) 1–190. PMID: 12043359.
[43] A. Sekkarie, J.A. Welsh, K. Northstone, A.D. Stein, U. Ramakrishnan, M.B. Vos, Associations of maternal diet and nutritional status with offspring hepatic steatosis in the Avon longitudinal study of parents and children, BMC Nutr 7 (1) (2021) 28, https://doi.org/10.1186/s40795-021-00433-3.
[44] O. Ajala, P. English, J. Pinkney, Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes, Am. J. Clin. Nutr. 97 (3) (2013) 505–516, https://doi.org/10.3945/ajcn.112.042457.
[45] S.L. Pagoto, B.M. Appelhans, A call for an end to the diet debates, JAMA 310 (7) (2013) 687–688, https://doi.org/10.1001/jama.2013.8601.
[46] A. Basu, D. Feng, P. Planinic, J.L. Ebersole, T.J. Lyons, J.M. Alexander, Dietary blueberry and soluble fiber supplementation reduces risk of gestational diabetes in women with obesity in a randomized controlled trial, J. Nutr. 151 (5) (2021) 1128–1138, https://doi.org/10.1093/jn/nxaa435.
[47] X. Zhang, Y. Gong, K. Della Corte, D. Yu, H. Xue, S. Shan, et al., Relevance of dietary glycemic index, glycemic load and fiber intake before and during pregnancy for the risk of gestational diabetes mellitus and maternal glucose homeostasis, Clin. Nutr. 40 (5) (2021) 2791–2799, https://doi.org/10.1016/j.clnu.2021.03.041.
[48] H.R. Hull, A. Herman, H. Gibbs, B. Gajewski, K. Krase, S.E. Carlson, et al., The effect of high dietary fiber intake on gestational weight gain, fat accrual, and postpartum weight retention: a randomized clinical trial, BMC Pregnancy Childbirth 20 (1) (2020) 319, https://doi.org/10.1186/s12884-020-03016-5.
[49] W.J. Ma, Z.H. Huang, B.X. Huang, B.H. Qi, Y.J. Zhang, B.X. Xiao, et al., Intensive low-glycaemic-load dietary intervention for the management of glycaemia and serum lipids among women with gestational diabetes: a randomized control trial, Public Health Nutr 18 (8) (2015) 1506–1513, https://doi.org/10.1017/s1368980014001992.
[50] S. Astbury, A. Song, M. Zhou, B. Nielsen, A. Hoedl, B.P. Willing, et al., High fructose intake during pregnancy in rats influences the maternal microbiome and gut development in the offspring, Front. Genet. 9 (2018) 203, https://doi.org/10.3389/fgene.2018.00203.
[51] Y. Li, H. Liu, L. Zhang, Y. Yang, Y. Lin, Y. Zhuo, et al., Maternal dietary fiber composition during gestation induces changes in offspring antioxidative capacity, inflammatory response, and gut microbiota in a sow model, Int. J. Mol. Sci. 21 (1) (2019), https://doi.org/10.3390/ijms21010031.
[52] H.Y. Fan, Y.T. Tung, Y.S.H. Yang, J.B. Hsu, C.Y. Lee, T.H. Chang, et al., Maternal vegetable and fruit consumption during pregnancy and its effects on infant gut microbiome, Nutrients 13 (5) (2021), https://doi.org/10.3390/nu13051559.
[53] M.L. Ruebel, S.P. Gilley, C.R. Sims, Y. Zhong, D. Turner, S.V. Chintapalli, et al., Associations between maternal diet, body composition and gut microbial ecology in pregnancy, Nutrients 13 (9) (2021) 3295, https://doi.org/10.3390/nu13093295.
[54] S. Wang, C.A. Ryan, P. Boyaval, E.M. Dempsey, R.P. Ross, C. Stanton, Maternal vertical transmission affecting early-life microbiota development, Trends Microbiol 28 (1) (2020) 28–45, https://doi.org/10.1016/j.tim.2019.07.010.
[55] S.R. Wesolowski, K.C.E. Kasmi, K.R. Jonscher, J.E. Friedman, Developmental origins of NAFLD: a womb with a clue, Nat. Rev. Gastroenterol. Hepatol. 14 (2) (2017) 81–96, https://doi.org/10.1038/nrgastro.2016.160.
[56] S. Lecoutre, C. Breton, Maternal nutritional manipulations program adipose tissue dysfunction in offspring, Front. Physiol. 6 (2015) 158, https://doi.org/10.3389/fphys.2015.00158.
[57] N. Murabayashi, T. Sugiyama, L. Zhang, Y. Kamimoto, T. Umekawa, N. Ma, et al., Maternal high-fat diets cause insulin resistance through inflammatory changes in fetal adipose tissue, Eur. J. Obstet. Gynecol. Reprod. Biol. 169 (1) (2013) 39–44, https://doi.org/10.1016/j.ejogrb.2013.02.003.
[58] L.W. Chen, A.M. Aubert, N. Shivappa, J.Y. Bernard, S.M. Mensink-Bout, A.A. Geraghty, et al., Associations of maternal dietary inflammatory potential and quality with offspring birth outcomes: an individual

participant data pooled analysis of 7 European cohorts in the ALPHABET consortium, PLOS Med 18 (1) (2021), e1003491, https://doi.org/10.1371/journal.pmed.1003491.
[59] P. Navarro, N. Shivappa, J.R. Hébert, J. Mehegan, C.M. Murrin, C.C. Kelleher, et al., Intergenerational associations of dietary inflammatory index with birth outcomes and weight status at age 5 and 9: results from the lifeways cross-generation cohort study, Pediatr. Obes. 15 (3) (2020), e12588, https://doi.org/10.1111/ijpo.12588.
[60] S. Sen, S.L. Rifas-Shiman, N. Shivappa, M.D. Wirth, J.R. Hébert, D.R. Gold, et al., Dietary inflammatory potential during pregnancy is associated with lower fetal growth and breastfeeding failure: results from project viva, J. Nutr. 146 (4) (2016) 728–736, https://doi.org/10.3945/jn.115.225581.
[61] S. Timmermans, R.P. Steegers-Theunissen, M. Vujkovic, H. den Breeijen, H. Russcher, J. Lindemans, et al., The Mediterranean diet and fetal size parameters: the Generation R Study, Br. J. Nutr. 108 (8) (2012) 1399–1409, https://doi.org/10.1017/S000711451100691X.
[62] L. Chatzi, M. Mendez, R. Garcia, T. Roumeliotaki, J. Ibarluzea, A. Tardón, et al., Mediterranean diet adherence during pregnancy and fetal growth: INMA (Spain) and RHEA (Greece) mother–child cohort studies, Br. J. Nutr. 107 (1) (2012) 135–145, https://doi.org/10.1017/s0007114511002625.
[63] S.F. Yisahak, S.L. Mumford, J. Grewal, M. Li, C. Zhang, K.L. Grantz, et al., Maternal diet patterns during early pregnancy in relation to neonatal outcomes, Am. J. Clin. Nutr. 114 (1) (2021) 358–367, https://doi.org/10.1093/ajcn/nqab019.
[64] C.C. Cohen, K.K. Harrall, S.P. Gilley, W. Perng, K.A. Sauder, A. Scherzinger, et al., Body composition trajectories from birth to 5 years and hepatic fat in early childhood, Am. J. Clin. Nutr. 116 (4) (2022) 1010–1018, https://doi.org/10.1093/ajcn/nqac168.
[65] R.S. Gibson, U.R. Charrondiere, W. Bell, Measurement errors in dietary assessment using self-reported 24-hour recalls in low-income countries and strategies for their prevention, Adv. Nutr. 8 (6) (2017) 980–991, https://doi.org/10.3945/an.117.016980.
[66] V. Kipnis, A.F. Subar, D. Midthune, L.S. Freedman, R. Ballard-Barbash, R.P. Troiano, et al., Structure of dietary measurement error: results of the OPEN biomarker Study, Am. J. Epidemiol. 158 (1) (2003) 14–21, https://doi.org/10.1093/aje/kwg091.
[67] Y.N. Zhang, K.J. Fowler, G. Hamilton, J.Y. Cui, E.Z. Sy, M. Balanay, et al., Liver fat imaging-a clinical overview of ultrasound, CT, and MR imaging, Br. J. Radiol. 91 (1089) (2018), 20170959, https://doi.org/10.1259/bjr.20170959.