Non-Hispanic Black Persons With Nonalcoholic Fatty Liver Disease Have Lower Rates of Advanced Fibrosis, Cirrhosis, and Liver-Related Events Even After Controlling for Clinical Risk Factors and *PNPLA3* Genotype

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INTRODUCTION: **Nonalcoholic fatty liver disease (NAFLD) is less frequent in non-Hispanic persons (NHB), but there are knowledge gaps in our understanding of disease severity and outcomes of NAFLD in NHB. We compared liver histology and clinical outcomes of NAFLD in non-Hispanic Black persons (NHB) and non-Hispanic White persons (NHW).**

METHODS: **We compared liver histology and outcomes of 109 NHB and 1,910 NHW adults with biopsy-proven NAFLD participating in the Nonalcoholic Steatohepatitis Clinical Research Network observational studies. The relationship between self-reported NHB race/ethnicity and advanced fibrosis was assessed through multivariable logistic regression after controlling for clinical covariates and *PNPLA3* genotype.**

RESULTS: **NHB and NHW with NAFLD had similar NAFLD activity scores (NAS, 4.4 vs 4.3, $P = 0.87$) and proportions with definite metabolic dysfunction-associated steatohepatitis (59% vs 58%, $P = 1.0$), but NHB had significantly lower rates of advanced fibrosis (22% vs 34%, $P = 0.01$) or cirrhosis (4.6% vs 12.1%, $P = 0.010$). Compared with NHW, NHB had significantly lower frequency of advanced fibrosis (Odds Ratio: 0.48, 95% Confidence Interval: 27–0.86, $P = 0.01$). In a comparison between 24 NHB and 655 NHW with advanced fibrosis, the NAS (5.6 vs 4.9, $P = 0.01$) and lobular inflammation grade (2.2 vs 1.7, $P < 0.002$) were significantly higher among NHB with advanced fibrosis. One NHB and 23 NHW died during follow-up (0.30 vs 0.28 per 100 person-year follow-up). Seven and zero liver-related deaths occurred in NHW and NHB with NAFLD, respectively.**

DISCUSSION: **The risk of advanced fibrosis in NHB with NAFLD is significantly lower, after controlling for clinical risk factors and *PNPLA3* genotype. Although their risk of advanced fibrosis was low, NHB with NAFLD and advanced fibrosis had higher NAS and lobular inflammation, indicating a difference in their relationship between necroinflammation and fibrosis.**

KEYWORDS: MASLD; NAFLD; advanced fibrosis; Non-Hispanic Black persons; *PNPLA3*

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/D218.

Am J Gastroenterol 2024;119:1857–1865. https://doi.org/10.14309/ajg.0000000000002756

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a common chronic liver disease in the United States and is a leading cause for cirrhosis, liver transplantation, and liver cancer (1–3). Racial and ethnic differences in its prevalence have been reported, but many knowledge gaps remain particularly in our understanding of the differences in the prevalence of NAFLD, nonalcoholic steatohepatitis (NASH), and advanced fibrosis among non-Hispanic

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Received November 16, 2023; accepted March 1, 2024; published online May 14, 2024

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Black persons (NHB) and non-Hispanic White persons (NHW) (4,5).

In aggregate, compared with NHW, Hispanic individuals seem to have higher and NHB to have lower prevalence of hepatic steatosis and NAFLD (6,7). However, studies investigating the prevalence of NASH and advanced fibrosis have yielded mixed results. In a prospective study published in 2011 from Brooke Army Medical Center in San Antonio, Texas, of 328 individuals screened with an ultrasound and clinically for NAFLD, there were 37 Black persons, and their prevalence of NAFLD was 35.1% and was lower than 56.3% prevalence in Hispanic and 44.6% in White persons. Interestingly, the prevalence of NASH in Black persons was 13.5%, and it was higher than in White persons (9.8%) and lower than in Hispanic individuals (19.4%) (8). More recently, Brill et al conducted a study consisting of 77 Black and 134 White persons who were matched for age, sex, body mass index (BMI), hemoglobin A1C, and type 2 diabetes mellitus (T2DM) (9). The participants were assessed for intrahepatic triglyceride content using proton magnetic resonance spectroscopy and participants with hepatic steatosis underwent liver biopsy. The prevalence of NAFLD was significantly lower in Black persons than in White persons (25.1% vs 51.9%, $P = 0.003$), but the frequency of NASH (57.1% Black persons vs 73.3% White persons, $P = 0.12$) and mean fibrosis stage ($P = 0.87$) were not different between the 2 groups (9). However, only 19 Black persons with NAFLD presumably underwent a liver biopsy in this study. In contrast to these reports, Satapathy et al reported a significantly lower prevalence of NASH and advanced fibrosis in Black persons in a retrospective study consisting of 677 White and 230 Black persons with NAFLD and a liver biopsy (10). The proportion of patients with NAFLD activity score ≥5 (a proxy for NASH) was 3% in Black persons with NAFLD vs 9.8% in White persons with NAFLD ($P < 0.001$), and similarly, the prevalence of advanced fibrosis was significantly lower in Black persons (2.6% vs 16.2% in White persons, $P < 0.001$) (10).

In this study, we compared the liver histology of self-reported NHB and NHW with NAFLD who were enrolled in the prospective studies of the NASH Clinical Research Network (NASH CRN). The NASH CRN systematically characterizes the disease phenotype including liver histology, and participants are followed annually for defining the natural histology of NAFLD. Our primary aim was to compare the NAFLD activity score and presence of NASH and advanced fibrosis between NHB and NHW with biopsy-proven NAFLD controlling for clinical risk factors and patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) genotype. We also examined the incidence of all-cause mortality and liver-related events during the longitudinal follow-up.

METHODS

This study was conducted on adult participants enrolled in 3 observational studies and the placebo arm of 2 clinical trials conducted by the NASH CRN. All participants had biopsy-proven NAFLD within 6 months of enrollment and were enrolled and followed at multiple clinical centers across the United States. These protocols were approved by the Institutional Review Board at the participating clinical centers and the Data Coordinating Center or by the single Institutional Review Board at Johns Hopkins School of Medicine. All participants signed informed consent before their enrollment. At the time of enrollment, participants were asked to provide self-reported race and ethnicity, and this study was limited to self-reported NHB and NHW. Detailed medical and medicinal history, laboratory values, and liver histology features were collected on all participants in a systematic fashion. Participants with self-reported significant alcohol consumption (≥2 drinks per day on average in women and ≥ 3 drinks per day on average in men) were ineligible. Alcohol Use Disorders Identification Test and Timeline Follow Back instruments were administered for obtaining alcohol consumption history. Participants were followed every 48 weeks, and clinical outcomes were captured during these visits or when reported by the participants or their family members. Liver histology was reviewed centrally in a blinded fashion by the pathology subcommittee, and the outcomes were adjudicated centrally in a structured fashion as described previously (11). *PNPLA3* rs738409 genotyping was performed by a TaqMan genotyping assay (12). The rs738409 is a missense coding variant (NM_025225.3: c.444C>G) and results in an Ile [ATC] to Met [ATG] substitution in codon 148. A TaqMan probe was used for allelic discrimination (ThermoFisher, Waltham, MA). The main clinical outcomes were all-cause and liver-related mortality, hepatic decompensation events (overt encephalopathy, ascites, or variceal hemorrhage), an increase in the model for end-stage liver disease score to ≥ 15, hepatic cancer, and liver transplant. Study flow diagram is shown as Figure 1, and it describes eligibility criteria for this analysis.

Statistical analysis

Descriptive statistics of participant demographics, comorbidities, *PNPLA3* genotype, and laboratory, anthropometric, and histological characteristics at baseline were presented by the self-reported racial categories of NHB and NHW. *P* values were derived from 2-sample *t*-tests for continuous measures and the Fisher exact test for categorical measures. Multivariable logistic regression analysis determined the independent association of advanced fibrosis (F3/F4) with NHB race/ethnicity, adjusting for age, sex, BMI, T2DM, hypertension, and triglycerides. A second multivariable logistic regression model adjusted for *PNPLA3* genotype, in addition to those factors in the first model. The analysis of liver-related outcomes and mortality excluded events that occurred at or before enrollment, and person-years of follow-up were calculated for each outcome. Rates of events were calculated as the number of new-onset events (only the first occurrence of an event was counted for an individual participant) divided by the number of person-years. Results are presented as events per 100 person-years and counts of events/number at risk by race category. Data analyses were performed using R version 4.3.0. *P* values <0.05 were considered statistically significant.

RESULTS

Study flow diagram is shown as Figure 1. Five NASH CRN studies enrolled 3,612 unique adult participants with biopsy-proven NAFLD between October 2004 and May 2023. After excluding 305 individuals who received active therapies in Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis (PIVENS) and Farnesoid X nuclear receptor ligand obeticholic acid for noncirrhotic, non-alcoholic steatohepatitis (FLINT) trials, 455 Hispanic individuals, 372 non-Hispanic individuals with race unknown or other than self-reported Black or White race, 393 without a liver biopsy within 6 months before screening, and 68 without a diagnosis of NAFLD or NASH by central pathology

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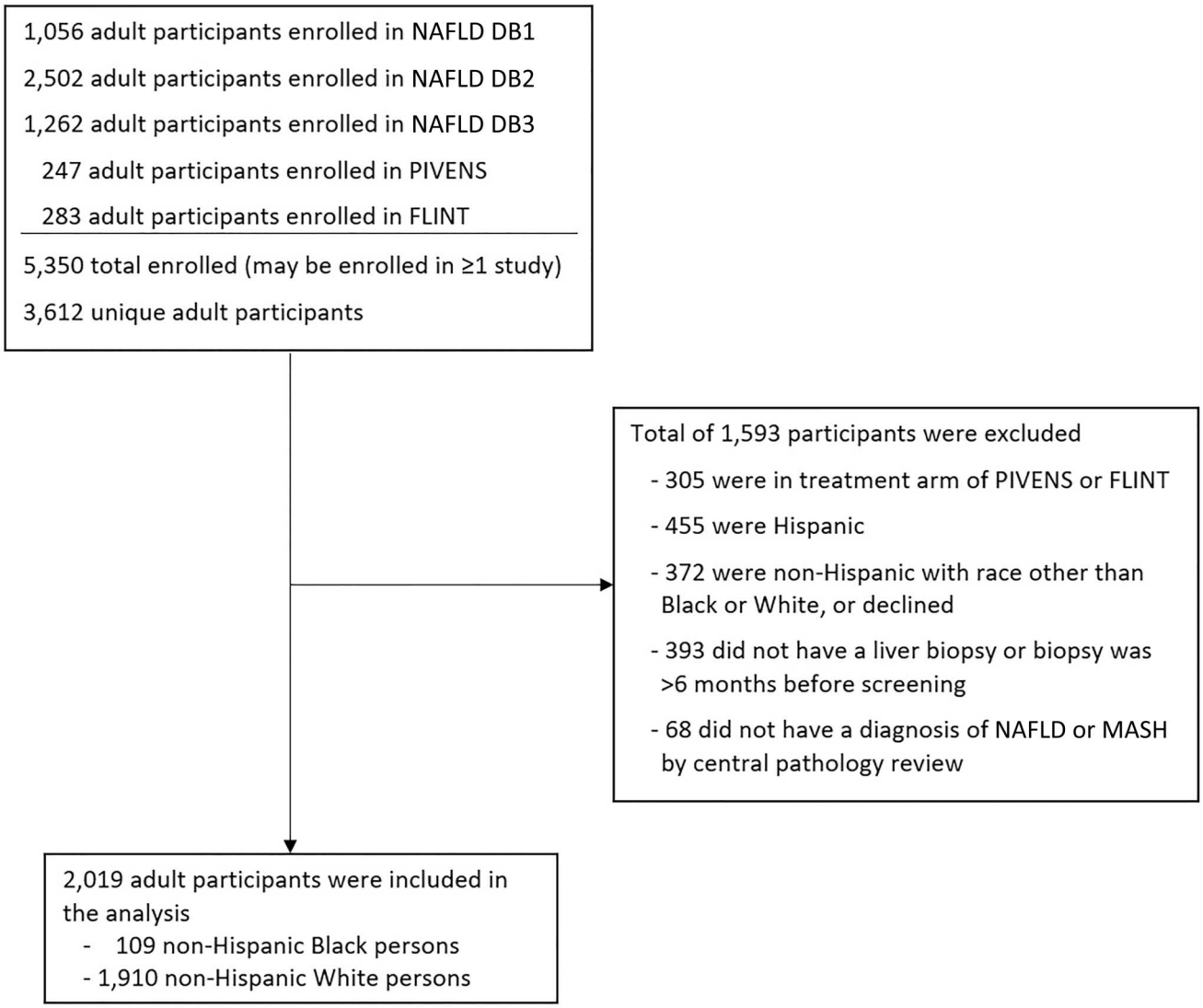

Figure 1. Flow diagram of participants included in this study.

review, 2,019 individuals were eligible for inclusion in this analysis. There were 109 NHB and 1,910 NHW. The *PNPLA3* genotyping data were available in 1,488 participants. The Median (Inter Quartile Range (IQR)) follow-up of the cohort combining NHB and NHW was 2.9 years (0.6–6.7 years) and was 3.0 (0.7–6.9) years for NHW and 2.0 (0–4.8) years for NHB.

Table 1 shows the selected clinical and laboratory characteristics of NHB and NHW included in this analysis. Age was similar between the 2 groups, but NHB with NAFLD were more likely to be women (75% vs 61% in NHW, $P = 0.003$), had higher BMI (36.9 vs 35.1 kg/m^2, $P = 0.006$), and higher prevalence of diabetes (57% vs 41%, $P = 0.001$) and hypertension (75% vs 57%, $P = 0.001$). The distribution of various BMI categories shows higher proportion of individuals with BMI $\geq$ 35 kg/m^2 among NHB, compared with NHW (Figure 2a). Interestingly, the prevalence of metabolic syndrome was lower in NHB as compared to NHW (55% vs 65%, $P = 0.05$), presumably because of their lower frequency of hypertriglyceridemia (23% in NHB vs 49% in NHW). There were no significant differences in liver biochemistries or fasting levels of glucose and insulin between 2 groups except for slightly lower serum albumin in NHB (4.2 vs 4.3 g/dL, $P = 0.01$). Although serum total cholesterol and low-density lipoprotein—cholesterol were similar between the groups, serum triglycerides were significantly lower (125 vs 178 mg/dL, $P < 0.001$) and high-density lipoprotein (HDL)-cholesterol was significantly higher (46 vs 44 mg/dL, $P = 0.04$) in NHB. Interestingly, the *PNPLA3* G-allele carriage rate among NHB was 57% and not significantly different from NHW (65%, $P = 0.14$). The comparison of liver histology between 2 groups showed similar NAFLD activity score (4.4 vs 4.3, $P = 0.9$), grades of steatosis (1.7 vs 1.8, $P = 0.2$), ballooning (1.0 vs 1.0, $P = 1.0$), and portal inflammation (1.1 vs 1.1, $P = 0.7$) but higher lobular inflammation grade among NHB (1.7 vs 1.5, $P = 0.04$). The frequency of definite NASH was similar between 2 groups (59% in NHB vs 58%) in NHW, and yet among NHB, there was significantly lower prevalence of advanced fibrosis (22% vs 34%, $P = 0.01$) and cirrhosis (4.6% vs 12.1%, $P = 0.01$) (Figure 2b).

Table 2 shows the results of multivariable logistic regression analysis, which demonstrates an independent association between NHB and a lower rate of advanced fibrosis. In a model that

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Table 1. Baseline characteristics of Non-Hispanic Black and White participants with NAFLD

Characteristic	Non-Hispanic Black persons (N = 109)	Non-Hispanic White persons (N = 1910)	*P*
Demographics			
Age at enrollment (yr)	51.6 ± 11.3	51.4 ± 11.9	0.87
Sex			0.003
Males	27 (25%)	745 (39%)	
Females	82 (75%)	1,165 (61%)	
Education level: Bachelor's degree or higher	32 (29%)	769 (40%)	0.03
Medical history			
Diabetes	62 (57%)	780 (41%)	0.001
Hypertension	82 (75%)	1,098 (57%)	<0.001
Coronary artery disease	7 (6%)	102 (5%)	0.66
Metabolic syndrome	59 (55%)	1,224 (65%)	0.05
Alcohol use			
Non-drinker (absence of any alcohol ≥2 yr before enrollment)	55 (51%)	820 (43%)	0.12
Harmful drinking (AUDIT score ≥7 in females or ≥8 in males)	0 (0%)	4 (0.2%)	1.00
BMI (kg/m^2)	36.9 ± 6.6	35.1 ± 6.7	0.006
Normal (<25 kg/m^2)	0 (0%)	55 (2.9%)	0.02
Overweight (25 to <30 kg/m^2)	16 (14.8%)	378 (19.8%)	
Obese (30 to <35 kg/m^2)	29 (26.9%)	629 (32.9%)	
Severely obese (≥35 kg/m^2)	63 (58.3%)	847 (44.4%)	
Waist (cm)	112.3 ± 16.2	111.9 ± 14.8	0.79
Hip (cm)	118.7 ± 16.4	117.8 ± 14.6	0.55
Waist/hip ratio	0.9 ± 0.1	1.0 ± 0.1	0.75
Systolic blood pressure (mm Hg)	130.4 ± 14	132.0 ± 15.1	0.29
Diastolic blood pressure (mm Hg)	77.3 ± 10.7	77.3 ± 10.6	0.95
Laboratory measures			
ALT (U/L)	62 ± 44	67 ± 50	0.25
AST (U/L)	49 ± 30	50 ± 36	0.69
Alkaline phosphatase (U/L)	91 ± 41	85 ± 33	0.14
GGT (U/L)	72 ± 68	73 ± 91	0.92
Bilirubin, total (mg/dL)	0.6 ± 0.4	0.7 ± 0.4	0.17
Albumin (g/dL)	4.2 ± 0.3	4.3 ± 0.4	0.01
INR	1.0 ± 0.1	1.0 ± 0.1	0.80
Fasting glucose (mg/dL)	114 ± 43	112 ± 40	0.62
Fasting insulin (uU/mL)	29 ± 25	26 ± 25	0.21
HOMA-IR	8.2 ± 8	7.6 ± 10.2	0.43
Total cholesterol (mg/dL)	181 ± 46	187 ± 44	0.13
HDL-cholesterol (mg/dL)	46 ± 13	44 ± 12	0.04
LDL-cholesterol (mg/dL)	113 ± 41	111 ± 38	0.74
Triglycerides (mg/dL)	125 ± 74	178 ± 137	<0.001
PNPLA3 Rs738409			0.31
CC	33 (43.4%)	490 (34.7%)	

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Table 1. (*continued*)

Characteristic	Non-Hispanic Black persons (N = 109)	Non-Hispanic White persons (N = 1910)	*P*
CG	31 (40.8%)	650 (46.0%)	
GG	12 (15.8%)	272 (19.3%)	
CG or GG	43 (56.6%)	922 (65.3%)	0.14
CC	33 (43.4%)	490 (34.7%)	
Liver histology			
Total NAS	4.4 ± 1.6	4.3 ± 1.6	0.87
Steatosis	1.7 ± 0.8	1.8 ± 0.8	0.19
Lobular inflammation	1.7 ± 0.8	1.5 ± 0.7	0.04
Ballooning	1.0 ± 0.8	1.0 ± 0.8	0.96
Portal inflammation	1.1 ± 0.5	1.1 ± 0.6	0.68
Fibrosis			0.01
0–2	85 (78.0%)	1,250 (65.6%)	
3–4	24 (22.0%)	655 (34.4%)	
Definite NASH	64 (58.7%)	1,115 (58.4%)	1.00
Cirrhosis	5 (4.6%)	231 (12.1%)	0.01

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUDIT, Alcohol Use Disorders Identification Test; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; INR, international normalized ratio; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD Activity Score; NASH, nonalcoholic steatohepatitis; *PNPLA3*, patatin-like phospholipase domain-containing protein 3.

adjusted for age, sex, BMI, T2DM, hypertension, and triglycerides, the risk of advanced fibrosis was significantly lower among NHB than in NHW (Odds Ratio (OR) 0.38, 95% 0.24–0.38, $P < 0.001$). In another model that adjusted for age, sex, BMI, T2DM, hypertension, triglycerides, and *PNPLA3* genotype, the risk of advanced fibrosis remained significantly lower in NHB than in NHW (OR: 0.48, 95% Confidence Interval (CI): 0.27–0.86, $P = 0.01$).

One NHB participant and 23 NHW died during follow-up, with a rate of 0.30 per 100 person-year follow-up among NHB and 0.28 per 100 person-year follow-up among NHW (Table 3). There were no liver-related deaths among NHB, whereas there were 7 liver-related deaths among NHW. There were no liver-related events among NHB except for 3 individuals who developed model for end-stage liver disease >15 during follow-up (Table 3).

In a comparison between 24 NHB and 655 NHW with advanced fibrosis (see Supplementary Table 1, http://links.lww.com/AJG/D218), we did not find significant differences in demographics, anthropometry, comorbidities, liver and glycemic biochemistries, and lipid parameters except for significantly lower serum triglycerides among NHB vs NHW with advanced fibrosis (141 vs 171 mg/dL, $P = 0.01$). The *PNPLA3* G-allele carriage rate was similar between the 2 groups (71% vs 68%, $P = 0.4$). Interestingly, the NAFLD activity score (5.6 vs 4.9, $P = 0.01$) and lobular inflammation grade (2.2 vs 1.7, $P < 0.002$) were higher, whereas portal inflammation grade was lower among NHB vs NHW with advanced fibrosis (1.2 vs 1.5, $P = 0.04$). The frequency of definite NASH was similarly high among NHB vs NHW with advanced fibrosis, but this difference did not reach statistical significance (96% vs 84%, $P = 0.15$).

Finally, when we compared 24 NHB with and 85 without advanced fibrosis (see Supplementary Table 2, http://links.lww.com/AJG/D218), we found those with advanced fibrosis more likely to have metabolic syndrome (71% vs 51%, $P = 0.10$) and trend toward older age (55 vs 51 years, $P = 0.09$) and higher prevalence of diabetes (71% vs 53%, $P = 0.16$), but these results were not statistically significant. NHB with advanced fibrosis had statistically significant higher levels of aspartate aminotransferase and gamma-glutamyl transferase than those with no or mild to moderate fibrosis; changes in alanine aminotransferase were not significant. Glycemic and lipid (including triglyceride levels) profiles were similar between the 2 groups. The *PNPLA3* G-allele carriage was higher among NHB with advanced vs lesser degrees of fibrosis, but this difference was not statistically significant (71% vs 53%, $P = 0.27$). Not unexpectedly, the presence of advanced fibrosis among NHB was associated with significantly higher NAFLD activity scores (5.6 vs 4.0, $P < 0.001$), grades of lobular inflammation (2.2 vs 1.5, $P < 0.001$) and ballooning (1.7 vs 0.8, $P < 0.001$), and the prevalence of definite NASH (96% vs 48%, <0.001).

DISCUSSION

The main findings of this study include (a) NHB with NAFLD have significantly lower prevalence of advanced fibrosis than NHW, although their NAFLD activity scores were similar and NHB had greater lobular inflammation; (b) NHB with advanced fibrosis had higher NAFLD activity score, lobular inflammation, and definite NASH than NHW with advanced fibrosis; (c) death from any cause was rare for both groups, whereas none of the 109 NHB with NAFLD died from a liver-related cause or underwent liver transplantation, 7 of 1910 NHW had liver-related death, and

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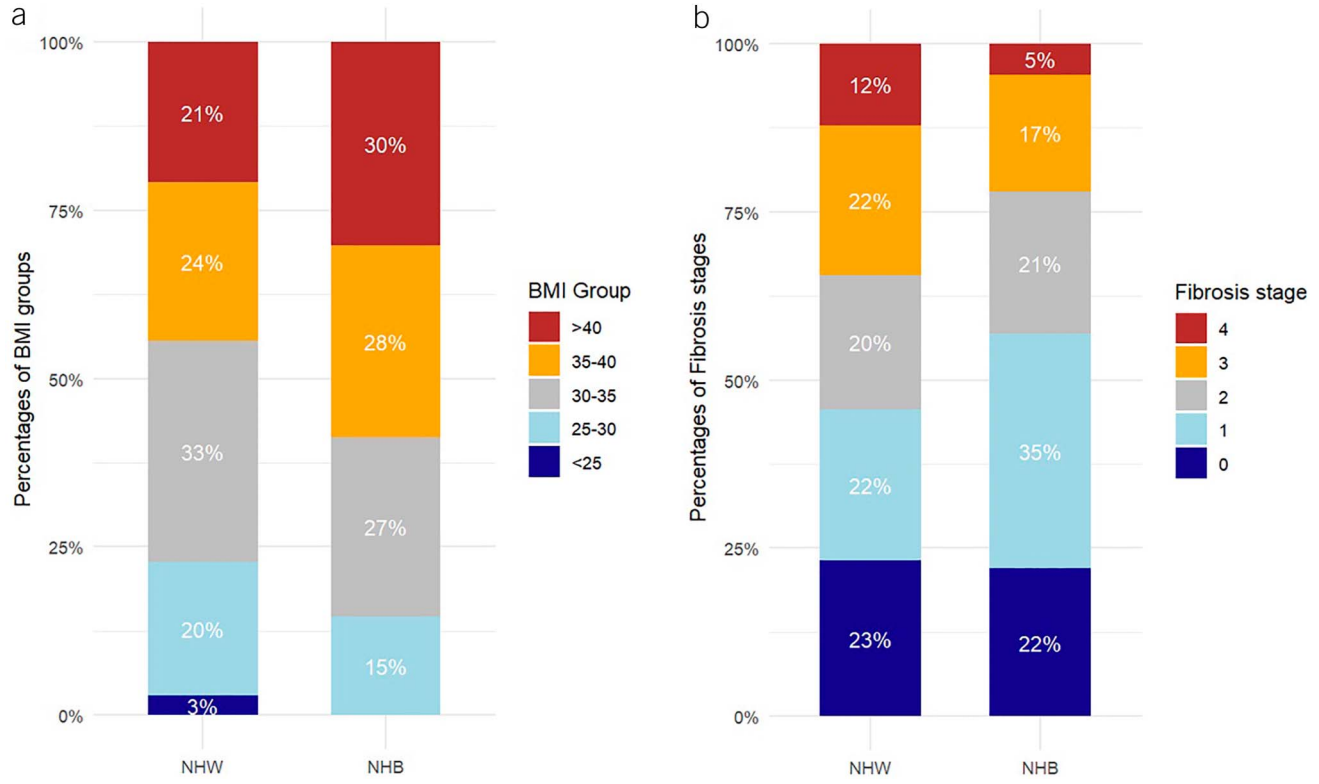

Figure 2. (**a**) The proportion of participants with BMI category <25 kg/m^2, 25–30 kg/m^2, 30–35 kg/m^2, 35–40 kg/m^2, and >40 kg/m^2 is shown for NHW and NHB participants. (**b**) The proportion of participants with fibrosis stage 0, 1 (combines 1a, 1b, and 1c), 2, 3, or 4 is shown for NHW and NHB participants. NHW, NHW, non-Hispanic White persons; NHB, non-Hispanic Black persons.

another 6 underwent liver transplantation; and (d) *PNPLA3* G-allele carriage rate of NHB with NAFLD is similar to that NHW with NAFLD, but the *PNPLA3* G-allele carriage rate was numerically higher among NHB with advanced fibrosis than NHB without advanced fibrosis. The main clinical implications of our study are that NHB may have lower risk of NAFLD, but their risk of NAFLD, NASH, and related cirrhosis is not absent. In this series, among NHB with biopsy-proven NAFLD, nearly 60% had NASH, and 5% had cirrhosis. This raises the possibility that there are sizable number of NHB with clinically significant NAFLD who are not being seen in the tertiary care clinics or being enrolled into clinical trials.

NHB are underrepresented in this study, which is consistent with several other studies that observed lower prevalence of hepatic steatosis and NAFLD among NHB. Because all participants in our study had NAFLD and there was not a control group without NAFLD, we are unable to investigate differences in the prevalence of NAFLD between NHB and NHW. In a retrospective single-center study (10), Satapathy et al observed a significantly lower prevalence of advanced fibrosis in Black persons with NAFLD (2.6% vs 16% in White persons with NAFLD) but also had lower NAFLD activity score (1.92 vs 2.8) and NASH, which was defined as NAFLD activity score ≥5 (3% vs 9.8%). In our prospective study where liver histology was centrally reviewed, we too observed lower prevalence of advanced fibrosis in NHB with NAFLD, but their NAFLD activity score and proportion of definite NASH were nearly identical to NHB with advanced fibrosis. This finding, together with our observation that NHB with

Table 2. Independent association of advanced fibrosis (stage 3–4 vs stage 0–2) at baseline with participant's self-reported race/ethnicity (NHB vs NHW), from multivariable logistic regression

	OR for Odds Ratio (OR) for advanced fibrosis	95% confidence interval	*P*
NHB vs NHW, adjusted for age, sex, BMI, T2DM, hypertension, and triglycerides[a]	0.38	0.24–0.63	0.0001
NHB vs NHW, adjusted for age, sex, BMI, T2DM, hypertension, triglycerides, and *PNPLA3* genotype[b]	0.48	0.27–0.86	0.01

BMI, body mass index; NHB, non-Hispanic Black persons; NHW, non-Hispanic White persons; *PNPLA3*, patatin-like phospholipase domain-containing protein 3; T2DM, type 2 diabetes.
[a]N = 2,008 because of missingness in covariates.
[b]N = 1,482 because of missingness in covariates and unavailable *PNPLA3* genotyping.

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Table 3. All-cause mortality and liver-related outcomes among non-Hispanic Black persons and non-Hispanic White persons with NAFLD

Outcome	Non-Hispanic Black persons		Non-Hispanic White persons	
	Rate per 100 person-year[a]	No. of events/no. at risk	Rate per 100 person-year[a]	No. of events/no. at risk
Death from any cause	0.30	1/109	0.28	23/1910
Liver-related death	0.00	0/109	0.09	7/1910
Liver-related events				
Variceal bleeding	0.00	0/109	0.06	5/1906
Ascites	0.00	0/109	0.24	19/1895
Hepatic encephalopathy	0.00	0/109	0.40	32/1902
Any hepatic decompensation event	0.00	0/109	0.48	38/1889
MELD score ≥15	0.93	3/109	0.52	41/1909
Hepatocellular carcinoma	0.00	0/109	0.15	12/1909
Liver transplant	0.00	0/109	0.07	6/1908

MELD, model for end-stage liver disease; NAFLD, nonalcoholic fatty liver disease.
[a]Person-year included 484/2019 (24%) with zero person-year of follow-up (only baseline obtained).
Median (Inter Quartile Range (IQR)) and min, max yr of follow-up.
Non-Hispanic Black persons: 1.99 (0.00–4.75); 0.00–15.56 years.
Non-Hispanic White persons: 3.00 (0.69–6.80); 0.00–17.97 years.
Overall: 2.91 (0.60–6.74); 0.00–17.97 years.

advanced fibrosis in comparison with NHW with advanced fibrosis had higher NAFLD activity score, lobular inflammation, and NASH, suggests a higher level of necroinflammation is necessary in NHB to develop advanced fibrosis than in NHW. Because the frequency of *PNPLA3* G-allele is similar between NHB and NHW with advanced fibrosis, other molecular and genetic factors are likely either predisposing NHW to fibrosis progression or protecting NHB against fibrosis progression. *In vitro* experiments on human-induced pluripotent stem cell–derived liver organoids developed from NHB and NHW might shed light on the mechanistic basis for this observation.

NHB are known to have a distinctive pattern of dyslipidemia where the total cholesterol and low-density lipoprotein—cholesterol levels are high but with HDL-cholesterol levels high and serum triglyceride levels low. In our study, NHB with NAFLD and with advanced fibrosis exhibited a similar pattern of dyslipidemia. This is similar to a study by Brill et al, which showed lower plasma triglyceride and higher HDL-cholesterol levels in Black persons with NAFLD in comparison with White persons with NAFLD (9). The significance of this phenomenon as it relates to lower frequency of NAFLD and less severe fibrosis in NHB is unclear and warrants further study.

There are limitations to our study. In this study, we identified NHB and NHW using self-reported population descriptors rather than genetic ancestry as we lacked the necessary genetic data to ascertain genetic ancestry. The number of NHB with biopsy-proven NAFLD in this study is modest, and as this study was limited to individuals with biopsy-proven NAFLD at tertiary care centers, there is likely selection bias. However, obtaining a liver biopsy on a large number of NHB with NAFLD in a community setting is practically very difficult. Racial and ethnic disparities in disease severity and outcomes are often related to social determinants of health (SDOH) such as living experiences and environmental influences. We were not able to investigate SDOH such as food insecurity, diet quality, and physical activity in depth because of our study design, and these and other SDOH should be carefully investigated in subsequent studies. The duration of follow-up was relatively modest, and importantly, there was difference in the median length of follow-up between NHB (2 years) and NHW (3 years). However, duration of follow-up was not significantly different after accounting for individuals who missed appointments for illness or temporarily away. But, this discrepancy is not expected to have influenced our cross-sectional or our reporting of events per year. Despite these limitations, our study makes important observations to enhance our understanding of the characteristics of NAFLD in NHB. Recently, after thorough and extensive efforts, multiple scientific societies developed a consensus recommendation to change the nomenclature from NAFLD to metabolic dysfunction-associated steatotic liver disease (MASLD) and from NASH to metabolic dysfunction-associated steatohepatitis (MASH). (13). As this study was performed before issuing this recommendation, we are adhering to the older terminology, but the NASH CRN is systematically evaluating the impact of new definitions on its data sets and analyses.

In summary, here we show that the risk of advanced fibrosis in NHB with NAFLD is significantly lower, even after controlling for important clinical risks and *PNPLA3* genotype. Although their risk of advanced fibrosis was low, NHB with NAFLD had higher NAFLD activity score and lobular inflammation, indicating a difference in the relationship between necroinflammation (ie, NAFLD activity score) and fibrosis between NHB and NHW. Further research using novel approaches such as induced pluripotent stem cell–derived liver organoids from NHB and NHW patients with NAFLD may shed light on the mechanistic basis for these findings.

ACKNOWLEDGEMENTS

The authors thank participants and their families, study coordinators, and study personnel. The authors thank the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) for its support of the NASH CRN. The authors thank Dr. Lauren

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Nephew for critically reviewing the appropriateness of population descriptors used in this article.
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CONFLICTS OF INTEREST

Conflicts of Interest: Drs. Samala and Hoofnagle, Laura Wilson, Katherine Yates and Yuchen Xin report no conflicts of interest.
Guarantor of the article: Naga Chalasani MD
Dr. Loomba: There are none for this paper. Dr. Loomba serves as a consultant or advisory board member for 89bio, Alnylam, Arrowhead Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, Bristol-Myer Squibb, Cirius, CohBar, DiCerna, Galmed, Gilead, Glympse bio, Intercept, Ionis, Metacrine, NGM Biopharmaceuticals, Novo Nordisk, Pfizer, Sagimet and Viking Therapeutics. In addition, his institution has received grant support from Allergan, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, Galmed Pharmaceuticals, Genfit, Gilead, Intercept, Inventiva, Janssen, Madrigal Pharmaceuticals, NGM Biopharmaceuticals, Novartis, Pfizer, pH Pharma, and Siemens. He is also co-founder of Liponexus, Inc.
Dr. Chalasani: There are none for this paper. For full disclosure, Dr. Chalasani has ongoing consulting activities (or had in preceding 12 months) with Madrigal, Zydus, Merck, Pfizer, GSK, Ipsen, and Altimmune. These consulting activities are generally in the areas of nonalcoholic fatty liver disease and drug hepatotoxicity. Dr. Chalasani receives research grant support from Exact Sciences, Zydus and DSM where his institution receives the funding. He has equity ownership in Avant Sante Therapeutics, LLC, a clinical research organization.
Specific author contributions: N.S., R.L., J.H.H., and N.C.: study design. N.S., Y.X., L.W., R.L., and N.C.: data collection. Y.X. and L.W.: statistical analysis. All authors: interpretation of the study results. N.S., N.C.: manuscript writing. Critical review and revision of manuscript: All investigators reviewed and approved the final manuscript. All investigators had access to the study data.
Financial support: The Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN) is supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (grants U01DK061713, U01DK061718, U01DK061728, U01DK061732, U01DK061734, U01DK061737, U01DK061738, U01DK061730, and U24DK061730). Additional support is received from the National Center for Advancing Translational Sciences (NCATS) (grants UL1TR000439, UL1TR000436, UL1TR000006, UL1TR000448, UL1TR000100, UL1TR000004, UL1TR000423, and UL1TR002649).
Potential competing interests: N.S., J.H.H., L.A.W., K.Y., and Y.X. report no conflicts of interest. R.L.: There are none for this article. R.L. serves as a consultant or advisory board member for 89bio, Alnylam, Arrowhead Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, Bristol-Myer Squibb, Cirius, CohBar, DiCerna, Galmed, Gilead, Glympse bio, Intercept, Ionis, Metacrine, NGM Biopharmaceuticals, Novo Nordisk, Pfizer, Sagimet, and Viking Therapeutics. In addition, his institution has received grant support from Allergan, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, Galmed Pharmaceuticals, Genfit, Gilead, Intercept, Inventiva, Janssen, Madrigal Pharmaceuticals, NGM Biopharmaceuticals, Novartis, Pfizer, pH Pharma, and Siemens. He is also cofounder of Liponexus, Inc. N.C.: There are none for this article. For full disclosure, N.C. has ongoing consulting activities (or had in preceding 12 months) with Madrigal, Zydus, Merck, Pfizer, GSK, Ipsen, and Altimmune. These consulting activities are generally in the areas of non-alcoholic fatty liver disease and drug hepatotoxicity. N.C. receives research grant support from Exact Sciences, Zydus, and DSM where his institution receives the funding. He has equity ownership in Avant Sante Therapeutics, LLC, a clinical research organization.
The content and opinion expressed in this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.

Study Highlights

WHAT IS KNOWN

✓ NAFLD is less frequent in non-Hispanic Black persons (NHB), but disease severity and clinical outcomes compared to non-Hispanic White persons (NHW) are not clear.

WHAT IS NEW HERE

✓ The risk of advanced fibrosis in NHB with NAFLD is significantly lower after controlling for risk factors, including the PNPLA3 genotype.

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REFERENCES

1. Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: Trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2018;15(1):11–20.
2. Paik JM, Golabi P, Younossi Y, et al. Changes in the global burden of chronic liver diseases from 2012 to 2017: The growing impact of NAFLD. Hepatology 2020;72(5):1605–16.
3. Wong RJ, Singal AK. Trends in liver disease etiology among adults awaiting liver transplantation in the United States, 2014-2019. JAMA Netw Open 2020;3(2):e1920294.
4. Browning MG, Khoraki J, DeAntonio JH, et al. Protective effect of black relative to white race against non-alcoholic fatty liver disease in patients with severe obesity, independent of type 2 diabetes. Int J Obes 2018;42(4):926–9.
5. Bambha K, Belt P, Abraham M, et al. Ethnicity and nonalcoholic fatty liver disease. Hepatology 2012;55(3):769–80.
6. Golabi P, Paik JM, Harring M, et al. Prevalence of high and moderate risk nonalcoholic fatty liver disease among adults in the United States, 1999–2016. Clin Gastroenterol Hepatol 2022;20(12):2838–47.e7.
7. Tota-Maharaj R, Blaha MJ, Zeb I, et al. Ethnic and sex differences in fatty liver on cardiac computed tomography: The multi-ethnic study of atherosclerosis. Mayo Clin Proc 2014;89(4):493–503.
8. Williams CD, Stengel J, Asike MI, et al. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: A prospective study. Gastroenterology 2011;140(1):124–31.
9. Bril F, Cusi K. Response to Comment on Bril et al. clinical and histologic characterization of nonalcoholic steatohepatitis in African American Patients. Diabetes Care 2018;41(9):e137–8.
10. Satapathy SK, Marella HK, Heda RP, et al. African Americans have a distinct clinical and histologic profile with lower prevalence of NASH and advanced fibrosis relative to Caucasians. Eur J Gastroenterol Hepatol 2021;33(3):388–98.
11. Sanyal AJ, Van Natta ML, Clark J, et al. Prospective study of outcomes in adults with nonalcoholic fatty liver disease. N Engl J Med 2021;385(17):1559–69.
12. Vilar-Gomez E, Pirola CJ, Sookoian S, et al. Impact of the association between PNPLA3 genetic variation and dietary intake on the risk of significant fibrosis in patients with NAFLD. Am J Gastroenterol 2021;116(5):994–1006.
13. Rinella ME, Lazarus JV, Ratziu V, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. J Hepatol 2023;79(6):1542–56.

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