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Gestational Diabetes Mellitus is Strongly Associated with Non-Alcoholic Fatty Liver Disease

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Abstract

Insulin resistance is central to the development of non-alcoholic fatty liver disease (NAFLD), and gestational diabetes mellitus (GDM) is an early marker of insulin resistance. We hypothesized that a history of GDM would identify women at higher risk of NAFLD in middle age. Women from the multicenter Coronary Artery Risk Development in Young Adults (CARDIA) cohort study who delivered ≥ 1 birth, were free of diabetes prior to pregnancy(ies), and underwent CT quantification of hepatic steatosis 25 years following cohort entry (Y25: 2010–2011) were included (n = 1115). History of GDM by self-report, validated in a subsample by review of antenatal glucose testing, and metabolic risk factors were assessed prospectively. NAFLD was defined by liver attenuation (LA) ≤ 40 Hounsfield Units on CT scan after exclusion of other causes of hepatic steatosis. Of 1,115 women meeting selection criteria (57% black, 43% white, median age 25 years at baseline), 124 (11%) reported a history of GDM and 75 (7%) met the CT definition for NAFLD at year 25. The crude risk of NAFLD at the 25-year visit was significantly higher in women with GDM compared to those without (14% vs. 5.8%, OR: 2.56, 95% CI: 1.44–4.55, p<0.01). History of GDM remained associated with NAFLD (OR: 2.29, 95% CI: 1.23–4.27, p=0.01) after adjustment for covariates in multivariable logistic regression. Addition of incident diabetes mellitus (DM) into the final model attenuated the association between GDM and NAFLD (OR: 1.48, 95% CI: 0.73 – 3.02, p=0.28).

Conclusion—GDM is a risk marker for NAFLD and represents an opportunity to identify women at risk for NAFLD at a young age and may be mediated by the development of incident DM.

Keywords

hepatic steatosis; gestational diabetes; pregnancy; women; preventive medicine

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most prevalent form of chronic liver disease in the United States affecting up to 20–30% of the western world.[1] NAFLD encompasses a spectrum of disease ranging from isolated hepatic steatosis to steatosis with inflammation and hepatocyte injury [non-alcoholic steatohepatitis (NASH)]. NAFLD is an increasingly common cause of cirrhosis and hepatocellular carcinoma and is on trajectory to become the most frequent indication for liver transplantation in the United States.[2,3] In light of the increasing prevalence and disease burden of NAFLD it is important to identify persons with NAFLD prior to the development of advanced liver disease.

NAFLD is recognized as the hepatic manifestation of the metabolic syndrome. The normal physiologic stress of pregnancy, which causes relative hypertriglyceridemia and increased insulin resistance, may help identify women at an early age who are at risk for the development of NAFLD.[4] Gestational diabetes mellitus (GDM), defined as glucose intolerance first recognized during pregnancy, represents a failure to adapt to the metabolic demands of pregnancy and has been shown to confer an increased risk of subsequent type 2 diabetes mellitus (DM), and the metabolic syndrome, as well as signify a marker for early atherosclerosis independent of pre-pregnancy metabolic risk factors.[5–8] A single cross-sectional, European study has shown that history of GDM is associated with a significantly higher prevalence of NAFLD compared to healthy volunteers in unadjusted analyses.[9] However, this study was limited by its small sample size, inability to adjust for pre-pregnancy metabolic risk factors and exclusion of women who subsequently developed DM.

Therefore, it remains unclear whether GDM is associated with NAFLD independent of other metabolic risk factors or progression to DM. We sought to evaluate the impact of previous GDM on the prevalence of NAFLD in middle age while controlling for known metabolic risk factors in a biracial cohort, which prospectively measured metabolic risk factors at regular intervals during 25 years. We hypothesized that a history of GDM would be directly associated with NAFLD despite adjustment for metabolic risk factors and would identify young women who would benefit from interventions to prevent future NAFLD.

Methods

Study Population

The CARDIA study is a multicenter community-based longitudinal cohort study of cardiovascular disease in young black and white adults 18–30 years of age recruited across 4 US cities (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA) in 1985–1986. Subjects were not selected based on risk factors for metabolic disease and were recruited by random-digit dialing from total communities, census tract information, or from their health-care plan. The study design has been published previously.[10] In 1985–1986 a total of 5115 subjects (2787 women, 50% black) were recruited and had scheduled follow up at years 2, 5, 7, 10, 15, 20, and 25. The retention rate was 72% of the surviving cohort at year 25. Institutional review boards at each center approved the study and informed consent was obtained from all of the participants. From the 2787 women enrolled at baseline we

selected women who delivered one or more births, were free of diabetes prior to pregnancy(ies), and underwent computed tomography (CT) quantification of hepatic steatosis 25 years following cohort entry (n=1,316). We excluded women with other potential causes of hepatic steatosis including alcohol use > 2 drinks/day (n=52), self-report of HIV or chronic hepatitis (n=26), and medication use associated with steatosis; amiodarone, methotrexate, valproic acid, tamoxifen, steroids, diltiazem, or hormone replacement therapy (n=123) (Figure 1). The 1,115 women included in this analysis had similar baseline characteristics to those excluded (Supplementary Table 1).

Measurements

Pregnancies and GDM Status—Pregnancies and deliveries were assessed by self-report at each exam. Participants reported the number of pregnancies and births, length(s) of gestation, gestational hypertensive disorders, and GDM, as well as how the pregnancy ended (abortion, miscarriage, and live or stillbirths). Births were defined as pregnancies of > 20 weeks gestation. Total parity was equal to the total number of live births. GDM was defined by self-report among those without overt diabetes before pregnancy based on CARDIA laboratory tests. Self-report of GDM has been previously validated in this cohort by review of prenatal glucose tolerance tests for a subsample of 165 women who delivered 200 births and revealed a sensitivity of 100% and specificity of 92%.[11]

Assessment of hepatic steatosis—The CT protocol used a non-contrast abdominal CT scan performed using GE [GE 750HD (64) at Birmingham and GE LightSpeed VCT (64) at Oakland; GE Healthcare, Waukesha, Wisconsin] or Siemens [Sensation 64 at Chicago and Minneapolis Centers; Siemens Medical Solutions, Erlangen, Germany] multidetector CT scanners and has been published previously.[12] Quality control and image analysis were performed at a core reading center (Wake Forest University Health Sciences, Winston-Salem, North Carolina). CT diagnosis of hepatic steatosis was made by measuring liver attenuation (LA) in Hounsfield Units (HU). NAFLD was defined as a LA value ≤ 40 HU. LA was the average of nine measurements on three CT slices of the right lobe of the liver. A cut-off of LA value ≤ 40 HU correlates with moderate-to-severe steatosis (>30%) in unenhanced CT scans in multiple studies.[13–15] The characterization of LA in this cohort used a dedicated workflow within the National Institute of Health's Center of Information Technology Medical Image Processing, Analysis, and Visualization application has previously published.[12] The interclass correlation coefficient between different readers on a random sample of 156 participants was 0.975 for LA, indicating high reproducibility of CT measured LA in this cohort.

Risk Factor Measurements—Participant demographics, medical history, and alcohol use were obtained through standardized surveys. Medication use was determined through self-report and participants brought medications to study visits for verification. Participants were asked to fast for ≥ 8 hours prior to venous blood draws at each visit. Procedures for specimen collection and methodologies to assay plasma triglycerides (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and total cholesterol (TC), and serum glucose and insulin were standandized.[16,17] Homeostatic model assessment index (HOMA-IR) was calculated using the equation: [fasting glucose (mmol/L)

x fasting insulin (mU/L)]/22.5. Certified technicians performed anthropometric measurements including weight, height and waist circumference using standardized protocols. Waist circumference was measured midway between the iliac crest and bottom of the rib cage. Change in BMI was calculated between baseline and Year 25.

Statistical Analyses

Baseline and follow up differences in participant characteristics were compared by GDM history using chi-square tests for categorical variables and Mann-Whitney U tests for continuous variables. Logistic regression was used to evaluate the association between previous GDM and NAFLD at year 25. Bivariate models assessed the association between variables chosen a priori for clinical relevance and known association with the outcome of NAFLD. These covariates included age, race, and baseline covariates [BMI, waist circumference, fasting LDL, HDL, triglycerides, and insulin resistance (HOMA-IR)]. Variables were selected for the final multivariate model by backwards elimination with p-value < 0.05 used as the threshold for variable inclusion. Change in BMI and incident DM after pregnancy were evaluated as mediators of GDM and NAFLD. Effect modification by race, baseline BMI, baseline HOMA-IR and incident DM after pregnancy on the association between GDM status and NAFLD were evaluated by adding the cross-product terms to the final model, with p values <0.10 used to identify statistically significant interactions. All p-values were two-sided and statistical significance was defined as a p-value < 0.05. Analyses were performed using STATA 13.1 (StataCorp, College Station, TX).

Results

Study Cohort Characteristics

Of the 1115 women meeting inclusion criteria, 57% and 43% were of black and white race, respectively, with a median (IQR) age of 25 (6) years at baseline. One hundred and twenty-four women (11%) reported a history of GDM and 75 (7%) met the CT definition for NAFLD at year 25. Forty-one (6.4%) black women and 34 (7.2%) white women had NAFLD at year 25. At baseline, compared to women without GDM, those who reported GDM at baseline (n=27) or developed GDM over the study period (n=97) had higher BMI [median (IQR), 23.8 (8.8) vs. 22.9 (6.2) kg/m^2], HOMA-IR [median (IQR), 1.6 (1.2) vs. 1.4 (0.77)], TG [median (IQR), 64 (30) vs. 56 (33) mg/dL] and waist circumference [median (IQR), 74 (17) vs. 71.3 (12.5) cm] (Table 1). At year 25 (Table 2), compared to women without GDM, those with a history of GDM had significantly higher HOMA-IR [median (IQR), 2.6 (2.9) vs. 2.0 (2.2)], incidence of DM (49% vs. 7.6%) and greater proportion with parity > 2 (32% vs. 24%). Moreover, at the 25-year exam, women with a history of GDM had a more than 2-fold higher prevalence of NAFLD compared to those without GDM (14% vs. 5.8%, p<0.01).

Gestational Diabetes and NAFLD at Year-25

In unadjusted logistic regression models, the odds of NAFLD at year 25 was 2.56-fold higher (95% CI: 1.44 – 4.55) in women with GDM than without GDM (Table 3). In multivariable models adjusted for age, parity, baseline BMI, waist circumference, HOMA-IR, HDL and TG, GDM remained strongly associated with NAFLD at year 25. In the final

multivariable model, GDM (OR: 2.29, 95% CI: 1.23–4.27, p=0.01), baseline HOMA-IR and baseline triglycerides levels were independently associated with NAFLD at year 25 (Table 3). Adjustment for time from births to year 25 did not affect the association between GDM and NAFLD (data not shown). The change in BMI per 1 kg/m^2 from baseline to year 25 was evaluated as a mediator (Table 4), but its addition to the fully adjusted multivariable model did not attenuate the GDM association with odds of NAFLD at year 25, which remained statistically significant (OR: 2.89, 95% CI 1.49–5.59, p=<0.01). Furthermore, the addition of year 25 BMI to the same model similarly had minimal impact on the GDM and NAFLD association (OR: 2.61, 95% CI 1.37–4.96, p<0.01). The association of GDM with higher odds of NAFLD at year 25 also remained after addition of the change in BMI from the first post-delivery exam to year 25 (data not shown).

The association between GDM and NAFLD was no longer statistically significant after addition of incident DM to the fully adjusted multivariable model (OR: 1.48, 95% CI 0.73 – 3.02, p=0.28) (Table 4). Incident DM was strongly associated with NAFLD in the fully adjusted models (OR: 2.77, 95% CI 1.41– 5.45 p<0.01), and independently associated with GDM (49% vs 7.6%) versus non-GDM, suggesting that incident DM may be a mediator on the pathway from GDM to NAFLD. Stratified analysis revealed that the association between GDM and NAFLD was no longer statistically significant among those without incident DM in the fully adjusted model(OR: 1.93, 95% CI (0.72 – 5.14), p=0.19) (Table 4) even though the prevalence of NAFLD at year 25 was almost twofold higher among women with GDM than without GDM (8.1% versus 4.5%; Figure 2). Among those who had developed incident DM, a history GDM was no longer significantly associated with NAFLD. Additional adjustment for number of years with DM did not impact the results (data not shown). Two-way interaction terms for GDM and race (p=0.64), baseline BMI (p=0.14), baseline HOMA-IR (p=0.20), and incident DM (p=0.47) were not significantly associated with NAFLD at year 25.

Discussion

Our findings demonstrate that a history of GDM is strongly associated with the presence of NAFLD in middle age after adjustment for other metabolic risk factors in early adulthood and may be mediated through the progression to incident DM after GDM pregnancy. This is the largest study examining the relationship between GDM and NAFLD and utilized a unique and well-characterized cohort of black and white women from multiple regions of the United States with 25 years of anthropometric and metabolic profiling. As an early risk marker for NAFLD, women with GDM may be viewed as a target group for lifestyle interventions aimed at preventing the sequelae of NAFLD.

The only previous study of the association between GDM and NAFLD included 223 women (110 GDM) retrospectively selected from a database that underwent ultrasound assessment of hepatic steatosis less than 10 years after pregnancy and had not subsequently developed DM.[9] The cross-sectional analysis did not have data on metabolic risk factors during the participants' childbearing years and all of the women in this study were of European descent. Furthermore, only two women had more than mild steatosis on ultrasound and the study was underpowered to perform adjusted analysis. Two studies from Europe have

evaluated other markers of fatty liver among women with GDM. One cross-sectional study of 31 European women showed an association between non-diabetic women with a history of GDM and increased hepatocellular lipids on MR spectroscopy, however did not evaluate for secondary causes of hepatic steatosis to make the diagnosis of NAFLD.[18] Another study of 97 European women (68 GDM) assessed within 3–6 months after pregnancy found that previous GDM was associated with a higher score on the fatty liver index (FLI), which is a weighted score based on BMI, waist circumference, triglycerides, and GGT that has been shown to correlate with the presence of NAFLD in a middle-aged European cohort.[19,20] Our study compared parous women in a large multicenter cohort with 25 years of follow up and was the first to find a significant association between GDM and NAFLD in midlife after adjusting for metabolic risk factors in early adulthood (age 18–30 years) in women without diabetes. We utilized computed tomography to evaluate for hepatic steatosis with a very high interclass correlation coefficient. Furthermore, our study population was diverse and is the only one to distinguish GDM history from subsequent development of DM.

Women with GDM in CARDIA have a fourfold greater risk of developing DM relative to women without previous GDM after controlling for preconception blood glucose and other risk factors.[11] A meta-analysis reported a 7-fold greater risk for developing DM relative to women who do not have GDM during pregnancy.[6] Furthermore, DM is a major risk factor for NAFLD; therefore we evaluated subsequent development of DM as a mediator of the relationship between GDM and NAFLD. We expanded on previous findings in CARDIA that GDM was strongly associated with incident DM.[11] We found that subsequent onset of DM mediated the GDM and NAFLD association. Previous studies that evaluated the association between GDM and hepatic steatosis restricted to women who had not developed incident DM reported a positive association without covariate adjustment. In our study the relationship between GDM and NAFLD was no longer statistically significant when analyses were restricted to women who had not developed incident DM. However, the prevalence of NAFLD was higher in the GDM group compared to the women without GDM during pregnancy, therefore our study may have been underpowered to assess for an association in this subgroup.

GDM represents a state of increased pancreatic beta cell dysfunction, particularly post-glucose load. Previous studies have shown that women with a history of GDM and postpartum weight retention have increased systemic inflammation and decreased insulin sensitivity.[21] In women with GDM plasma TNF-α levels and skeletal muscle TNF-α mRNA remain elevated one-year post-partum.[22] A dose response effect with increasing number of GDM pregnancies would support the hypothesis that GDM is associated with NAFLD independent of DM, however our study was underpowered to assess for this. GDM was associated with NAFLD independent of weight gain over 25 years, age at first pregnancy and age at last pregnancy. The temporal relationship between NAFLD and the development of DM could not be explored in this study, however a previous study with 10-year follow up of women with GDM showed a higher incidence of DM among women with the highest values on fatty liver index (FLI) testing.[19] In our study the only baseline factors associated with NAFLD on multivariable analysis were HOMA-IR and fasting triglycerides, which coincides with previous data on risk factors for the development of NAFLD.[23] We explored possible interactions between GDM and baseline BMI, HOMA-IR and race, however none

met our threshold for statistical significance. In our study, the association between GDM and NAFLD did not vary significantly by race and our study is the first to establish this association in African-American women.

A limitation of our study is the measurement of liver attenuation on non-contrast CT scan at the year 25 follow up visit only, which limits our ability to exclude presence of NAFLD before GDM. However, NALFD at baseline is of low likelihood based on the women's age of enrollment and the low prevalence of NAFLD in young adulthood at time of study enrollment in the mid-1980s.[24] Furthermore, even if women with GDM had NAFLD at baseline, GDM would remain an early marker able to identify women with NAFLD before they developed overt metabolic disease. The lack of liver biochemistry is another limitation, however laboratory testing is neither sensitive nor specific for the diagnosis of NAFLD and we excluded secondary causes of hepatic steatosis (e.g. alcohol, medications, and concomitant liver disease) through detailed surveys.[25] Additional laboratory testing, that could have allowed risk stratification by fibrosis severity among women with GDM and NAFLD through the use of validated scoring systems, was unavailable in this study. Our study identified GDM history by self-report, a method previously validated by chart review of antenatal records of glucose testing and had excellent sensitivity and specificity.[11] Our outcome of NAFLD was measured by liver attenuation on non-contrast CT scan. While liver biopsy remains the gold standard for diagnosis of NAFLD, it is invasive and subject to sampling error. We chose our LA cutoff based off of previous studies correlating liver attenuation with histology, which showed excellent specificity but lower sensitivity for the detection of NAFLD.[15] Maintaining high specificity minimizes the impact of measurement bias on our measure of association,[26] however our liver attenuation cutoff could not detect lesser degrees of pathologic steatosis between 5% and 30%. Magnetic resonance spectroscopy is a more sensitive non-invasive tool for the measurement of hepatic fat content and may have increased the number of women with image-detected steatosis, however it was not available in our cohort. The absence of significant racial differences in our study may have resulted from our inability to detect lesser degrees of steatosis. Our cohort also did not include Hispanic women or data on genetic polymorphisms including patatin-like phospholipase domain containing protein 3 (PNPLA3), which partially explain racial differences in NAFLD. Future studies of the association between GDM and NAFLD should include a multi-ethnic cohort and evaluate patients with lesser degrees of steatosis.

In conclusion, our study shows that GDM history is risk marker for NAFLD in middle-aged women separate from metabolic risk factors in young adulthood. We found that progression to DM after pregnancy likely mediates this relationship, however the prevalence of NAFLD remained higher among those with GDM who had not developed incident DM, suggesting a continuum of risk with increasing insulin resistance. In women with a history of GDM both lifestyle and pharmacologic intervention with metformin yielded an approximately 50% reduction in the incidence of DM compared to placebo in the Diabetes Prevention Program.[27] Currently, there are no guidelines recommending who should be screened for NAFLD, and some societal guidelines specifically recommend against screening for NAFLD.[23] However, as therapeutic options for treatment of NAFLD increase and screening modalities improve, this may change. Our study shows that a history of GDM may help to

identify young women at risk and allow targeted strategies to prevent morbidity and mortality related to NAFLD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
GDM	gestational diabetes mellitus
CARDIA	Coronary Artery Risk Development in Young Adults
CT	computed tomography
LA	liver attenuation
DM	diabetes mellitus
TG	fasting plasma triglycerides
HDL	fasting plasma high-density lipoprotein cholesterol
LDL	fasting plasma low-density lipoprotein cholesterol
TC	fasting plasma total cholesterol
BMI	body mass index
HOMA-IR	homeostatic model assessment of insulin resistance
IQR	interquartile range
OR	odds ratio
TNF-α	tumor necrosis factor alpha
FLI	fatty liver index

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Study Highlights

1. WHAT IS CURRENT KNOWLEDGE

- NAFLD is an increasingly common cause of liver related morbidity and mortality.
- Early identification with the goal of preventing NAFLD is an important strategy to decrease the disease burden.

2. WHAT IS NEW HERE

- Gestational diabetes mellitus is an early risk marker for the presence of NAFLD in middle age.
- Subsequent progression to diabetes mellitus mediates the relationship between gestational diabetes and NAFLD.
- The physiologic stress of pregnancy is a unique setting to identify women at risk for NAFLD.

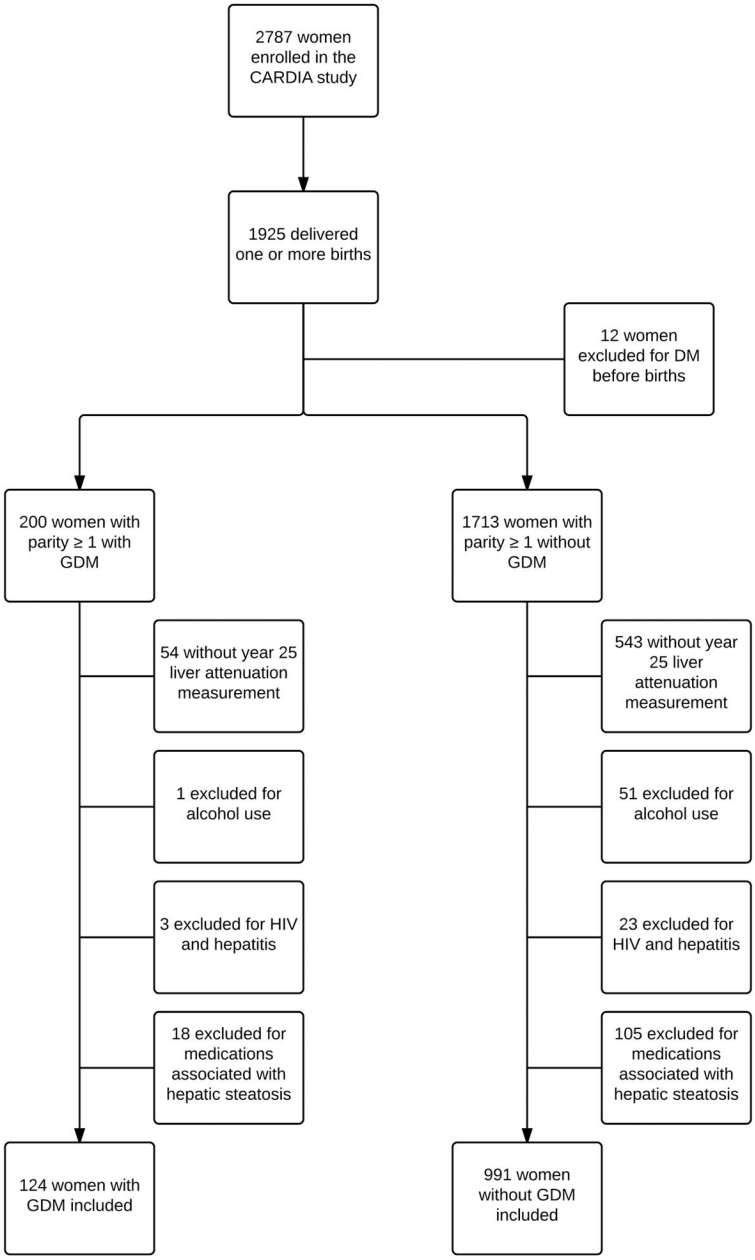

Figure 1.

Cohort of CARDIA participants meeting inclusion and exclusion criteria. Alcohol use defined as > 14 drinks/week. Medications leading to exclusion; amiodarone, methotrexate, valproic acid, tamoxifen, steroids, diltiazem, or hormone replacement therapy.

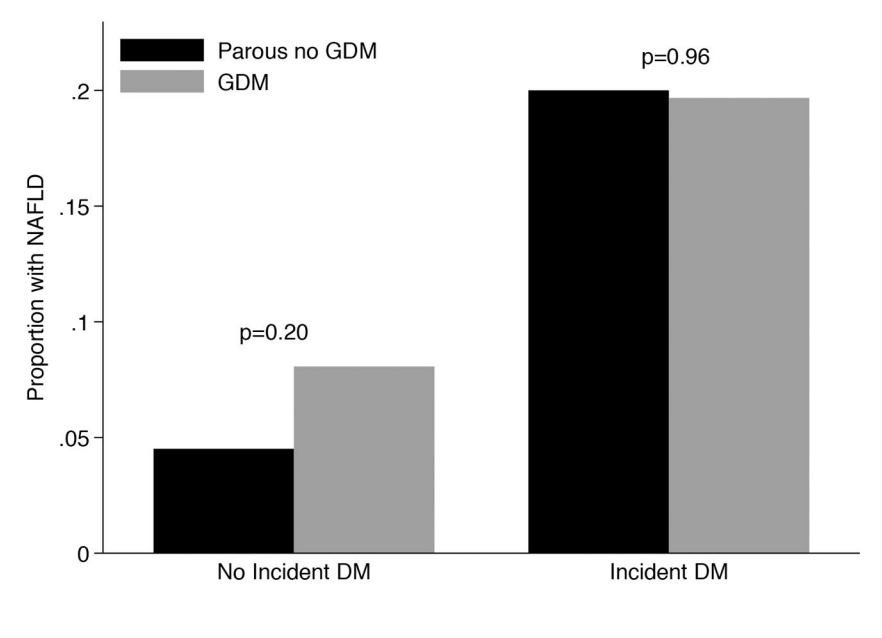

Figure 2.
Proportion of participants with NAFLD by DM and GDM status

Table 1

Baseline Visit Characteristics of Women with One or More Births, by History of GDM (n= 1,115) *

Characteristic	GDM (n=124)	Non-GDM (n=991)	p†
Age, median (IQR) years	26 (8)	25 (6)	0.48
Race, n (%)			0.40
African American	68 (55)	573 (58)	
Caucasian	56 (45)	418 (42)	
BMI, median (IQR) kg/m^2	**23.8 (8.8)**	**22.9 (6.2)**	**0.03**
HOMA-IR, median (IQR)	**1.6 (1.2)**	**1.4 (0.77)**	**< 0.01**
Total cholesterol, median (IQR) mg/dL	172 (49)	174 (44)	0.27
LDL, median (IQR) mg/dL	103 (40)	106 (40)	0.31
HDL, median (IQR) mg/dL	53 (16)	55 (16)	0.12
Triglycerides, median (IQR) mg/dL	**64 (30)**	**56 (33)**	**< 0.01**
Waist circumference, median (IQR) cm	**74 (17)**	**71.3 (12.5)**	**0.04**
Hypertension, n (%)	4 (3)	18 (2)	0.29

*All variables have < 1% missing data, except HOMA-IR for which GDM n = 104 (84%) and Non-GDM n= 809 (82%)

†Calculated by Mann Whitney U test for continuous variables, chi squared for categorical variables

Table 2

Year 25 Characteristics of Women with One or More Births and Liver Attenuation Measurement at Year 25 by History of GDM (n= 1,115)*

Characteristic	GDM (n=124)	Non-GDM (n=991)	p†
Age, median (IQR) years	51 (8)	50 (6)	0.48
BMI, median (IQR) kg/m^2	31.1 (12.3)	30.0 (10.7)	0.13
HOMA-IR, median (IQR)	**2.6 (2.9)**	**2.0 (2.2)**	**0.04**
Diabetes mellitus, n (%)	**61 (49)**	**75 (7.6)**	**< 0.01**
Total cholesterol, median (IQR) mg/dL	188 (50.5)	192 (48)	0.13
LDL, median (IQR) mg/dL	107 (45)	109.5 (43)	0.26
HDL, median (IQR) mg/dL	57 (22.5)	60 (22)	0.09
Triglycerides, median (IQR) mg/dL	87 (57.5)	83 (56)	0.12
Waist circumference, median (IQR)	93.5 (26.3)	90 (22.3)	0.11
Hypertension, n (%)	53 (43)	376 (38)	0.30
Total parity > 2, n (%)	**40 (32)**	**238 (24)**	**0.05**
Alcohol use, mean +/−SD units/week	2.4 +/− 3.1	3.0 +/− 3.8	0.14‡
NAFLD§, n (%)	**17 (14)**	**58 (5.8)**	**< 0.01**

*All variables have < 1% missing data

†Calculated by Mann Whitney U test for continuous variables, chi squared for categorical variables unless otherwise specified

‡Calculated by student's t test

§NAFLD defined by liver attenuation ≤ 40 Hounsfield units

Table 3

Association between Characteristics of Women and NAFLD at 25 Years: Unadjusted and Multivariable Adjusted Odds Ratios (95%CI)

	Unadjusted		Multivariable*	
Characteristic	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
Gestational Diabetes	**2.56 (1.44 – 4.55)**	**< 0.01**	**2.29 (1.23 – 4.27)**	**0.01**
Age (per 1 year)	**1.07 (1.01 – 1.15)**	**0.03**		
White race (vs Black)	1.13 (0.71 – 1.81)	0.51		
Total parity > 2 (vs ≤2)	0.62 (0.37 – 1.05)	0.08		
Baseline Risk Factors				
BMI (per 1 kg/m^2 increase)	**1.06 (1.02 – 1.09)**	**< 0.01**		
Waist (per 1 cm increase)	**1.04 (1.02 – 1.05)**	**< 0.01**		
HOMA-IR (per 1 unit increase)	**1.77 (1.38 – 2.27)**	**< 0.01**	**1.56 (1.2 – 2.04)**	**< 0.01**
Total cholesterol (per 10 mg/dL increase)	1.01 (0.94 – 1.08)	0.74		
LDL (per 10 mg/dL increase)	1.01 (0.93 – 1.09)	0.85		
HDL (per 5 mg/dL increase)	**0.89 (0.81 – 0.99)**	**0.03**		
Triglycerides (per 10 mg/dL increase)	**1.09 (1.03 – 1.14)**	**< 0.01**	**1.05 (1.01 – 1.11)**	**0.03**
Hypertension	1.40 (0.32 – 6.09)	0.66		

*Multivariable model included baseline HOMA-IR and Triglycerides and history of GDM (n=911)

Table 4

Multivariable Adjusted Models for NAFLD by GDM History (n= 903)

Model	OR for NAFLD	95% CI	P†
GDM unadjusted	**2.97** *	**(1.64 – 5.37)**	**< 0.01**
Model 1: GDM + Baseline HOMA-IR and Triglycerides	**2.35**	**(1.26 – 4.39)**	**0.01**
Model 2: Model 1 + Change in BMI	**2.89**	**(1.49 – 5.59)**	**<0.01**
Model 3: Model 1 + Incident DM	1.48	(0.73 – 3.02)	0.28
Model 4: Model 1 among those with incident DM	1.18	(0.45 – 3.10)	0.74
Model 5: Model 1 among those without incident DM	1.93	(0.72 – 5.14)	0.19

*Point estimate differs from table 3 as the sample size is limited to participants with complete data for all covariates (n= 903) included in the models

†Calculated by logistic regression

NAFLD: non-alcoholic fatty liver disease; GDM: gestational diabetes mellitus; DM: diabetes mellitus

Interaction p-value = 0.47 (GDM and NAFLD association by incident DM)