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TITLE PAGE:

"Exposure to maternal fuels during pregnancy and offspring hepatic fat in early childhood: The Healthy Start Study"

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ABSTRACT:

Background: Intrauterine overnutrition has been associated with pediatric nonalcoholic fatty liver disease (NAFLD), but the exact mechanisms involved remain unclear.

Objective: To examine whether maternal fuels and metabolic markers during pregnancy are associated with offspring hepatic fat in childhood.

Methods: This analysis included 286 mother-child pairs from the Healthy Start Study, a longitudinal pre-birth cohort in Colorado. Fasting blood draws were collected in early pregnancy (~17 weeks) and mid pregnancy (~27 weeks). Offspring hepatic fat was assessed by magnetic resonance imaging (MRI) at ~5 years.

Results: In early pregnancy, maternal triglycerides (TGs) and free fatty acids (FFAs) were positively associated with offspring hepatic fat [Back-transformed β (95% CI): 1.15 (1.05,1.27) per 1 standard deviation (SD) TGs; 1.14 (1.05,1.23) per 1 SD FFAs]. Maternal total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) were also associated with offspring hepatic fat, but only among boys [1.22 (1.08,1.37) per 1 SD TC; 1.21 (1.07,1.37) per 1 SD LDL-C]. In mid pregnancy, only maternal TGs remained associated with offspring hepatic fat. Adjusting for potential confounders or mediators did not affect associations.

Conclusions: Maternal lipid concentrations, especially in early pregnancy, are associated with higher offspring hepatic fat, and may, therefore, be targeted in future interventions among pregnant women.

INTRODUCTION:

The prevalence of pediatric nonalcoholic fatty liver disease (NAFLD) has increased steadily over recent decades, particularly among those with obesity[1,2]. While the etiology is complex, evidence suggests that NAFLD pathogenesis begins in utero[3]. Notably, studies have shown that exposure to maternal obesity defined by pre-pregnancy body mass index (BMI) is associated with higher hepatic fat in infancy[4,5], and adolescence[6-8]. Given that maternal obesity is associated with hyperglycemia and dyslipidemia during gestation[9] and these maternal fuels (primarily glucose, TGs, and FFAs] are available to the fetus across the placenta[10], it is hypothesized that increased fuel exposure is an underlying mechanism that persistently alters offspring metabolism and increases the risk of obesity-related diseases, including NAFLD. To this point, prospective studies have revealed positive associations between maternal glucose and lipids during pregnancy and offspring adiposity[11-15], even after controlling for pre-pregnancy BMI and gestational diabetes mellitus (GDM). However, it is unknown whether there are similar associations between different maternal fuels during pregnancy and offspring hepatic fat.

The purpose of this study was to examine whether maternal fuels and other markers of metabolic homeostasis during pregnancy, including fasting insulin, insulin resistance [homeostatic method of assessment (HOMA-IR)], and hemoglobin A1C (HbA1C), are associated with offspring hepatic fat in early childhood (~5 years) (**Figure S1**). This was done using data/samples from the Healthy Start Study, a longitudinal pre-birth cohort study of generally healthy pregnant mothers and their offspring in Colorado. We also explored whether associations were mediated by postnatal markers of offspring obesity

(BMI z-score) or metabolic function (fasting glucose, HOMA-IR, or triglycerides) in early childhood, which we previously found to be associated with offspring hepatic fat in early childhood in a cross-sectional analysis of this same cohort[16].

METHODS:

Study population:

The Healthy Start Study is an observational, pre-birth cohort study in Colorado that enrolled pregnant women from obstetric clinics at the University of Colorado from 2010 to 2014. Inclusion criteria for pregnant women at enrollment were: >15 years old, no prior stillbirths, <24 weeks gestation, singleton birth, and no pre-existing serious chronic disease (cancer, psychiatric disease, steroid-dependent asthma, or non-gestational diabetes). In-person visits were completed during early pregnancy (median 17 weeks) and mid pregnancy (median 27 weeks), delivery (median postnatal age 1 day), infancy/toddlerhood (two visits; median age 5 months and 22 months), and early childhood (median age 4.6 years, also referred to as the "early childhood visit"). All participants provided written informed consent and the study was approved by the Colorado Multiple Institutional Review Board. Healthy Start is registered as an observational study at clinicaltrials.gov (NCT02273297).

A flow chart summarizing the selection of participants for this analysis is shown in **Figure 1.** Of the 1410 mother-child dyads enrolled in Healthy Start, 931 offspring returned for the early childhood visit as of January 1st, 2021, among whom 585 were invited to return for an abdominal MRI within 3 months of the first visit. This invitation was extended to all

participants whom the research team determined would likely tolerate the confined space and movement restrictions of the MRI procedure, which was based on how well they tolerated the body composition procedure at the first visit. Among the children invited to the MRI, 299 participants were excluded due to: lost to follow-up (n=119), declined to participate (n=69), child refused (n=37), poor MRI quality (n=2), and other/unknown reasons (n=73), resulting in an eligible sample of 286 offspring with a valid hepatic fat measurement by MRI in early childhood. The characteristics of the eligible sample were similar to the full sample at the early childhood visit (n=931) in terms of demographics, anthropometrics, birth outcomes, and maternal/perinatal variables (**Table S1**).

Maternal metabolic markers during pregnancy (exposure)

Fasting venous blood samples were collected from mothers at both visits during pregnancy. Insulin was measured by radioimmunoassay (Millipore). Glucose, TC, high-density lipoprotein cholesterol (HDL-C), TGs, and FFAs were measured by enzymatic kits and the AU400e Chemistry Analyzer (Olympus America Inc.). LDL-C was calculated using the Friedewald equation[17]. HOMA-IR was calculated using fasting glucose and insulin [glucose (mg/dL)*insulin (uIU/mL)/405][18]. In mid pregnancy only, HbA1c was measured from whole blood using a potassium ferricyanide assay by DCA Vantage® Analyzer (Siemens Healthcare Inc.). All assays were performed by the University of Colorado Hospital Clinical and Translational Research Center (CTRC) Core Laboratory.

Offspring hepatic fat during early childhood (outcome)

At the early childhood visit, abdominal MRIs were performed to measure hepatic fat content, as previously described[16]. Briefly, a series of T1-weighted coronal images were acquired by trained technicians using a 3T HDx imager (General Electric) with participants in the supine position. Hepatic imaging was performed using a validated, breath-hold, multi-inference, 6-point MRI-proton density fat fraction (PDFF) technique, where hepatic fat was calculated from the mean pixel signal intensity for each flip angle acquisition [$(SI_{in-phase} - SI_{out-of-phase})/2\ SI_{in-phase}$)] using the Osirix, Lipoquant plug-in[19].

Other maternal covariate assessments

Other maternal assessments performed during pregnancy have been described in detail [12,13]. Maternal age and household income were ascertained by surveys. Maternal height and weight were measured at in-person visits and abstracted from the medical record. Maternal pre-pregnancy BMI (kg/m^2) was calculated using pre-pregnancy weight [last clinically measured weight before pregnancy in the medical record (89%) or self-report (11%)] and measured height. Gestational weight gain (GWG) was estimated by subtracting pre-pregnancy weight from the last clinically measured weight during pregnancy. All women were screened for GDM at 24-28 weeks and results were abstracted from medical records. Maternal diet during pregnancy was assessed by monthly 24-hour dietary recalls starting at enrollment using the Automated Self-Administered (ASA) 24-Hour Dietary Recall tool [20]. Dietary data were processed by the University of North Carolina Nutrition Obesity Research Center and Healthy Eating Index (HEI)-2010 total scores were calculated as a measure of maternal diet quality[21]. The Pregnancy Physical Activity Questionnaire[22] was used to estimate maternal physical

activity in average metabolic equivalents (METs) in hours per week. Prenatal smoking was ascertained through questionnaires at both study visits during pregnancy.

Other offspring covariate assessments:

Offspring birth weight was abstracted from the medical record. Gestational age was calculated based on an average conception date, which was determined using estimates from the medical record in early pregnancy (last menstrual period) and in late pregnancy (ultrasound reports) [12]. Weight-for-gestational age z-scores were calculated using U.S. reference values in 1999-2000 [23]. At infancy and toddlerhood visits, mothers reported via questionnaire the duration and exclusivity of child breastfeeding and offspring were dichotomized based on exclusive breastfeeding status at 6 months. At the early childhood visit, offspring standing height (cm) and weight (kg) were measured and BMI z-scores and percentiles were calculated using Centers for Disease Control and Prevention 2000 Growth Charts[24]. Offspring fat mass (FM), fat-free mass (FFM), and percent body fat were assessed using air displacement plethysmography [BODPOD (COSMED Inc.)]. Fasting blood draws were performed after an overnight fast and several laboratory assays were completed by the University of Colorado Hospital CTRC Core Laboratory. In this analysis, we focused on select metabolic markers (fasting glucose, HOMA-IR, and TGs) that were cross-sectionally associated with hepatic fat in early childhood in this same cohort [16]. Offspring dietary intake in early childhood was assessed by two, interview-administered 24-hour dietary recalls, which were employed using the Nutrition Data System for Research (NDSR; Nutrition Coordinating Center, University of Minnesota), and this data was used to calculate HEI-2015[25] total scores as a measure of child diet quality.

Statistical analyses:

All analyses were done in SAS (v9.4, SAS Institute Inc.). Descriptive statistics were used to summarize the characteristics of the sample. Multivariable-adjusted linear regression models were constructed to examine associations of maternal metabolic markers in early and mid pregnancy with offspring hepatic fat in early childhood. Hepatic fat was log-transformed in all regression models to ensure normally distributed residuals. Because maternal metabolic markers in early and mid pregnancy were significantly correlated (r ranging from 0.35 for FFAs to 0.82 for HDL cholesterol based on Spearman correlations, all $p<0.0001$), we performed residual adjustment to break the correlation between repeated measurements. Potential confounders were selected *a priori* and adjusted for in a stepwise manner as follows: Model 1 adjusted for the residual effect of the metabolic marker at the other visit; Model 2 adjusted for Model 1 covariates plus offspring demographics (sex, race/ethnicity, and age); Model 3 adjusted for Model 2 covariates plus maternal/prenatal variables [age and household income at enrollment, gestational age when the marker was assessed, parity, pre-pregnancy BMI, smoking status, physical activity, and HEI-2010 total score]. Results were reported as back-transformed β-coefficients and 95% confidence intervals (CIs) representing the ratio of geometric means for offspring hepatic fat per 1 standard deviation (SD) increase in each maternal metabolic marker during pregnancy. In base models, we tested for effect modification by offspring sex, due to evidence that males and females differentially respond to nutritional exposures in utero [26,27], and stratified if p-interaction$\leq$0.05. Of the maternal metabolic markers that were significantly associated with offspring hepatic fat in the prior association analyses, we formally assessed mediation by select postnatal variables using

criteria by Baron and Kenny[28]. Potential mediators were selected based on previous associations with offspring hepatic fat in early childhood in the same cohort[16] and included BMI z-score, fasting glucose, HOMA-IR, and TGs in early childhood.

Several sensitivity analyses were performed. First, we re-analyzed data without residually adjusting each maternal metabolic marker for the other visit during pregnancy. Second, we excluded small-for-gestational-age children (weight-for-gestational age <10th percentile) or low birth weight (<2,500 g) due to potential associations between these birth outcomes and hepatic fat [29,30]. Third, we assessed whether results differed if Model 3 was additionally adjusted for maternal GDM or GWG during pregnancy, or offspring postnatal dietary exposures, including exclusive breastfeeding status at 6 months or diet quality in early childhood (HEI-2015 total scores).

RESULTS:

Sample Characteristics

Characteristics of the analytical sample of offspring (n=286) at the early childhood visit are shown in **Table 1**. The mean age was 4.8±0.8 years and the sex and race/ethnicity distribution were as follows: 49% male, 53% non-Hispanic white, 27% Hispanic, and 20% non-Hispanic other. Most children (79%) were classified as normal weight based on BMI percentile at the early childhood visit. The median (IQR) for hepatic fat measured by MRI-PDFF was 1.6% (1.2%, 2.1%).

Associations of maternal metabolic markers in early pregnancy with offspring hepatic fat

Estimates for associations of maternal metabolic markers in early pregnancy (~17 weeks) with offspring hepatic fat in early childhood (~5 years) are shown in **Table 2**. In base models (Model 1), higher maternal TGs, TC, LDL-C, and FFAs in early pregnancy were associated with higher offspring hepatic fat in early childhood (**Table 2**). Adjusting models for offspring demographics in Model 2 and maternal covariates in Model 3 did not change results (**Table 2**). We did, however, find evidence of effect modification by offspring sex on associations of maternal TC and LDL-C in early pregnancy with offspring hepatic fat (p-interaction=0.056 for TC and p-interaction=0.035 for LDL-C). After stratifying by sex, maternal TC and LDL-C in early pregnancy were associated with offspring hepatic fat in boys, but not in girls in base models (Model 1) (**Table 3**). Findings were unchanged after adjusting for confounders (**Table 3**). The relationships between select maternal metabolic markers during early pregnancy and offspring hepatic fat are visualized in **Figure 2**.

Associations of maternal metabolic markers in mid pregnancy with offspring hepatic fat

In mid pregnancy (~27 weeks), only maternal TGs were associated with offspring hepatic fat in early childhood (**Table 2**). There were no other associations of maternal metabolic markers in mid pregnancy with offspring hepatic fat.

Mediation by offspring adiposity or metabolic markers in early childhood

Of the maternal metabolic markers that were associated with offspring hepatic fat in **Table 2** (*i.e.,* maternal TGs, TC, LDL-C, and FFAs), we assessed the extent to which the relationships were mediated by offspring adiposity and metabolic profile. In assessing exposure-mediator associations, we identified offspring TGs and HOMA-IR as potential

mediators, given maternal TGs in early and mid pregnancy were positively associated with offspring TGs in early childhood, and maternal FFAs in early pregnancy were positively associated with offspring HOMA-IR in early childhood (**Table S2**). Next, we estimated associations of maternal TGs or FFAs with offspring hepatic fat adjusted for the potential offspring mediators described above (*i.e.,* offspring TGs as a mediator for maternal TGs and offspring HOMA-IR as a mediator for maternal FFAs). As shown in **Table S3**, the inclusion of these potential mediators did not appreciably change associations between these maternal lipids and offspring hepatic fat.

Sensitivity analyses:

Table S4 summarizes the results from sensitivity analyses without residually adjusting each maternal metabolic marker for the other visit during pregnancy, which shows that the magnitude and directionality of associations were relatively unchanged. Results were also relatively unchanged if we excluded children who were small-for-gestational-age or low birth weight, if we additionally adjusted Model 3 for maternal GDM or GWG, or if we additionally adjusted Model 3 for child dietary exposures (results not shown).

DISCUSSION:

In this study, we examined associations between maternal metabolic markers in early and mid pregnancy and offspring hepatic fat in early childhood using data from a prospective, pre-birth cohort of generally healthy mothers and their offspring in Colorado (the Healthy Start Study). The main finding was that maternal lipids in early pregnancy, particularly TGs and FFAs, were associated with higher offspring hepatic fat in early childhood (~15%

change in offspring hepatic fat per 1 SD increase in each maternal TGs and FFAs in fully adjusted models). We also found positive associations between maternal TC and LDL-C in early pregnancy and offspring hepatic fat in boys. All associations were independent of key confounders, including maternal pre-pregnancy BMI, and there was no evidence of mediation by offspring obesity or metabolic markers in early childhood, suggesting an independent pathway linking maternal lipids during pregnancy with offspring hepatic fat susceptibility. In contrast, in mid pregnancy, only the association between maternal TGs and offspring hepatic fat in early childhood remained significant, supporting that early pregnancy may be a sensitive window when fetal exposure to maternal lipids has a stronger influence on offspring hepatic fat.

Prior studies showing associations of maternal obesity with offspring hepatic steatosis[4-8] have served as initial support that the pathophysiology of NAFLD begins in utero, but the exact mechanisms involved have been unclear. Significant physiological changes occur during pregnancy to accommodate the energy and nutrient needs of the fetus and mother, including increases in maternal insulin resistance, insulin production, and circulating lipids, especially triglycerides. It is hypothesized that perturbations in these metabolic processes resulting in excess nutrient delivery to the fetus may have long-lasting effects on offspring physiology and future disease risk. In testing this hypothesis regarding NAFLD risk, we found that maternal early-pregnancy lipids were associated with offspring hepatic fat in early childhood independent of maternal BMI, supporting that maternal dyslipidemia may be a more robust predictor of offspring NAFLD risk than maternal obesity. It should be noted that some of these associations, particularly between maternal

cholesterol in early pregnancy and offspring hepatic fat, were stronger in boys than girls. Although we did not find evidence that boys had higher hepatic fat in early childhood compared to girls[16], this sex-specific finding may reflect sexually dimorphic patterns of placental function, epigenetic regulation, and gene expression that, in turn, result in differential responses to nutritional exposures[31], which need to be investigated further.

We also found that most associations between maternal lipids and offspring hepatic fat were no longer significant in mid pregnancy, which aligns with findings from the Project Viva cohort showing that excess GWG in early pregnancy is more strongly associated with certain cord blood hormones related to glycemia[32], and with offspring adiposity in childhood[33], compared to late pregnancy GWG. One explanation may be that fetal subcutaneous stores are not adequately developed in early pregnancy to accommodate excess lipid transfer across the placenta[34], resulting in more deleterious, lipotoxic effects. This pattern also suggests that interventions aiming to reduce offspring NAFLD risk may need to target women early in pregnancy, if not before pregnancy.

In comparison, we found no significant associations between maternal glucose, estimated insulin resistance, or HbA1C and offspring hepatic fat. This conflicts with a recent analysis of the Generation R Study (Rotterdam, Netherlands), which showed a positive association between maternal glucose in early pregnancy (~13 weeks' gestation) and offspring odds of NAFLD (MRI hepatic fat≥5%) assessed slightly later in mid childhood (~10 yrs old)[35]. However, this association was only observed among women of European ancestry, and similar to our study, there were no significant associations between maternal glycemia

and offspring hepatic fat as a *continuous* variable. Thus, an association between maternal glycemia and offspring hepatic fat may become more prominent in our study as children reach pubertal onset and the prevalence of clinical NAFLD increases. A null association between maternal glycemia and offspring hepatic fat also conflicts with prior studies of this cohort[12,13] and others[15,36] that observed a direct relationship between maternal glycemia and offspring *total* adiposity. However, since we did not find evidence of mediation by offspring BMI z-score for any associations in this study, our data suggest that the mechanisms by which maternal lipids drive offspring hepatic fat may be distinct from those linking maternal glycemia with offspring adiposity in these prior studies.

Additional studies will be needed to further explore such mechanisms, but evidence from animal studies suggests several avenues by which maternal overnutrition may 'program' offspring NAFLD risk. For instance, fetal exposure to excess maternal lipids in utero may induce epigenetic modifications, mitochondrial dysfunction, hepatic inflammation, and/or microbiome dysbiosis, leading to alterations in hepatic lipid pathways, such as impaired fat β-oxidation and upregulated de novo lipogenesis[37-39]. Studies will also be needed to understand factors influencing variations in maternal lipids during pregnancy. On one hand, maternal insulin resistance before or during pregnancy could be one factor driving higher maternal lipids during pregnancy[40]. However, since we did not find a parallel association between maternal HOMA-IR and offspring hepatic fat, we believe it is more likely that other factors were involved, such as genetics or maternal diet.

This study has strengths and limitations. Healthy Start is a large, diverse, prospective cohort, which enrolled mothers across the spectrum of pre-pregnancy BMI and glycemia during pregnancy. The sample in this analysis was representative of the larger Healthy Start cohort in terms of key characteristics, which increases the generalizability of findings. The longitudinal nature of the cohort enabled us to establish temporality in associations and generate insights to inform prevention efforts. Offspring hepatic fat was assessed by sophisticated MRI-PDFF, which increases our confidence in the reproducibility of our findings. Mothers underwent blood draws twice throughout pregnancy to assess a variety of metabolic markers. This was accompanied by data collection on several key covariates, including pre-pregnancy BMI, GDM, and lifestyle factors during pregnancy, allowing us to adjust for potential confounders.

Limitations include the observational nature of this study, which limits causal inference. Only a sub-sample completed the MRI in early childhood, resulting in a smaller analytical sample, which may have limited our statistical power. Maternal metabolic markers were based on fasting blood draws; whereas, no post-prandial measurements were available, which could provide complementary insights into the link between maternal metabolic homeostasis and offspring hepatic fat[14]. The mothers enrolled in this study had no history of serious chronic disease, and both mothers and children had a lower prevalence of obesity (24% for mothers and 5% for children; **Table S1**) compared to estimates in a nationally representative U.S. sample (~35-43% for women 20-59 yrs and ~13-19% for children 2-11 yrs)[41]. In addition, only 4 children had hepatic fat levels above clinical thresholds for NAFLD (>5%), Thus, associations may differ in other populations with

higher rates of obesity and NAFLD, compared to the relatively healthy mother-child dyads in this study, which will need to be tested as a future direction. The clinical significance of our findings is also unclear given the low prevalence of clinical NAFLD in offspring. At the same time, in this same cohort, we have previously shown that hepatic fat is significantly associated with markers of metabolic dysfunction[16], including estimated insulin resistance, which supports the clinical importance of higher hepatic fat at this young age despite being within the “normal” range.

In summary, this study provides evidence that maternal lipids in early pregnancy are associated with higher offspring hepatic fat in early childhood – a difference that could track over time and translate into increased metabolic risk later in childhood/adolescence. Although these findings need to be confirmed by other prospective studies, they provide initial insight into metabolic markers during pregnancy that could be targeted by interventions, either dietary or pharmacological, aiming to reduce offspring susceptibility to hepatic fat. The stronger associations for lipids in early pregnancy also support that interventions aiming to reduce NAFLD risk should begin as early as possible during pregnancy. Research evaluating the underlying biological mechanisms linking maternal lipids with offspring fatty liver susceptibility, as well as the determinants of higher maternal lipids during pregnancy, are critical future directions.

CONFLICTS OF INTEREST:

No conflicts of interest to disclose.

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C.C.C. and D.D. conceptualized the manuscript. C.C.C. performed data analyses and wrote the first draft of the manuscript. E.C.F., D.G., W.P., K.A.S., S.S., and K.S. contributed to the design of the analysis, interpretation of results, and reviewed/edited the manuscript. A.S. assisted with imaging data acquisition and reviewed/edited the manuscript. D.D. obtained funding for the study.

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TABLES:

Table 1: Characteristics of the multi-ethnic sample of offspring at ~5 years of age (n=286): The Healthy Start study

Characteristic	N Obs.	Mean (SD) or n (%)
Age (years), mean (SD)	286	4.8 (0.8)
Male sex, n (%)	286	140 (49%)
Race/ethnicity, n (%)	284	
Hispanic		76 (27%)
Non-Hispanic white		151 (53%)
Non-Hispanic black		33 (12%)
Non-Hispanic other		24 (8%)
BMI percentile category, n (%)	285	
Underweight (<5th percentile)		22 (8%)
Normal (5th to <85th percentile)		226 (79%)
Overweight (85th to <95th percentile)		22 (8%)
Obesity (≥95th percentile)		15 (5%)
Body composition, mean (SD)		
Fat mass (kg)	283	3.7 (1.6)
Fat-free mass (kg)	283	14.3 (6.7)
Percent body fat (%)	283	20.6 (6.7)
Hepatic fat (%), median (IQR)	286	1.6 (1.2-2.1)
Birth outcomes, n (%)		
Low birth weight (birth weight <2500 g)	286	17 (6%)
Macrosomia (birth weight>4000 g)	286	13 (5%)
Preterm birth (gestational age <37 weeks)	286	18 (6%)
Small-for-gestational age (<10th percentile)	286	42 (15%)
Maternal markers in early pregnancy, mean (SD)		
Glucose (mg/dL)	283	77 (6.1)
Insulin (uIU/mL)	277	13.7 (8.8)
HOMA-IR	277	2.7 (1.9)
TGs (mg/dL)	282	120.4 (45.0)
TC (mg/dL)	282	184.3 (36.9)
LDL-C (mg/dL)	282	98.7 (29.0)
HDL-C (mg/dL)	282	61.5 (12.6)
FFAs (uEq/L)	277	376.7 (166.4)
Maternal markers in mid pregnancy, mean (SD)		
Glucose (mg/dL)	264	78.2 (9.3)
Insulin (uIU/mL)	259	17.9 (13.9)
HOMA-IR	259	3.6 (4)
TGs (mg/dL)	263	159.9 (55.4)
TC (mg/dL)	263	212.3 (40.1)
LDL-C (mg/dL)	263	116.9 (34.9)
HDL-C (mg/dL)	263	63.4 (12.8)
FFAs (uEq/L)	257	373.1 (146.2)
Hemoglobin A1C (%)	260	5 (0.3)

Abbreviations: BMI, body mass index; HOMA-IR, homeostatic model of assessment-insulin resistance; TGs, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; FFAs, free fatty acids.

Table 2: Associations of select maternal metabolic markers in early pregnancy (~17 weeks) and mid pregnancy (~27 weeks) with offspring log-hepatic fat in early childhood (~5 years)

	Model 1[a]			Model 2[b]			Model 3[c]		
Metabolic Marker:	**n**	**β (95% CI)[d]**	**p**	**n**	**β (95% CI)[d]**	**p**	**n**	**β (95% CI)[d]**	**p**
Early Pregnancy:									
Glucose, mg/dL	263	0.97 (0.90, 1.04)	0.40	261	0.97 (0.9, 1.04)	0.41	256	0.96 (0.88, 1.04)	0.32
Insulin, uIU/mL	258	1.01 (0.94, 1.08)	0.77	256	1.00 (0.93, 1.07)	0.92	251	1.00 (0.92, 1.10)	0.91
HOMA-IR	258	1.01 (0.94, 1.08)	0.79	256	1.00 (0.93, 1.07)	0.93	251	1.00 (0.92, 1.09)	0.94
TGs, mg/dL	262	1.15 (1.06, 1.25)	**0.001**	260	1.13 (1.04, 1.23)	**0.004**	255	1.15 (1.05, 1.27)	**0.003**
TC, mg/dL	262	1.13 (1.03, 1.24)	**0.011**	260	1.14 (1.04, 1.25)	**0.007**	255	1.16 (1.04, 1.29)	**0.007**
LDL-C, mg/dL	262	1.13 (1.02, 1.25)	**0.024**	260	1.13 (1.02, 1.26)	**0.018**	255	1.15 (1.03, 1.29)	**0.014**
HDL-C, mg/dL	262	1.00 (0.90, 1.11)	0.99	260	1.02 (0.92, 1.13)	0.76	255	1.00 (0.89, 1.12)	0.97
FFAs, uEq/L	256	1.11 (1.04, 1.19)	**0.002**	254	1.10 (1.03, 1.18)	**0.004**	249	1.14 (1.05, 1.23)	**0.002**
Mid Pregnancy:									
Glucose, mg/dL	263	0.99 (0.92, 1.07)	0.80	261	0.99 (0.92, 1.06)	0.77	256	0.97 (0.90, 1.06)	0.55
Insulin, uIU/mL	258	1.01 (0.94, 1.08)	0.74	256	1.00 (0.93, 1.07)	0.91	251	1.00 (0.92, 1.09)	0.97
HOMA-IR	258	1.01 (0.94, 1.08)	0.79	256	1.00 (0.93, 1.07)	0.94	251	1.00 (0.92, 1.08)	0.99
TGs, mg/dL	262	1.15 (1.06, 1.25)	**0.001**	260	1.14 (1.05, 1.24)	**0.002**	255	1.15 (1.06, 1.26)	**0.002**
TC, mg/dL	262	1.09 (0.99, 1.20)	0.06	260	1.10 (0.99, 1.21)	0.06	255	1.10 (0.99, 1.22)	0.09
LDL-C, mg/dL	262	1.05 (0.95, 1.17)	0.32	260	1.05 (0.95, 1.17)	0.34	255	1.05 (0.94, 1.18)	0.39
HDL-C, mg/dL	262	1.02 (0.92, 1.13)	0.77	260	1.02 (0.92, 1.14)	0.66	255	1.00 (0.89, 1.13)	0.96
FFAs, uEq/L	256	1.04 (0.98, 1.12)	0.21	254	1.04 (0.97, 1.11)	0.23	249	1.04 (0.97, 1.12)	0.25
HbA1C, %	260	1.06 (0.99, 1.12)	0.08	258	1.05 (0.98, 1.12)	0.15	253	1.04 (0.97, 1.11)	0.31

[a] **Model 1**: Adjusted for the residual effect of the fuel at the other visit.
[b] **Model 2:** Model 1 plus offspring sex, race/ethnicity (Hispanic, non-Hispanic white, or non-Hispanic other), and age (years) in early childhood.
[c] **Model 3:** Model 2 plus maternal age (years) at enrollment, household income (<$40,000, $40-70,000, >$70,000) at enrollment, gestational age (weeks) when the marker was assessed, parity (0, 1, ≥2), pre-pregnancy BMI (kg/m^2), smoking status during pregnancy, physical activity (METs-hours/week) during pregnancy, and diet quality (HEI-2010 score) during pregnancy.
[d] Coefficients are back-transformed and represent the ratio of geometric means for the dependent variable (i.e., the percent change in offspring hepatic fat) per 1 standard deviation (SD) increase in each maternal metabolic marker during pregnancy. SDs were calculated for each variable after residual adjustment for the other visit during pregnancy (except for HbA1C, which was only measured in mid pregnancy) and were as follows for early and mid pregnancy, respectively: Glucose: 5.2 and 7.7 mg/dl; Insulin: 8.0 and 12.4 uIU/mL; HOMA-IR: 1.7 and 1.9; TGs: 32.6 and 45.0 mg/dL; TC: 23.7 and 37.0 mg/dL; LDL-C: 16.9 and 29.0 mg/dL; HDL-C: 7.4 and 7.4 mg/dL; FFAs: 149.7 and 132.9 uEq/L; HbA1C: 0.3%.

Abbreviations: HOMA-IR, homeostatic model of assessment-insulin resistance; TGs, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; FFAs, free fatty acids; HbA1C, hemoglobin A1C.

Table 3: Sex-specific associations of maternal TC and LDL-C in early pregnancy (~17 weeks) with offspring log-hepatic fat in early childhood (~5 years)

		Model 1[a]			Model 2[b]			Model 3[c]		
Metabolic Marker:	**Sex**	**n**	**β (95% CI)[d]**	**p**	**n**	**β (95% CI)[d]**	**p**	**n**	**β (95% CI)[d]**	**p**
TC, mg/dL	Girls	132	1.08 (0.96, 1.22)	0.18	130	1.09 (0.97, 1.23)	0.14	129	1.12 (0.99, 1.28)	0.08
	Boys	130	1.18 (1.07, 1.32)	**0.002**	130	1.20 (1.08, 1.33)	**0.001**	126	1.22 (1.08, 1.37)	**0.001**
LDL-C, mg/dL	Girls	132	1.05 (0.93, 1.19)	0.41	130	1.07 (0.94, 1.21)	0.32	129	1.09 (0.96, 1.25)	0.19
	Boys	130	1.18 (1.06, 1.33)	**0.003**	130	1.20 (1.07, 1.34)	**0.002**	126	1.21 (1.07, 1.37)	**0.002**

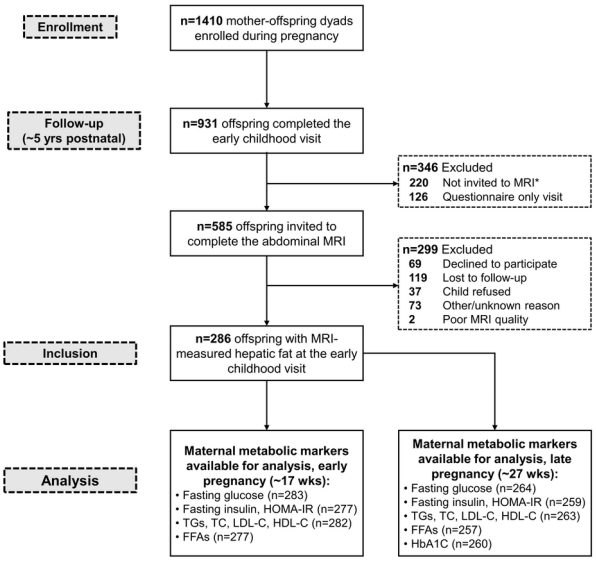
[a] **Model 1**: Adjusted for the residual effect of the fuel at the other visit.
[b] **Model 2:** Model 1 plus offspring race/ethnicity (Hispanic, non-Hispanic white, or non-Hispanic other), and age (years) in early childhood.
[c] **Model 3:** Model 2 plus maternal age (years) at enrollment, household income (<$40,000, $40-70,000, >$70,000) at enrollment, gestational age (weeks) when the marker was assessed, parity (0, 1, ≥2), pre-pregnancy BMI (kg/m^2), smoking status during pregnancy, physical activity (METs-hours/week) during pregnancy, and diet quality (HEI-2010 score) during pregnancy.
[d] Coefficients are back-transformed and represent the ratio of geometric means for the dependent variable (i.e., the percent change in offspring hepatic fat) per 1 standard deviation (SD) increase in each maternal metabolic marker during pregnancy. SDs were calculated for TC and LDL-C after residual adjustment for the other visit during pregnancy and were as follows for girls and boys, respectively: TC: 26.2 and 20.9 mg/dL; LDL-C: 18.9 and 16.0 mg/dL.

Abbreviations: TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol

FIGURE LEGENDS:

Figure 1: Flow chart for the selection of participants for this study examining associations of maternal metabolic markers during early pregnancy (~17 weeks) and mid pregnancy (~27 weeks) with offspring hepatic fat in early childhood (~5 years)

Figure 2: Scatter plots showing associations of maternal metabolic markers during early pregnancy with offspring log-hepatic fat in early childhood. (A) Maternal TGs (r=0.20, p<0.001); (B) Maternal FFAs (r=0.15, p=0.014); (C) Maternal TC stratified by sex (Boys: r=0.18, p=0.038; Girls: r=0.06, p=0.46); (D) Maternal LDL-C stratified by sex (Boys: r=0.18, p=0.035; Girls: r=0.01, p=0.96). In sex-stratified models, (+) symbol represents girls and (o) symbol represents boys. Correlation coefficients and p-values above were calculated by Spearman correlations. Abbreviations: TGs, triglycerides; FFAs, free fatty acids; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol.



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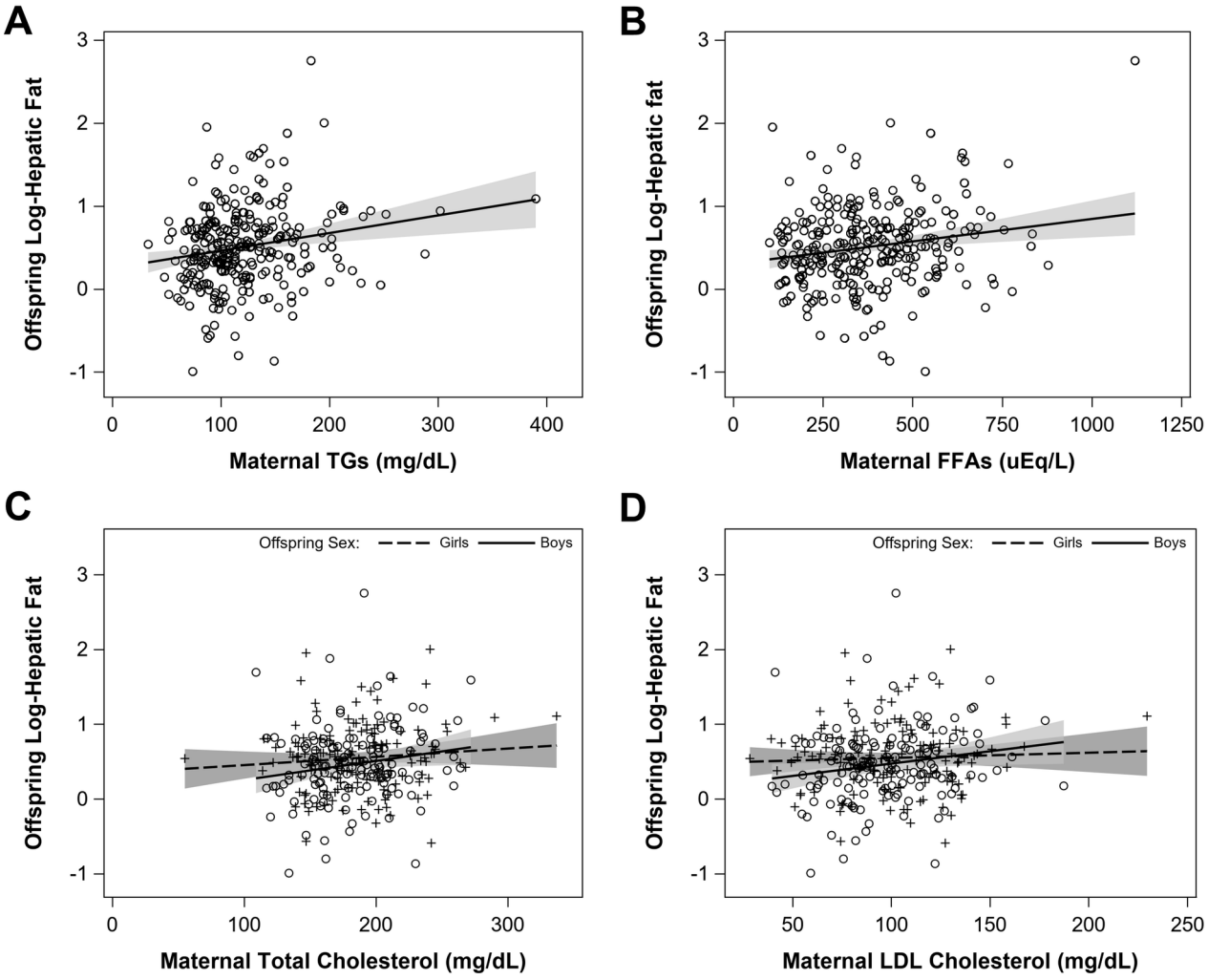

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1. Given Name (First Name): Dana
2. Surname (Last Name): Dabelea
3. Date: 10/25/21

4. Are you the corresponding author? ☐ Yes ☒ No

5. Manuscript Title: Exposure to maternal fuels during pregnancy and offspring hepatic fat in early childhood: The Healthy Start Study

6. Manuscript Identifying Number (if you know it):

Section 2. The Work Under Consideration for Publication

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Section 4. Intellectual Property -- Patents & Copyrights

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Section 1. Identifying Information

1. Given Name (First Name): Ellen
2. Surname (Last Name): Francis
3. Date: 10/25/2021

4. Are you the corresponding author? ☐ Yes ☒ No

5. Manuscript Title: Exposure to maternal fuels during pregnancy and offspring hepatic fat in early childhood: The Healthy Start Study

6. Manuscript Identifying Number (if you know it):

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Section 1. Identifying Information

1. Given Name (First Name): Katherine
2. Surname (Last Name): Sauder
3. Date: 10/25/21

4. Are you the corresponding author? ☐ Yes ☒ No

5. Manuscript Title: Exposure to maternal fuels during pregnancy and offspring hepatic fat in early childhood: The Healthy Start Study

6. Manuscript Identifying Number (if you know it):

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Kartik
2. Surname (Last Name): Shankar
3. Date: 10/25/2021

4. Are you the corresponding author? ☐ Yes ☒ No

5. Manuscript Title: Exposure to maternal fuels during pregnancy and offspring hepatic fat in early childhood: The Healthy Start Study

6. Manuscript Identifying Number (if you know it):

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Section 1. Identifying Information

1. Given Name (First Name): Shikha
2. Surname (Last Name): Sundaram
3. Date: 10/25/2021

4. Are you the corresponding author? ☐ Yes ☒ No

5. Manuscript Title
Exposure to maternal fuels during pregnancy and offspring hepatic fat in early childhood: The Healthy Start Study

6. Manuscript Identifying Number (if you know it)

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1. Given Name (First Name): Wei
2. Surname (Last Name): Perng
3. Date: 10/25/21

4. Are you the corresponding author? ☐ Yes ☒ No

5. Manuscript Title: Exposure to maternal fuels during pregnancy and offspring hepatic fat in early childhood: The Healthy Start Study

6. Manuscript Identifying Number (if you know it):

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