HEPATOLOGY

HEPATOLOGY, VOL. 74, NO. 4, 2021

Maternal Early-Pregnancy Glucose Concentrations and Liver Fat Among School-Age Children

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BACKGROUND AND AIMS: Gestational diabetes seems to be associated with offspring NAFLD. We hypothesized that maternal glucose concentrations across the full range may have persistent effects on offspring liver fat accumulation.

APPROACH AND RESULTS: In a multiethnic, population-based, prospective cohort study among 2,168 women and their offspring, maternal early-pregnancy glucose concentrations were measured at a median of 13.1 weeks' gestation (95% CI, 9.6-17.2). Liver fat fraction was measured at 10 years by MRI. NAFLD was defined as liver fat fraction ≥5.0%. We performed analyses among all mothers with different ethnic backgrounds and those of European ancestry only. The multiethnic group had a median maternal early-pregnancy glucose concentration of 4.3 mmol/L (interquartile range, 3.9-4.9) and a 2.8% (n = 60) prevalence of NAFLD. The models adjusted for child age and sex only showed that in the multiethnic group, higher maternal early-pregnancy glucose concentrations were associated with higher liver fat accumulation and higher odds of NAFLD, but these associations attenuated into non-significance after adjustment for potential confounders. Among mothers of European ancestry only, maternal early-pregnancy glucose concentrations were associated with increased odds of NAFLD (OR, 1.95; 95% CI, 1.32; 2.88, after adjustment for confounders) per 1-mmol/L increase in maternal early-pregnancy glucose concentration. These associations were not explained by maternal prepregnancy and childhood body mass index, visceral fat, and metabolic markers.

CONCLUSIONS: In this study, maternal early-pregnancy glucose concentrations were only among mothers of European ancestry associated with offspring NAFLD. The associations of higher maternal early-pregnancy glucose concentrations with offspring NAFLD may differ between ethnic groups. (Hepatology 2021;74:1902-1913).

Pre-existing diabetes and gestational diabetes are complicating up to 25% of pregnancies.[1-3] Recent studies suggest that gestational diabetes leads to impaired offspring cardiovascular and metabolic health in childhood and adulthood.[4-7] The observed associations seem not to be restricted to the clinical diagnosis of gestational diabetes, but are also present across the full range of maternal glucose concentrations.[8-10] Previous studies suggest that gestational diabetes is also associated with offspring markers of liver pathology.[11-16] Results from animal studies suggest that offspring of maternal pregnancy hyperglycemia are predisposed to develop liver steatosis.[13-16] In humans, a case-control study among 25 mothers showed that intrahepatocellular lipid content, as measured by MR spectroscopy, was increased in neonates of mothers with both obesity and gestational diabetes compared to neonates of mothers with both normal

Abbreviations: BMI, body mass index; IDEAL IQ, iterative decomposition of water and fat with echo asymmetry and least squares estimation; SDS, standard deviation score.

Received January 11, 2021; accepted May 12, 2021.

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.31910/suppinfo.

The general design of the Generation R Study was made possible by financial support from the Erasmus University Medical Center, the Netherlands Organization for Health Research and Development, and the Ministry of Health, Welfare, and Sport. The study was supported, in part, by the European Research Council (Consolidator Grant ERC-2014-CoG-648916; to V.W.V.J.); the European Union's Horizon 2020 Research and Innovation programme LifeCycle (733206; to V.W.V.J.); the European Joint Programming Initiative "A Healthy Diet for a Healthy Life" (JPI HDHL, NutriPROGRAM project, and ZonMw the Netherlands project [529051022; to J.F.F.] and Precise project [529051023; to J.F.F.]); the Dutch Heart Foundation (2017T013; to R.G.); the Dutch Diabetes Foundation (2017.81.002; to R.G.); and the Netherlands Organisation for Health Research and Development (NWO, ZonMw; 543003109; to R.G.).

weight and without gestational diabetes.[12] Another study among 1,215 mother-child pairs reported that maternal pregnancy diabetes or glycosuria was associated with an increased risk for ultrasound-diagnosed NAFLD at 17.8 years of age, independent of maternal prepregnancy body mass index (BMI).[11] We have previously shown that maternal early-pregnancy glucose metabolism is associated with childhood glucose metabolism, but not with other childhood cardiometabolic outcomes, after adjustment for maternal prepregnancy BMI.[9] Also, liver fat accumulation is related to risk factors for cardiometabolic disease, independent of total body fat.[17,18] We hypothesized that higher maternal glucose concentrations across the full range in early pregnancy are associated with liver fat accumulation in offspring. Such associations may predispose persons to liver and cardiometabolic disease in later life.

We assessed the associations of maternal early-pregnancy glucose concentrations with offspring liver fat accumulation and NAFLD with MRI at 10 years of age in a multiethnic, population-based, prospective cohort among 2,168 mothers and their children. Because both glucose concentrations, liver fat, and the associations between them may differ between ethnic groups, we performed analyses in the full multiethnic group and in the group of European ancestry only.

Participants and Methods

STUDY POPULATION

This study was embedded in the Generation R Study. This is a multiethnic, population-based, prospective cohort from early fetal life onward, based in Rotterdam, The Netherlands.[19] The study has been approved by the Medical Ethical Committee of the Erasmus University Medical Center in Rotterdam (MEC 198.782/2001/31). Written informed consent was obtained for all participants.[20] All pregnant women were enrolled between 2001 and 2005. The enrollment procedure has been described in detail.[21] In total, 8,879 women were enrolled during pregnancy, of whom 6,099 were enrolled in early pregnancy, had measurements of glucose concentrations available, and had singleton pregnancies. MRI-based liver fat measurements at 10 years of age were available in a subgroup of 2,168 of their children (Fig. 1). None of these children had a history of jaundice, medication use, alcohol use, smoking, or drug use, based on information from questionnaires at 10 years of age. Missing measurements were mainly attributable to whether or not the child attended the MRI subgroup study at 10 years of age, lost to follow-up, no data on liver fat, or MRI artifacts.[20]

MATERNAL EARLY-PREGNANCY GLUCOSE AND INSULIN CONCENTRATIONS

Nonfasting blood samples were collected once in early pregnancy at 13.1 median weeks' gestation (95% CI, 9.6-17.2), as described.[8,22] Briefly, venous blood samples were collected from pregnant women. Although samples were ≥30 minutes postmeal, we had no information on the exact time interval of the postmeal fasting duration and therefore consider all samples random. Glucose concentration (mmol/L) is an enzymatic quantity and was measured with the

View this article online at wileyonlinelibrary.com.
DOI 10.1002/hep.31910

Potential conflict of interest: Nothing to report.

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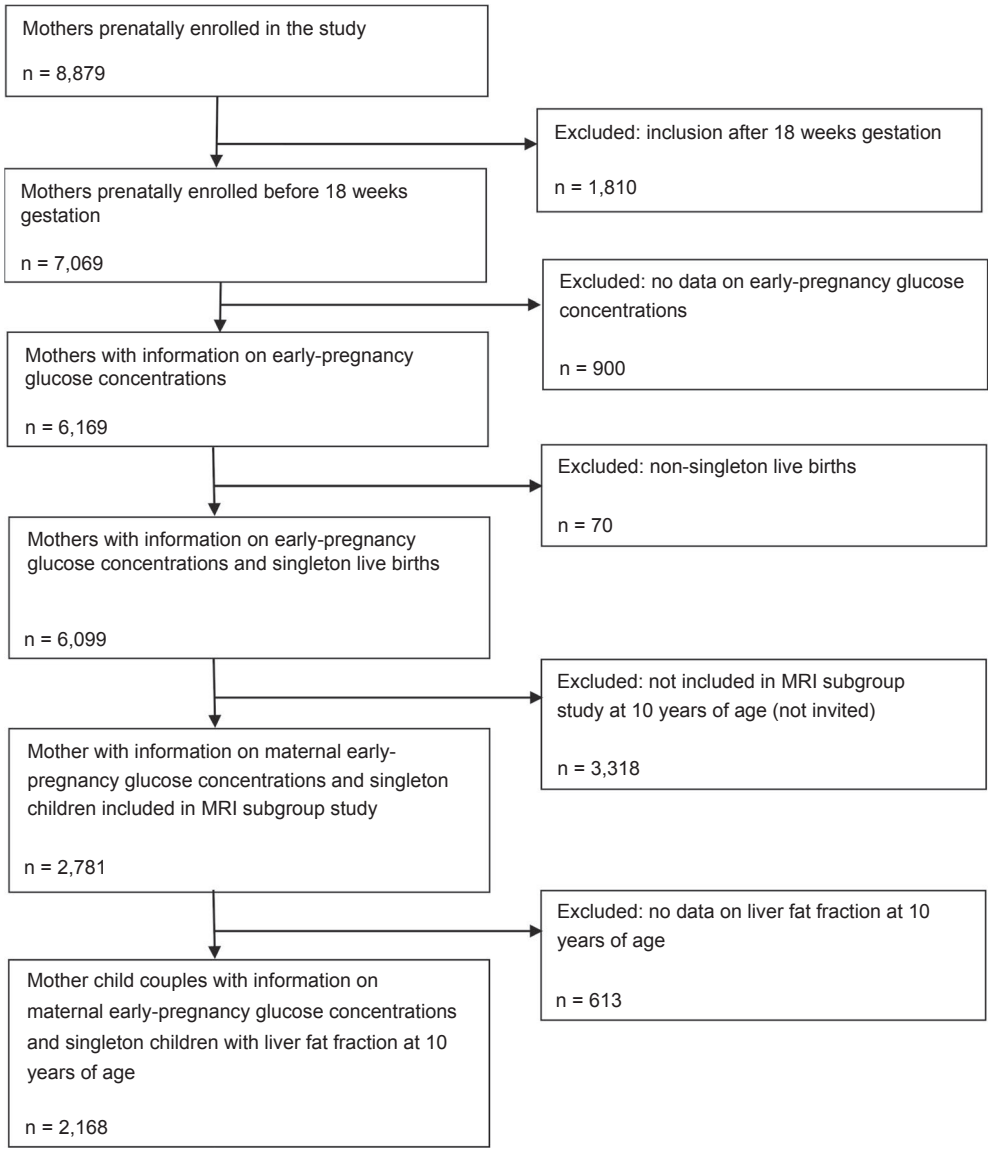

FIG. 1. Study participants flowchart.

c702 module on the Cobas 8000 analyzer (Roche, Almere, The Netherlands). Insulin concentration (pmol/L) was measured with electrochemiluminescence immunoassay on the Cobas e411 analyzer (Roche). Quality-control samples demonstrated intra- and interassay coefficients of variation of 0.9% and 1.2% for glucose concentrations and 1.3% and 2.5% for insulin concentrations, respectively. Information on pre-existing diabetes was obtained from self-reported questionnaires and on gestational diabetes from medical records after delivery.[20] Gestational diabetes was diagnosed by a community midwife or an obstetrician according to Dutch midwifery and obstetric guidelines.[20,23] The following criteria were used: either a random glucose level >11.0 mmol/L, a fasting glucose ≥7.0 mmol/L, or a fasting glucose between 6.1 and 6.9 mmol/L with a subsequent abnormal glucose tolerance test.[23] In clinical practice, and for this study sample, an abnormal glucose tolerance test was defined as a glucose level >7.8 mmol/L after glucose intake.

LIVER FAT AT 10 YEARS

We measured liver fat using a 3.0 Tesla MRI scanner (Discovery MR750w; GE Healthcare, Milwaukee,

WI) as described.[20,24-26] A liver fat scan was performed using a single-breath-hold, three-dimensional volume and a special 3-point proton-density–weighted Dixon technique (iterative decomposition of water and fat with echo asymmetry and least squares estimation; IDEAL IQ) for generating a precise liver fat fraction image.[27] The IDEAL IQ scan is based on a carefully tuned six-echo, echo planar imaging acquisition. The obtained fat fraction maps were analyzed by the Precision Image Analysis company (PIA; Kirkland, WA) using the sliceOmatic (TomoVision, Magog, Québec, Canada) software package. All extraneous structures and any image artifacts were removed manually.[28] Liver fat fraction was determined by taking four samples of ≥4 cm^2 from the central portion of the hepatic volume. Subsequently, mean signal intensities were averaged to generate an overall mean liver fat estimation. Liver fat measured with IDEAL IQ using MRI is reproducible, highly precise, and validated in adults.[29,30] NAFLD was defined as liver fat ≥5.0%.[24,30,31] We studied liver fat fraction across the full range and dichotomized in low, <5.0%, and high, ≥5.0%, based on the clinical cutoff for NAFLD.[32] As a sensitivity analysis, we dichotomized liver fat into low, ≤2.0%, and high, >2.0%, based on the median liver fat fraction in our population and on previous work from our group describing that liver fat accumulation above 2.0% is already associated with an increased cardiometabolic risk profile in children.[17]

COVARIATES

Information was obtained by questionnaires on maternal age, parity, ethnicity, education level, smoking, alcohol consumption, folic acid supplement use, prepregnancy weight, and total daily energy intake during pregnancy.[19] We categorized ethnicity into European (Dutch n = 1,258 [58.8%] and other European n = 168 [7.7%]) versus non-European (Cape Verdean n = 98 [4.6%], other African n = 21 [1.0%], Dutch Antillean n = 42 [2.0%], Surinamese n = 172 [8.0%], American n = 43 [2.0%], Asian n = 48 [2.1%], Indonesian n = 75 [3.5%], Turkish n = 117 [5.5%], Moroccan n = 95 [4.4%], and Oceanian n = 4 [0.2%]). We measured maternal height without shoes at intake and calculated prepregnancy BMI. Nonfasting venous blood samples were obtained in early pregnancy, total cholesterol (mmol/L), triglyceride (mmol/L), and HDL-cholesterol (mmol/L) concentrations were analyzed. LDL (mmol/L) concentrations were calculated using the Friedewald equation.[33] Maternal dyslipidemia was defined as having three or more out of the following four adverse factors: total cholesterol above the 75th percentile; triglycerides above the 75th percentile; HDL-cholesterol below the 25th percentile; and LDL-cholesterol above the 75th percentile of our study population. Information on child gestational age at birth, sex, and birth weight was obtained from medical records.[20] We obtained information on breastfeeding in infancy by questionnaire.[20] Nonfasting blood samples were collected to determine concentrations of insulin, total cholesterol, triglycerides, and HDL- and LDL-cholesterol at 6 years of age.[34] At the 10 years of age follow-up visit, we measured childhood height and weight, both without shoes and heavy clothing, and calculated BMI and sex- and age-adjusted childhood BMI standard deviation score (SDS) based on Dutch reference growth charts (Growth Analyzer 4.0; Dutch Growth Research Foundation, Rotterdam, The Netherlands).[35] Visceral fat mass was obtained by MRI scans, as described.[20,36] Physical activity and screen time were assessed with questionnaires at 10 years of age.[37] Nonfasting venous blood samples were obtained, and we measured glucose and insulin concentrations.

STATISTICAL ANALYSIS

We conducted a nonresponse analysis to compare characteristics of mothers and children with and without liver MRI scan measurements with Student *t* tests, Mann-Whitney U tests, and chi-square tests. Second, we used linear and logistic regression models to assess associations of maternal early-pregnancy glucose concentrations across the full range with liver fat accumulation and with the odds of NAFLD. Potential covariates were first selected based on previous literature, their association with both the exposure and outcome, or a change in the effect estimates of >10% in the basic model as shown with the Directed Acyclic Graph (Supporting Fig. S1); subsequently, we performed a backward model-selection analysis.[11,38] The basic model was adjusted for child sex and age 10 years at follow-up measurements. The main confounder model was additionally adjusted for maternal ethnicity, education, and child physical activity. We further adjusted any significant association in the

main model for maternal prepregnancy BMI, dyslipidemia, and child metabolic markers at 6 years, BMI at 10 years, visceral fat mass at 10 years, and glucose concentrations at 10 years to explore whether any significant association was explained by these covariates.[3,9,39]

Because both glucose concentrations, liver fat, and the associations between them may differ between ethnic groups, we performed analyses in the full multiethnic group and in the European-ancestry-only groups (Supporting Table S1).[40] Unfortunately, the other ethnic subgroups were too small to perform ethnic-specific analyses. As sensitivity analysis, first we repeated all analyses using maternal early-pregnancy insulin concentrations as exposure as another marker of maternal glucose metabolism in early pregnancy. Maternal early-pregnancy insulin concentrations were natural log-transformed before the SDS construction because of the skewed distribution. Second, to assess the associations of maternal early-pregnancy glucose concentrations with a potentially clinically relevant liver fat cutoff, we repeated the analyses using liver fat dichotomized in low, ≤2.0%, and high, >2.0%, liver fat. Third, we explored whether our observed associations were affected by specific subgroups in our study population. We first excluded women with pre-existing diabetes or gestational diabetes (total n = 28) to focus specifically on a nondiabetic population. Second, we excluded women with glucose concentrations sampled at >14 weeks' gestation to assess the associations of first-trimester maternal glucose concentrations with liver fat accumulation at school age (n = 702). The distribution of liver fat was skewed, and natural log-transformed values were used in all linear regression analyses. Missing data in the covariates were multiple-imputed using the Markov chain Monte Carlo approach. Five imputed data sets were created and analyzed together. All statistical analyses were performed using the Statistical Product and Service Solutions (SPSS) Statistics software (version 25.0 for Windows; IBM, Chicago, IL).

Results

SUBJECT CHARACTERISTICS

Median maternal early-pregnancy glucose concentration was 4.3 mmol/L (95% CI, 3.0-6.4; interquartile range [IQR], 3.9-4.9). Median liver fat fraction was 2.0% (95% CI, 1.2-5.2, IQR, 1.7-2.5), and the prevalence of NAFLD was 2.8% (n = 60) in children at 10 years of age (Table 1). Mothers of children with NAFLD had a higher BMI, were less often from European ancestry, and had a slightly higher level of educational attainment, and those children had higher BMI and visceral fat mass compared to children without NAFLD in the full multiethnic group (Table 1). In the European-ancestry-only group, mothers of children with NAFLD had higher glucose concentrations in early pregnancy, and those children were less active compared to children without NAFLD (Table 2). Mothers of the European-ancestry-only group had similar glucose concentrations and had a slightly higher level of educational attainment compared to the full multiethnic group (Supporting Table S2). The correlation coefficient for the correlation between maternal early-pregnancy glucose and maternal prepregnancy BMI was 0.15 (Supporting Table S3). Nonresponse analyses showed that participants without outcome measurements had mothers with a slightly lower level of educational attainment (Supporting Table S4).

MATERNAL EARLY-PREGNANCY GLUCOSE CONCENTRATIONS AND CHILDHOOD LIVER FAT

In the full multiethnic group, results from the basic models showed that higher maternal early-pregnancy glucose concentrations were associated with higher liver fat accumulation (difference, 0.04; 95% CI, 0.02; 0.07) SDS per 1-mmol/L increase in maternal early-pregnancy glucose concentration and with increased odds of NAFLD (OR, 1.27; 95% CI, 1.10; 1.46) per 1-mmol/L increase in maternal early-pregnancy glucose concentration (Table 3). These associations attenuated into nonsignificance in the main confounder model. In mother-child pairs of European ancestry only, higher maternal early-pregnancy glucose concentrations were associated with increased odds of NAFLD (OR, 1.95; 95% CI, 1.32; 2.88) per 1-mmol/L increase in maternal early-pregnancy glucose concentration in the main confounder model. These associations were not explained by maternal prepregnancy BMI and dyslipidemia. Also, childhood metabolic markers at 6 years, BMI and visceral fat mass or glucose concentrations at 10 years of age, did not explain the observed associations (Table 4).

TABLE 1. Maternal and Child Characteristics by Offspring NAFLD Status: Full Multiethnic Group

	Total Group n = 2,168	NAFLD No n = 2,108	NAFLD Yes n = 60	*P* Value
Maternal characteristics				
Age at enrollment, years	30.8 ± 4.6	30.9 ± 4.6	30.1 ± 6.0	0.36
Gestational age at glucose/insulin measurement, weeks	13.1 (9.6, 17.2)	13.1 (9.6, 17.2)	13.1 (11.2, 17.9)	0.20
Prepregnancy BMI, kg/m^2	22.5 (18.1, 35.2)	22.4 (18.1, 34.9)	24.9 (18.3, 42.8)	<0.01
Parity, nulliparous	1,317 (61.0)	1,284 (61.2)	33 (55.0)	0.33
Ethnicity, European	1,426 (66.6)	1,401 (67.3)	25 (42.4)	<0.01
Education, higher	1,115 (53.6)	1,099 (54.2)	16 (29.1)	<0.01
Smoking during pregnancy, continued	334 (18.7)	329 (19.0)	5 (10.4)	0.14
Alcohol consumption, during pregnancy	622 (37.2)	609 (37.5)	13 (28.3)	0.20
Folic acid supplement use, yes	1,024 (71.4)	994 (71.5)	30 (68.2)	0.64
Daily energy intake, kcal/d	2,060 ± 572	2,061 ± 571	2,053 ± 610	0.93
Dyslipidemia	233 (10.7)	226 (10.7)	7 (11.7)	0.82
Glucose, mmol/L	4.4 ± 0.8	4.4 ± 0.8	4.6 ± 1.0	0.12
Insulin, pmol/L	113.1 (19.8, 669.6)	112.8 (19.7, 673.2)	171.0 (22.8, 672.6)	0.09
Pre-existing diabetes	6 (0.3)	5 (0.3)	1 (1.9)	0.04
Gestational diabetes	22 (1.1)	22 (1.1)	0 (0)	0.43
Child characteristics				
Sex, female	1,113 (51.3)	1,082 (51.3)	31 (51.7)	0.96
Birth weight, g	3,447 ± 548	3,475 ± 549	3,347 ± 535	0.15
Gestational age at birth, weeks	40.3 (36.0, 42.4)	40.3 (36.0, 42.4)	39.9 (34.5, 42.8)	0.08
Ever breastfed, yes	1,761 (93.0)	1,721 (93.1)	40 (87.0)	0.11
Insulin at 6 years, pmol/L	113.5 (18.1, 409.9)	113.1 (17.7, 409.8)	130.7 (34.1, 412.5)	0.42
Total cholesterol at 6 years, mmol/L	4.2 ± 0.6	4.2 ± 0.6	4.4 ± 0.7	0.09
LDL-cholesterol at 6 years, mmol/L	2.4 ± 0.6	2.4 ± 0.6	2.4 ± 0.6	0.61
HDL-cholesterol at 6 years, mmol/L	1.3 ± 0.3	1.3 ± 0.3	1.4 ± 0.3	0.49
Triglycerides at 6 years, mmol/L	1.0 (0.4, 2.4)	1.0 (0.4, 2.4)	1.1 (0.4, 3.1)	0.10
Age 10 years at outcome follow-up measurements, years	9.8 ± 0.4	9.8 ± 0.3	9.9 ± 0.5	0.34
Playing sports at 10 years, h/d	1.3 (0.3, 3.5)	1.3 (0.3, 3.5)	1.1 (0.1, 3.5)	0.15
Screen time at 10 years, ≥2 h/d	852 (51.5)	824 (51.2)	28 (62.2)	0.15
BMI at 10 years, kg/m^2	16.9 (14.0, 24.3)	16.9 (14.0, 23.9)	21.9 (15.5, 31.0)	<0.01
Visceral fat mass at 10 years, g	369.0 (164, 1,005)	364.1 (163, 948)	804.4 (242, 1,849)	<0.01
Glucose at 10 years, mmol/L	5.2 ± 0.9	5.3 ± 0.9	5.1 ± 0.7	0.34
Insulin at 10 years, pmol/L	180.8 (37.1, 625.7)	180,0 (36.8, 610.5)	208.8 (41.7, 830.5)	0.09
Liver fat fraction at 10 years, %	2.0 (1.2, 5.2)	2.0 (1.2, 4.0)	6.5 (5.1, 20.4)	<0.01
Liver fat dichotomized, high ≥2.0%	1,086 (50.1)	1,026 (48.7)	60 (100)	<0.01
NAFLD	60 (2.8)	—	—	—

Values are observed and represent numbers (valid %), means ± SD, or medians (95% CI).

Maternal glucose concentrations were not associated with liver fat accumulation among mother-child pairs of European ancestry only (Table 4).

SENSITIVITY ANALYSES

When we repeated the main analyses by using insulin concentrations, we observed largely the same patterns and tendencies as for glucose concentrations (Supporting Table S5). When we repeated the analyses with childhood liver fat accumulation categorized into ≤2.0% versus >2%, we observed odds in a similar direction but smaller as for maternal early-pregnancy glucose concentrations with NAFLD (Supporting Table S6). No differences in findings were present when mothers with pre-existing diabetes or gestational diabetes or mothers with glucose measurements after 14 weeks' gestation were excluded from the analyses in both the full multiethnic group and the European-ancestry-only group. (Supporting Tables S7 and S8).

TABLE 2. Maternal and Childhood Characteristics by Offspring NAFLD Status: European-Only Group

	Europeans Only n = 1,426	NAFLD No n = 1,401	NAFLD Yes n = 25	*P* Value
Maternal characteristics				
Age at enrollment, years	31.7 ± 4.0	31.7 ± 4.0	31.1 ± 5.0	0.49
Gestational age at glucose/insulin measurement, weeks	12.8 (9.6, 17.0)	12.9 (9.6, 16.8)	12.4 (10.9, 17.0)	0.62
Prepregnancy BMI, kg/m^2	22.2 (18.1, 34.3)	22.2 (18.1, 31.3)	24.3 (18.1, 34.2)	0.05
Parity, nulliparous	901 (63.3)	513 (36.7)	10 (40.0)	0.73
Education, higher	923 (65.4)	914 (65.9)	9 (36.0)	<0.01
Smoking during pregnancy, continued	217 (18.7)	215 (18.9)	2 (9.5)	0.28
Alcohol consumption, during pregnancy	414 (38.2)	407 (38.3)	7 (33.3)	0.64
Folic acid supplement use, yes	662 (70.6)	648 (70.4)	14 (77.8)	0.50
Daily energy intake, kcal/d	2,053 ± 587	2,055 ± 586	1,966 ± 651	0.51
Dyslipidemia	141 (9.9)	140 (10.0)	1 (4.0)	0.32
Glucose, mmol/L	4.4 ± 0.8	4.4 ± 0.8	5.0 ± 1.2	<0.01
Insulin, pmol/L	102.1 (19.2, 518.6)	102.1 (19.1, 440.7)	103.9 (19.8, 846.0)	0.15
Pre-existing diabetes	2 (0.2)	2 (0.2)	0 (0)	0.85
Gestational diabetes	15 (1.1)	15 (1.1)	0 (0)	0.61
Child characteristics				
Sex, female	722 (50.6)	708 (50.5)	14 (56.0)	0.59
Birth weight, g	3,500 ± 540	3,500 ± 540	3,447 ± 521	0.62
Gestational age at birth, weeks	40.3 (36.0, 42.4)	40.3 (36.0, 42.1)	40.0 (37.0, 42.6)	0.62
Ever breastfed, yes	1,195 (92.1)	1,177 (92.0)	18 (94.7)	0.66
Insulin at 6 years, pmol/L	115.1 (18.5, 394.3)	114.1 (18.3, 394.5)	155.4 (60.3, 398.2)	0.06
Total cholesterol at 6 years, mmol/L	4.2 ± 0.6	4.2 ± 0.6	4.4 ± 0.8	0.15
LDL-cholesterol at 6 years, mmol/L	2.3 ± 0.6	2.3 ± 0.6	2.5 ± 0.7	0.45
HDL-cholesterol at 6 years, mmol/L	1.3 ± 0.3	1.3 ± 0.3	1.4 ± 0.3	0.34
Triglycerides at 6 years, mmol/L	1.0 (0.4, 2.3)	1.0 (0.4, 2.3)	0.9 (0.4, 2.4)	0.60
Age 10 years at outcome follow-up measurements, years	9.8 ± 0.3	9.8 ± 0.3	9.8 ± 0.3	0.82
Playing sports at 10 years, h/d	1.4 (0.4, 3.5)	1.4 (0.4, 3.5)	1.2 (0.1, 2.5)	<0.01
Screen time at 10 years, ≥2 h/d	552 (45.9)	538 (45.6)	14 (63.6)	0.09
BMI at 10 years, kg/m^2	16.6 (14.0, 22.6)	16.6 (14.0, 22.0)	21.3 (16.2, 28.6)	<0.01
Visceral fat mass at 10 years, g	371.7 (168, 981)	369.9 (168, 920)	782,1 (301, 1,360)	<0.01
Glucose at 10 years, mmol/L	5.3 ± 1.0	5.3 ± 1.0	5.2 ± 0.8	0.76
Insulin at 10 years, pmol/L	172.1 (34.9, 577,9)	171.2 (34.8, 573.7)	212.8 (40.8, 826.0)	0.15
Liver fat fraction at 10 years, %	2.0 (1.2, 4.5)	2.0 (1.2, 4.0)	6.2 (5.1, 14.0)	<0.01
Liver fat dichotomized, high ≥2.0%	687 (48.2)	662 (47.3)	25 (100.0)	<0.01
NAFLD	25 (1.8)	—	—	—

Values are observed and represent numbers (valid %), means ± SD, or medians (95% CI).

Discussion

In this prospective cohort study, we observed that maternal early-pregnancy glucose concentrations were only among mothers of European ancestry associated with offspring NAFLD. These associations were not explained by maternal prepregnancy BMI and dyslipidemia. Also, childhood metabolic markers at 6 years, or BMI, visceral fat mass, and glucose concentrations at 10 years, did not explain the observed associations. No associations were observed in the full group.

INTERPRETATION OF MAIN FINDINGS

NAFLD ranges from liver steatosis, to fibrosis, cirrhosis, and eventually end-stage liver disease.[41] In adults, NAFLD is associated with type 2 diabetes,

TABLE 3. Associations Between Maternal Early-Pregnancy Glucose Concentrations With Childhood Liver Fat Fraction and NAFLD in the Full Multiethnic Group

Maternal Early-Pregnancy Glucose mmol/L	Liver Fat at School Age n = 2,168			
	Difference Liver Fat Fraction SDS (95% CI)	*P* Value	OR NAFLD Yes/No (95% CI)	*P* Value
Basic model	0.04 (0.01; 0.07)	0.12	1.26 (1.09; 1.45)	0.11
Main confounder model	0.03 (–0.02; 0.08)	0.27	1.20 (0.90; 1.59)	0.21
Maternal BMI model	0.01 (–0.04; 0.05)	0.84	1.18 (0.87, 1.59)	0.30
Maternal dyslipidemia model	0.03 (–0.02; 0.08)	0.29	1.25 (0.93, 1.67)	0.14
Child metabolic markers at 6 years model	0.03 (–0.02, 0.08)	0.27	1.24 (0.93, 1.66)	0.15
Child BMI at 10 years model	0.01 (–0.04, 0.06)	0.68	1.13 (0.84, 1.53)	0.42
Child visceral fat mass at 10 years model	0.02 (–0.02, 0.06)	0.47	1.30 (0.95, 1.79)	0.11
Child glucose concentrations at 10 years model	0.03 (–0.02, 0.08)	0.30	1.26 (0.94; 1.69)	0.12

TABLE 4. Associations Between Maternal Early-Pregnancy Glucose Concentrations With Childhood Liver Fat Fraction and NAFLD in the Group of European Ancestry Only

Maternal Early-Pregnancy Glucose mmol/L	Liver Fat at School Age n = 1,426			
	Difference Liver Fat Fraction SDS (95% CI)	*P* Value	OR NAFLD Yes/No (95% CI)	*P* Value
Basic model	0.03 (–0.03; 0.08)	0.38	1.93 (1.31; 2.84)	<0.01
Main confounder model	0.02 (–0.04; 0.08)	0.49	1.95 (1.32; 2.88)	<0.01
Maternal BMI model	0.00 (–0.06; 0.06)	0.90	1.86 (1.24; 2.78)	<0.01
Maternal dyslipidemia model	0.02 (–0.04; 0.08)	0.49	1.92 (1.30; 2.86)	<0.01
Child metabolic markers at 6 years model	0.02 (–0.04; 0.08)	0.50	1.96 (1.31; 2.95)	<0.01
Child BMI model	0.01 (–0.05; 0.06)	0.78	1.66 (1.04; 2.64)	0.03
Child visceral fat mass at 10 years model	0.00 (–0.05; 0.06)	0.89	1.82 (1.19; 2.79)	<0.01
Child glucose concentrations model	0.02 (–0.04; 0.08)	0.50	1.95 (1.32; 2.88)	<0.01

Values are regression coefficients (95% CIs) from linear regression models that reflect differences in liver fat fraction in SDS per maternal early-pregnancy glucose concentrations in mmol/L in mother-child pairs of European ancestry only. Values are ORs (95% CIs) that reflect the risk of NAFLD per maternal early-pregnancy glucose concentrations in mmol/L. Basic model: adjusted for child sex and age at outcome follow-up measurements. Main model: basic model additionally adjusted for maternal education, and child physical activity. Maternal BMI model: main model additionally adjusted for maternal prepregnancy BMI. Maternal dyslipidemia model: main model additionally adjusted for maternal dyslipidemia in early pregnancy. Child metabolic markers at 6 years model: main model additionally adjusted for child insulin, total cholesterol, LDL- and HDL-cholesterol, and triglycerides concentrations at 6 years of age. Child BMI model: main model additionally adjusted for child BMI at 10 years of age. Child visceral fat mass model: main model additionally adjusted for child MRI-measured visceral fat mass at 10 years of age. Child glucose concentrations model: main model additionally adjusted for child glucose concentrations at 10 years of age. NAFLD was defined as "yes" when liver fat was ≥5.0% and as "no" when liver fat was <5.0%.

cardiovascular disease, dyslipidemia, and metabolic syndrome.[17,32,41,42] We previously reported that elevated liver fat is associated with an adverse cardiometabolic risk profile in children.[17] Gestational diabetes and hyperglycemia diagnosed in the second half of pregnancy are associated with an altered offspring body fat composition, as well as cardiovascular and metabolic health.[4-6,39,43] Studies in women with gestational diabetes showed an association with offspring markers of liver pathology.[11,12] These findings, together with observations from animal studies, suggest that maternal gestational hyperglycemia might be related to offspring liver fat development.[13-15] More specifically, early pregnancy might be a critical period for effects of intrauterine maternal glucose exposure on liver health, because the embryonic development of the metabolic systems and of the placenta already occurs in the first weeks after conception.[44] Therefore, we hypothesized that higher maternal glucose concentrations across the full range in early pregnancy are associated with liver fat accumulation in offspring.

In this study, in children 10 years of age, we did not observe that maternal early-pregnancy glucose concentrations were associated with childhood liver fat accumulation and with risk of NAFLD. Because both glucose concentrations and liver fat and the associations between ethnic subgroups strongly differ, we performed analyses in the full multiethnic group and in the group of European ancestry only. In the European-ancestry-only group, the largest ethnic subgroup, we observed an almost 2-fold increase in odds of NAFLD, independent of maternal prepregnancy BMI and dyslipidemia, childhood metabolic markers at 6 years, or BMI, visceral fat mass, and glucose concentrations at 10 years. This may suggest that there is also an intrauterine effect of maternal early-pregnancy glucose concentrations on childhood liver fat accumulation through other pathways than through maternal prepregnancy or child BMI or child glucose concentrations in this subgroup. Because of smaller sample sizes for the other individual ethnic subgroups, we could not test these associations in each ethnic subgroup separately. We did not observe associations of maternal early-pregnancy glucose concentrations with liver fat across the full range in the total study sample and in the largest ethnic subgroup. The lack of association in the total group might be attributable to a modifying effect of ethnicity with per ethnic subgroup opposite directions of effect estimates. The lack of association in the largest ethnic subgroup could be attributable to the moderate sample size, together with the relatively small variability in liver fat accumulation in this population of children. Further studies are needed to explore these associations among higher-risk populations and evaluate liver fat accumulation in older offspring.

The underlying pathogenic mechanisms behind the abnormal metabolic risk profile in offspring of mothers with gestational diabetes are largely unknown. Animal studies have suggested that *in utero* exposure to high glucose concentrations may induce ectopic fat storage.[13-15] For instance, mouse models of maternal insulin resistance have shown impairment of gene expression involved in fatty acid oxidative capacity and lipogenesis in offspring liver.[15,16,45] Accelerated hepatic fat storage in mouse offspring appears to persist into adulthood, suggesting a lasting impact of the maternal intrauterine environment on pathways of hepatic lipid metabolism.[16,45] Another speculation is that the higher insulin resistance in the offspring of mothers with gestational diabetes is associated with a higher liver fat accumulation, although the direction of effect is not yet defined.[8,17] In mothers with gestational diabetes, a higher risk for NAFLD after pregnancy is observed, supporting the hypothesis of a link between insulin resistance and liver fat accumulation.[46]

Given the high prevalence of both obesity and impaired glucose metabolism in preconceptional women, these may represent pivotal targets if proven causal for public health in preventing offspring obesity and metabolic disease, like NAFLD.[1-3] Our findings emphasize the importance of developing preventive strategies before and in early pregnancy to improve liver and metabolic health outcomes in children. Further studies should characterize the maternal metabolic environment in early pregnancy to provide insights into the causality of early-life determinants of NAFLD, taking into account ethnic background.

METHODOLOGICAL CONSIDERATIONS

The population-based, prospective, longitudinal design of this study, together with the large sample size with data collection from early pregnancy onward and the availability of MRI-measured liver fat fraction at 10 years of age, are major strengths of this study. The children who underwent MRI measurements at 10 years of age constitute a subgroup of the full Generation R Study population. This may have led to biased effect estimates if associations were different between those included and not included in the analyses, which seems unlikely given that the nonresponse analysis showed hardly any differences. The prevalence of gestational diabetes in our sample was lower than expected (1.1% vs. 2%-5% in the general Dutch population[47]), likely attributable to the use of medical records after delivery to obtain information on the diagnosis of gestational diabetes and lack of universal screening, which may have led to misclassification. The low prevalence of gestational diabetes may also indicate a selection toward a nondiabetic population and might affect the generalizability of our findings. Accurate diagnosis of gestational diabetes is difficult. A fasting glucose >7.0 mmol/L might also represent pre-existing diabetes, and a fasting glucose between 6.1 and 6.9 mmol/L might also represent impaired glucose tolerance, instead of gestational diabetes. We verified information about gestational diabetes from

medical records. However, glucose testing for diagnosis of gestational diabetes was not yet routinely performed in our cohort study. Therefore, we may have missed the clinical diagnosis of gestational diabetes among women with relatively higher glucose concentrations. Our findings might be partly explained by women with higher glucose concentrations who were not diagnosed with gestational diabetes. Further studies are needed to replicate our findings among more higher-risk populations, including women with impaired glucose tolerance from preconception and early pregnancy onward and women at higher risk to develop gestational diabetes. The small number of children with NAFLD is likely explained by the fact that we measured liver fat in a relatively healthy study population at a young age, which could have limited our statistical power to detect significant associations and may affect the generalizability of our findings. The main analyses focused on NAFLD were based on only 60 in the full and 25 children in the Europeans-ancestry-only group with MRI-diagnosed NAFLD. Therefore, these results need to be interpreted carefully and need further replication. We obtained random maternal glucose concentrations once during pregnancy at nonfixed times throughout the day. Because of our study design, we were not able to collect repeated fasting blood samples. Given that glucose concentrations throughout the day are influenced by multiple factors, such as dietary intake and exercise, this may have led to nondifferential misclassification, causing an underestimation of our associations. We did not have information on 1- and 2-hour postprandial glucose concentrations available. However, previous studies, including studies from our cohort, have shown that random maternal gestational glucose concentrations in pregnancy are related to the risks of gestational diabetes, adverse birth outcomes, childhood obesity, childhood cardiac ventricular structure and function, and altered childhood glucose metabolism.[8,9,22,48,49] These associations were in the same direction as the associations shown for maternal fasting glucose concentrations and postprandial glucose concentrations with these adverse outcomes.[38,50] Further studies are needed using repeated detailed maternal glucose measurements, including fasting glucose concentrations and postprandial glucose measurements, to replicate our findings. Ideally, these studies should already measure maternal glucose metabolism before pregnancy to reflect maternal glucose metabolism in the preconception period. Information on many covariates was available, yet some residual confounding may have influenced the results.

Maternal early-pregnancy glucose concentrations were only among mothers of European ancestry associated with offspring NAFLD. These associations were independent of maternal prepregnancy and childhood BMI, visceral fat, and metabolic markers. No associations were observed in the full multiethnic group. Further studies are needed to explore the causality of the observed associations. Optimizing maternal prepregnancy BMI and glucose concentrations could be starting points for prevention strategies to improve liver health among future generations.

Acknowledgment: We gratefully acknowledge the contribution of general practitioners, hospitals, midwives, and pharmacies in Rotterdam.

Author Contributions: M.L.G., R.G., and V.W.V.J. designed and constructed the research, wrote the manuscript, and had primary responsibility for the final content. M.L.G. and R.J.W. performed the statistical analysis. J.F.F., R.G., and V.W.V.J. coordinated data acquisition and critically reviewed and revised the manuscript. All authors approved the final manuscript and agreed to be accountable for all aspects of the work. M.L.G. and V.W.V.J. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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