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## Low and High Birth Weights are Risk Factors for Nonalcoholic Fatty Liver Disease in Children

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### Abstract

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**Objective**—To examine the distribution of birth weight in children with NAFLD compared with the general U.S. population and the relationship between birth weight and severity of NAFLD.

**Study design**—A multi-center, cross-sectional study of children with biopsy-proven NAFLD enrolled in the Nonalcoholic Steatohepatitis Clinical Research Network Database. Birth weights were categorized as low birth weight (LBW), normal birth weight (NBW), or high birth weight (HBW) and compared with distribution of birth weights in the general US population. The severity of liver histology was assessed by birth weight category.

**Results**—Children with NAFLD (n=538) had overrepresentation of both LBW and HBW compared with the general US population (LBW 9.3%, NBW 75.8%, HBW 14.9% vs. LBW 6.1%, NBW 83.5%, HBW 10.5%;  $p<0.0001$ ). Children with HBW had significantly greater odds of having more severe steatosis (OR 1.82, 95% CI 1.15–2.88) and NASH (OR 2.03, 95% CI 1.21–3.40) than children with NBW. Additionally, children with NAFLD and LBW had significantly greater odds of having advanced fibrosis (OR 2.23; 95% CI 1.08–4.62).

**Conclusion**—Birth weight involves maternal and in utero factors which may have long-lasting consequences. Children with both LBW and HBW may be at increased risk for developing NAFLD. Among children with NAFLD, those with LBW or HBW appear to be at increased risk for more severe disease.

### Keywords

nonalcoholic fatty liver disease; nonalcoholic steatohepatitis; birth weight; obesity; children; epidemiology

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Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in the pediatric population. (1, 2) NAFLD encompasses a broad spectrum of disease severity ranging from isolated steatosis in its mildest form, to nonalcoholic steatohepatitis (NASH) accompanied by inflammation and hepatocellular injury with or without fibrosis in its more severe form. (3) NAFLD is typically discovered in early adolescence with the average age of diagnosis being 12 years of age. (3) Children have varying degrees of disease severity at the time of diagnosis, with 20–30% of those with NAFLD having NASH, and 10–15% of those with NAFLD having advanced fibrosis. (4, 5) However, exposure variables that are meaningfully associated with the onset of the pathologic process or the range of outcome severity in children with NAFLD are underexplored.

The perinatal period is a critical time in development that may have long lasting influences on the development of NAFLD. From animal studies, we have learned that both the state of under-nutrition(6) and over-nutrition *in utero*(7) have the capacity to program the developing fetus in terms of lipid and glucose metabolism, thereby altering risk for development of a range of cardiometabolic diseases in later life. Birth weight is a concrete measure of this fetal adaptation and programming during pregnancy, and has been examined as a risk factor for conditions associated with NAFLD in humans, such as type 2 diabetes mellitus(8) and hypertension. (9) The presence of hepatic steatosis in the neonatal period has been demonstrated via imaging and histopathology in several studies supporting the concept that the potential for NAFLD is influenced by the intrauterine environment. (10–12)

Data in both children and adults suggest that low birth weight is associated with a greater risk for development of NAFLD. (13, 14) There is no data on the relationship between high birth weight and NAFLD. We hypothesized that birth weights outside of the normal range, either low or high, influence the risk for NAFLD. Therefore, the study aims were to evaluate the distribution of birth weight in children with NAFLD compared with the general U.S. population and the association of low birth weight and high birth weight with the severity of NAFLD as determined by liver histology.

## METHODS

Data were obtained from children who were enrolled in the Database of the National Institute of Diabetes and Digestive and Kidney Diseases NASH Clinical Research Network (NASH CRN). Participants in this study were selected from those enrolled in NASH CRN studies at 13 participating clinical centers between 2004 and 2012. (15, 16) Inclusion criteria for this analysis were age less than 21 years at registration, having a parent-reported birth weight, and having NAFLD. The decision for inclusion of subjects was based on the prevailing National Institutes of Health definition of child (under 21 years of age) at the time this study was designed and implemented. A diagnosis of NAFLD was based on liver histology with  $\geq 5\%$  of hepatocytes containing macrovesicular fat and exclusion of other causes of chronic liver disease by clinical history, laboratory studies, and histology. Children were excluded if they had implausible birth weights (i.e. numeric value representing height recorded instead of weight) or if they had very low birth weight ( $< 1,500$  grams; VLBW) because the children with VLBW were excluded from the 1977 National Center for Health Statistics and 2000 Center for Disease Control and Prevention growth charts.

The Institutional Review Board at each participating center approved this study. Written informed consent for all participants was obtained from the participant (if age  $\geq 18$  years of age) or from a parent or guardian, and written informed assent was obtained from all children 8 years or older prior to participation.

### Phenotyping of cohort

Demographic data on study participants were obtained via a structured interview. Weight and height were measured to the nearest 0.1kg and 0.1 cm respectively. Weight, height, and waist measurements were performed in duplicate while wearing light clothing without shoes. BMI was calculated as weight (kg) divided by height (m) squared. BMI percentile was determined according to age and sex based on data from the Centers for Disease Control and Prevention. To compare BMI among different ages and in both boys and girls, the BMI Z-score was calculated.

Participants fasted overnight for 12 hours before phlebotomy via venipuncture. Each clinical center performed reported laboratory assays on site to include the following tests: glucose, insulin, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma glutamyltransferase (GGT).

## Liver Histology

A diagnosis of NAFLD was based on liver histology with  $\geq 5\%$  of hepatocytes containing macrovesicular fat and exclusion of other causes of chronic liver disease by clinical history, laboratory studies, and histology. Liver biopsy specimens were stained with hematoxylin-eosin and Masson's trichrome stain and centrally reviewed by the Pathology Committee of the NASH CRN according to the NASH CRN scoring system. (17) Members of the Pathology Committee were blinded to all demographic and clinical data. Biopsies were scored for the degree of steatosis present in hepatocytes as follows: grade 0,  $< 5\%$  steatosis; grade 1, 5 to 33%; grade 2, 34 to 66%; and grade 3,  $> 66\%$ . Liver biopsies were diagnosed as nonalcoholic steatohepatitis (NASH), borderline NASH, "NAFLD, not NASH," or not NAFLD based on the aggregate presence and degree of the individual features of NAFLD. A typical set of minimum criteria to diagnose NASH would include  $> 5\%$  macrovesicular steatosis, lobular inflammation and hepatocyte injury as manifest by ballooning degeneration. Cases determined to be NAFLD not NASH showed  $> 5\%$  steatosis with no or minimal inflammation. Cases diagnosed as "Borderline NASH" had steatosis and inflammation but equivocal or no ballooning degeneration with or without a fibrosis pattern typical of NASH. Also included in the "Borderline NASH" category (type 2) were cases with portal inflammation and/or fibrosis, with a zone 1 or panacinar distribution of steatosis, that is, the pattern of fatty liver disease common in children. (1, 18) This assignment of NASH, borderline NASH, or NAFLD was made as a consensus agreement of the NASH CRN pathology group at the time of central review of cases as per protocol.

## Exposure Variable: Birth Weight Category

Parents were asked for the participating child's birth weight. Birth weights were categorized as low birth weight (1,500 to 2,499 grams; LBW), normal birth weight (2,500 to 3,999 grams; NBW), or high birth weight ( $\geq 4,000$  grams; HBW).

## Data Analysis Plan

Descriptive statistics used to compare characteristics in children with LBW, NBW, or HBW included means, standard deviations, medians, ranges, frequencies, and percentages. Analysis of variance and Tukey's test for pairwise comparisons were used to obtain p-values for continuous variables. Chi-square and Fisher exact tests were used to obtain p-values for categorical variables. Severity of NAFLD was determined using three different histologic measures: grade of steatosis, the presence of NASH, and the presence of advanced fibrosis. For the ordinal outcome of steatosis grade, ordinal logistic regression was used. For the dichotomous outcomes of NASH diagnosis and advanced fibrosis, logistic regression models were constructed. Covariates were assessed as confounders by determining if they resulted in a greater than a ten percent change in the main exposure of interest. Age, sex, race/ethnicity, and BMI were found to be confounders in at least one of the outcome models and were included in all final multivariate models.

The distribution of the birth weight categories of this study cohort was compared with the distribution of the birth weight categories in the general US population for 1995 (median year of birth for study sample). (19) A one-sample Chi-square test was used to determine the

p-value. SAS version 9.3 (SAS Institute) was used to perform all analyses. Statistical significance was defined as  $p < 0.05$ .

## RESULTS

There were 605 children enrolled in the NASH CRN for initial consideration for study participation, and of these, 34 subjects were excluded for missing birth weight data, 17 subjects were excluded because they did not have biopsy-confirmed NAFLD, 12 subjects were excluded because reported birth weight was implausible, and four subjects were excluded because they were VLBW. The remaining 538 children were included in this analysis. The demographic and clinical measures are shown in Table I. The mean age of the participants was  $13 \pm 3$  years. The median BMI of participants was  $32.0 \text{ Kg/m}^2$ , with a median BMI z-score of 2.33. The majority of participants (71%) were boys. Among children with NAFLD, 9.3% (50 of 538) had LBW, 75.8% (408 of 538) had NBW, and 14.9% (80 of 538) had HBW. Definite NASH was present in 26.6%.

### Distribution of Birth Weight in Children with NAFLD Compared with the General U.S. Population

The distribution of birth weight categories was significantly different for children with NAFLD compared with the general US population, such that both low and high birth weights were overrepresented, (LBW 9.3% vs. 6.1%, NBW 75.8% vs. 83.5%, HBW 14.9% vs. 10.5%;  $p < 0.0001$ ).

### Relationship Between Birth Weight and Clinical Characteristics of Children with NAFLD

Among children with NAFLD, there was no significant difference by age, sex, or ethnicity between children with LBW, NBW, or HBW. (Table I.) However, at the time of diagnosis of NAFLD, there was a significant ( $p < 0.001$ ) difference in height and weight by birth weight category. At the time of enrollment in the NASH CRN, at a mean age of 13 years, children in the HBW group were significantly heavier (90 kg vs. 83 kg) and taller (166 cm vs. 159 cm) than children in the NBW group, and children in the LBW group were significantly shorter (157 cm vs. 166 cm) and lighter (71 kg vs. 90 kg) than children in the HBW group. Similarly, median BMI (HBW  $33.3 \text{ Kg/m}^2$ , NBW  $32.0 \text{ Kg/m}^2$ , LBW  $30.4 \text{ Kg/m}^2$ ,  $p = 0.02$ ) and BMI z-scores (HBW 2.37, NBW 2.33, LBW 2.31,  $p = 0.05$ ) were significantly higher in HBW compared with NBW and LBW groups. There was no significant difference in ALT, AST, GGT, total cholesterol or triglycerides by birth weight group.

### The Relationship Between Birth Weight and Severity of NAFLD

**Steatosis Grade**—The distribution of steatosis grade by birth weight category is shown in Table II. Notably, 51.3% (41 of 80) of children with HBW had severe steatosis. After controlling for age, sex, height, weight, race and ethnicity, children with HBW had 1.82 times the odds of having more severe steatosis than children with NBW (OR 1.82, 95% CI 1.15–2.88,  $p = 0.01$ ). The distribution of steatosis did not differ between children with LBW compared with children with NBW. (Table III)

**NASH**—As shown in Table II, the presence of steatohepatitis varied significantly by birth weight category. NASH was present in 30.0% (15 of 50) of those with LBW, 23.5% (96 of 408) of those with NBW, and 40.0% (32 of 80) of those with HBW, ( $p < 0.01$ ). After controlling for age, sex, height, weight, race and ethnicity, among children with NAFLD, the odds of having NASH was 2.03 times higher in those with HBW compared with children with NBW (OR 2.03, 95% CI 1.21–3.40,  $p < 0.01$ ). The diagnosis of NASH did not differ between children with LBW compared with children with NBW. (Table III)

**Advanced Fibrosis**—Advanced fibrosis was present in 24.0% (12 of 50) of those with LBW, 12.8% (52 of 406) of those with NBW, and 16.3% (13 of 80) of those with HBW, ( $p = 0.09$ ). After controlling for age, sex, height, weight, race and ethnicity, children with LBW had 2.23 times greater odds of having advanced fibrosis than children with NBW (OR 2.23; 95% CI 1.08–4.62,  $p = 0.03$ ). Advanced fibrosis did not differ between children with HBW compared with children with NBW. (Table III)

## DISCUSSION

We studied birth weight in a large multi-center cohort of children with NAFLD from pediatric centers across the United States. Children with NAFLD had a significantly different distribution of birth weights compared with the general US population, with overrepresentation of both low and high birth weight. Children with HBW had significantly greater odds of having more severe steatosis and NASH than children with NBW. In contrast, children with LBW had twice the odds of having advanced fibrosis than children with NBW.

There has been an increasing awareness of the potential for perinatal factors to have lifelong ramifications for future morbidity and mortality. (20), (21) Studies primarily focused on the relationship between LBW with cardiovascular disease(22) and type 2 diabetes (23) have found an inverse relationship between birth weight and future disease risk. A study investigating the relationship between birth weight and NAFLD in the pediatric population previously, showed a fourfold increased prevalence of children born small for gestational age in those with NAFLD compared with a control population.(13) Overall, fewer studies have focused on HBW and long-term health, and results have been less consistent. (24) However, the frequency of children born with HBW has greatly increased recently (25) in parallel with the epidemic of obesity, and thus implications of HBW for future health have not been fully characterized. This study demonstrated a bimodal distribution of risk for NAFLD related to birth weight. Although both low and high birth weight were associated with increased risk for NAFLD, distinctive pathophysiologic mechanisms are likely involved, supported by our finding of disparate hepatic phenotypic tendencies observed between birth weight categories.

In children with NAFLD, LBW was associated with a higher risk of advanced fibrosis. This finding is consistent with data from a study by Andersen and Osler that demonstrated a strong and graded inverse relationship between small birth size and death from cirrhosis in young adult men. (26) A potential explanation was provided in a guinea pig model that showed that LBW was associated with changes in hepatic pro-fibrotic genes and liver fibrosis independent of obesity. (27) As fibrosis is the most important measure with respect

to liver-related morbidity and mortality, a better understanding of these early life events that influence fibrosis potential is essential to reduce negative hepatic outcomes.

Unexpectedly, children with NAFLD who were born with HBW remained larger by all measures at a mean age of 13 years than children with NAFLD who were born with NBW or LBW, thus reinforcing that the risk for more severe obesity is associated with HBW. (28–30) In keeping with more severe obesity, children with HBW had greater severity of steatosis. One possible explanation for this finding is that children with HBW develop steatosis earlier than other children. Although obtaining maternal health information was beyond the scope of this investigation, prior studies have shown that mothers with elevated BMI and diabetes are prone to have children born large for gestational age, and that hepatic steatosis is more likely to be present at birth in these infants. (10, 11) Data from animal studies have shown that a maternal high fat diet can produce offspring with HBW and neonatal hepatic steatosis that persists with maturation. (31, 32) Importantly, in our study, children with HBW not only had more severe steatosis, but also had greater odds of having NASH. Studies in animal models have also shown that a maternal high fat diet can cause life long impairment of hepatic mitochondrial metabolism in the offspring that is associated with steatohepatitis. (33) Thus, HBW may be an early marker for imprinting that predisposes a child to both NAFLD itself as well as for more severe disease in the form of steatohepatitis.

This study was performed by the NASH CRN, which has diverse geographic representation of children with accurate and rigorously characterized NAFLD. A limitation was that some factors with the potential to influence the relationship between birth weight and NAFLD were not fully captured. Examples of such factors include gestational age at birth, maternal weight and health status during pregnancy, and post-natal factors such as breastfeeding, antibiotic administration, and post-natal growth trajectories. Although we did exclude children with VLBW, we did not have the gestational age at birth, and thus may have included children born preterm. Moreover, we could not distinguish LBW from small for gestational age. Additionally, original birth records of weight were not available and thus, the potential for error exists, however, prior studies have shown that a majority of mothers can correctly recall a child's birth weight within 100 grams. (34) Prospective studies are needed to include this information in risk assessment related to birth weight.

From the beginning of a child's life, HBW and LBW identify children who have increased risk for health-related issues, one being NAFLD. Although abnormal birth weight accounted for a minority of children with NAFLD in our study, it was associated with increased risk of disease severity. LBW and HBW were associated with the severity of different histologic features of NAFLD, thus the underlying mechanism linking LBW or HBW with NAFLD may also be different. In conclusion, birth weight involves both maternal and in utero factors, which may have long-lasting hepatic consequences.

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## Appendix

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## Abbreviations

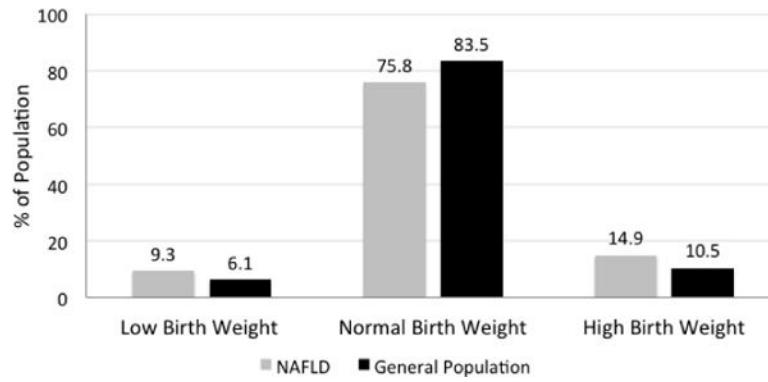
<b>ALT</b>	alanine aminotransferase
<b>AST</b>	aspartate aminotransferase
<b>BMI</b>	body mass index
<b>CI</b>	confidence interval
<b>GGT</b>	gamma glutamyltransferase
<b>HDL</b>	high-density lipoprotein cholesterol
<b>LDL</b>	low-density lipoprotein cholesterol
<b>NAFLD</b>	nonalcoholic fatty liver disease
<b>NASH</b>	nonalcoholic steatohepatitis
<b>NASH CRN</b>	Nonalcoholic Steatohepatitis Clinical Research Network
<b>OR</b>	odds ratio

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**Figure 1.** The distribution of birth weight in children with NAFLD compared to the general population. NAFLD is shown in light grey, and the US population is shown in black. Both LBW and HBW are significantly over-represented in children with NAFLD compared the general US population, (p value <0.0001).

Table 1

Descriptive Characteristic by Birth Weight Categories

Characteristics	Birth Weight Category n (% column)			p-value*
	Low Birth Weight n=50	Normal Birth Weight n=408	High Birth Weight n=80	
Age (years) mean (±SD)	13.1 (±3.4)	13.1 (±2.9)	13.8 (±2.5)	0.11
Sex				0.23
Male	32 (64.0)	287 (70.3)	62 (77.5)	
Female	18 (36.0)	121 (29.7)	18 (22.5)	
Race/Ethnicity				0.90
Non-Hispanic White	19 (38.0)	132 (32.4)	25 (31.3)	
Hispanic	28 (56.0)	255 (62.5)	51 (63.8)	
Other	3 (6.0)	21 (5.2)	4 (5.0)	
Weight (kilograms at baseline physical exam) median (range: 25 <sup>th</sup> , 75 <sup>th</sup> ) <sup>a</sup>	71 (59, 97) <sup>a</sup>	83 (66, 99) <sup>a</sup>	90 (75, 117) <sup>b,c</sup>	<0.001
Height (centimeters at baseline physical exam) median (range: 25 <sup>th</sup> , 75 <sup>th</sup> ) <sup>a</sup>	157 (145, 173) <sup>a</sup>	159 (151, 169) <sup>a</sup>	166 (156, 173) <sup>b,c</sup>	<0.001
BMI median (range: 25 <sup>th</sup> , 75 <sup>th</sup> ) <sup>a</sup>	30.4 (27.2, 34.5) <sup>a</sup>	32.0 (28.3, 35.9)	33.3 (29.8, 38.6) <sup>c</sup>	0.02
BMI Z Score median (range: 25 <sup>th</sup> , 75 <sup>th</sup> ) <sup>a</sup>	2.31 (2.05, 2.46) <sup>a</sup>	2.33 (2.00, 2.54)	2.37 (2.15, 2.62) <sup>c</sup>	0.05
ALT (U/L) median (range: 25 <sup>th</sup> , 75 <sup>th</sup> ) <sup>a</sup>	77 (55, 119)	78 (55, 123)	91 (62, 140)	0.42
AST (U/L) median (range: 25 <sup>th</sup> , 75 <sup>th</sup> ) <sup>a</sup>	50 (32, 77)	49 (36, 69)	54 (41, 79)	0.39
GGT (U/L) median (range: 25 <sup>th</sup> , 75 <sup>th</sup> ) <sup>a</sup>	38 (28, 53)	36 (24, 54)	40 (27, 57)	0.64
Serum glucose (mg/dL) median (range: 25 <sup>th</sup> , 75 <sup>th</sup> ) <sup>a</sup>	86 (79, 94)	86 (80, 94) <sup>a</sup>	88 (82, 99) <sup>b</sup>	<0.01
Serum insulin (microU/mL) median (range: 25 <sup>th</sup> , 75 <sup>th</sup> ) <sup>a</sup>	25.5 (13.3, 44.5)	25.0 (15.1, 38.0) <sup>a</sup>	33.0 (17.0, 49.1) <sup>b</sup>	<0.01
Total cholesterol (mg/dL) median (range: 25 <sup>th</sup> , 75 <sup>th</sup> ) <sup>a</sup>	168 (145, 193)	167 (143, 189)	171 (152, 187)	0.94
Triglycerides (mg/dL) median (range: 25 <sup>th</sup> , 75 <sup>th</sup> ) <sup>a</sup>	136 (91, 204)	122 (86, 181)	140 (90, 177)	0.36

Characteristics	Birth Weight Category n (% column)			Total n=538	p-value*
	Low Birth Weight n=50	Normal Birth Weight n=408	High Birth Weight n=80		
HDL (mg/dL) median (range: 25 <sup>th</sup> , 75 <sup>th</sup> )	35 (31, 39) <sup>b</sup>	38 (32, 44) <sup>c</sup>	38 (30, 44)	38 (32, 43)	0.05

Abbreviations: ANOVA = Analysis of Variance; BMI = Body Mass Index; SD=Standard Deviation; NASH=Nonalcoholic Steatohepatitis

\* p-value is from comparison of low, normal, and high birth weight groups from ANOVA (continuous data; pairwise comparisons were conducted using Tukey test) or Chi-square test or Fisher exact depending on cell size (categorical tables)

<sup>a</sup>Significantly different from the high birth weight group

<sup>b</sup>Significantly different from the normal birth weight group

<sup>c</sup>Significantly different from the low birth weight group

**Table 2**

Liver Histology by Birth Weight Categories

Liver Histology	Birth Weight Category n (% column)			Total n=538	p-value*
	Low Birth Weight n=50	Normal Birth Weight n=408	High Birth Weight n=80		
Steatosis Grade					
<34%	17 (34.0)	120 (29.4)	16 (20.0)	153 (28.4)	0.17
34–66%	14 (28.0)	134 (32.8)	23 (28.8)	171 (31.8)	
>66%	19 (38.0)	154 (37.8)	41 (51.3)	214 (39.8)	
NASH diagnosis					
NASH	15 (30.0)	96 (23.5)	32 (40.0)	143 (26.6)	<0.01
Not NASH	35 (70.0)	312 (76.5)	48 (60.0)	395 (73.4)	
Fibrosis					
Advanced Fibrosis	12 (24.0)	52 (12.8)	13 (16.3)	77 (14.4)	0.09
Not Advanced Fibrosis	38 (76.0)	354 (87.2)	67 (83.8)	459 (85.6)	

\* p-value is from comparison of low, normal, and high birth weight groups from Chi-square test



**Table 3**

## Adjusted Odds Ratios

Liver Histology	Birth Weight Category		
	Low	Normal	High
Steatosis Grade	0.93 (0.54, 1.61)	1.00 (ref)	<b>1.82 (1.15, 2.88)</b>
NASH Diagnosis	1.39 (0.71, 2.70)	1.00 (ref)	<b>2.03 (1.21, 3.40)</b>
Advanced Fibrosis	<b>2.23 (1.08, 4.62)</b>	1.00 (ref)	1.43 (0.73, 2.81)

Values shown are adjusted odds ratios and 95% confidence interval. Adjustments were made for age, sex, race/ethnicity, and body mass index.

Bolded OR are significant.