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Racial and Ethnic Disparities in Non-alcoholic Fatty Liver Disease Prevalence, Severity, and Outcomes in the United States: A Systematic Review and Meta-analysis

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Abstract

Background & Aims—Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the United States, affecting 75–100 million Americans. However, the disease burden may not be equally distributed among races or ethnicities. We conducted a systematic review and meta-analysis to characterize racial and ethnic disparities in NAFLD prevalence, severity, and prognosis.

Methods—We searched MEDLINE, EMBASE, and Cochrane databases through August 2016 for studies that reported NAFLD prevalence in population-based or high-risk cohorts, NAFLD severity including presence of nonalcoholic steatohepatitis (NASH) and significant fibrosis, and NAFLD prognosis including development of cirrhosis complications and mortality. Pooled relative risks, according to race and ethnicity, were calculated for each outcome using the DerSimonian and Laird method for a random-effects model.

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Nicole E. Rich was involved in study concept and design, acquisition of data, interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content.

Stefany Oji was involved in acquisition of data, interpretation of data, and critical revision of the manuscript for important intellectual content.

Arjmand R. Mufti was involved in interpretation of data and critical revision of the manuscript for important intellectual content.

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Amit G. Singal was involved in study concept and design, acquisition of data, analysis and interpretation of data, and drafting of the manuscript, critical revision of the manuscript for important intellectual content, and study supervision.

Results—We identified 34 studies comprising 368,569 unique patients that characterized disparities in NAFLD prevalence, severity, or prognosis. NAFLD prevalence was highest in Hispanics, intermediate in Whites, and lowest in Blacks, although differences between groups were smaller in high-risk cohorts (range 47.6%–55.5%) than population-based cohorts (range, 13.0%–22.9%). Among patients with NAFLD, risk of NASH was higher in Hispanics (relative risk, 1.09; 95% CI, 0.98–1.21) and lower in Blacks (relative risk, 0.72; 95% CI, 0.60–0.87) than Whites. However, the proportion of patients with significant fibrosis did not significantly differ among racial or ethnic groups. Data were limited and discordant on racial or ethnic disparities in outcomes of patients with NAFLD.

Conclusion—In a systematic review and meta-analysis, we found significant racial and ethnic disparities in NAFLD prevalence and severity in the United States, with the highest burden in Hispanics and lowest burden in Blacks. However, data are discordant on racial or ethnic differences in outcomes of patients with NAFLD.

Keywords

fatty liver disease; disparities; nonalcoholic steatohepatitis; ethnicity

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), the hepatic manifestation of the metabolic syndrome, is the most common chronic liver disease in the U.S., affecting up to 100 million Americans¹. NAFLD encompasses a spectrum of disease, including simple steatosis, nonalcoholic steatohepatitis (NASH), and NASH-related cirrhosis. Over one-third of children and adults in the U.S. are obese and over 20 million Americans are diabetic, resulting in a large at-risk population for NAFLD.² Approximately 2–5% of patients with NAFLD will progress to NASH, among whom a subset will develop cirrhosis and cirrhosis-related complications including hepatocellular carcinoma (HCC).³

Prior studies have suggested Hispanics may have disproportionately higher and Blacks may have lower NAFLD prevalence and severity compared to non-Hispanic Whites^{4, 5}. Additionally, NAFLD is increasingly being recognized in Asian patients, even at “normal” BMI values.⁶ However, the magnitude of these disparities is currently poorly characterized, as prior studies have been underpowered. Further, most studies evaluated NAFLD prevalence, severity or prognosis, with no studies evaluating disparities across the entire NAFLD spectrum. Racial/ethnic disparities in NAFLD prevalence and severity can be multifactorial, driven not only by genetic and environmental factors but also socioeconomic status and differential access to health care. Further these influences may differ in significance along the NAFLD spectrum, with some influences playing a central role in NAFLD development and others being more important for disease progression or NAFLD prognosis. Having a better understanding of what disparities exist and their magnitude is the first step to identifying contributing factors and reducing disparities through targeted interventions. Thus, the aim of this meta-analysis was to characterize racial/ethnic disparities in NAFLD prevalence, disease severity, and prognosis among patients in the U.S.

METHODS

Literature search strategy

We searched Ovid MEDLINE, Ovid MEDLINE In-Process, Ovid EMBASE, and the Cochrane Library from inception to August 2, 2016 using search terms described in Supplemental Methods. A manual search of references from relevant articles was performed to identify publications missed by search terms. A manual search of American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver, Digestive Diseases Week, and American College of Gastroenterology meeting abstracts from 2014–2016 was performed. The study was conducted in accordance with Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines⁷.

Eligibility Criteria

Included studies met the following criteria: 1) cohort, cross-sectional, or case-control trials including original data characterizing NAFLD-related racial/ethnic disparities among adult patients in the U.S., 2) NAFLD diagnosed using biochemical, radiologic, or histologic criteria per AASLD guidelines, and 3) reported at least one of the following: NAFLD prevalence, severity, or prognosis. We excluded studies that: 1) did not stratify NAFLD prevalence, severity, or prognosis by race/ethnicity, 2) had insufficient data to determine necessary denominator for prevalence or severity, or 3) included patients with other causes of hepatic steatosis (e.g. alcoholic liver disease, medication-induced, or HIV infection). Additional exclusion criteria included: 1) lack of original data (e.g. commentaries, review articles), 2) non-human studies; 3) incomplete data, and 4) non-English language. For studies with overlapping cohorts, articles with the most contemporary cohort or complete data were selected.

Study Selection and Data Extraction

Studies were screened and reviewed in a collaborative, multi-step process. After removing duplicates, two investigators (N.R. and S.O.) independently reviewed publications identified by the search strategy. Articles were screened based on title and abstract for relevance, followed by full text review to assess for inclusion. Disagreements between authors were resolved by discussion with a third reviewer (A.S.). Using standardized forms, two authors (N.R. and S.O.) independently extracted data including patient demographics (including race/ethnicity), method of NAFLD diagnosis, NAFLD prevalence, NAFLD severity, and NAFLD prognosis outcomes (including liver-related and all-cause mortality). Study quality was assessed using a modified checklist based upon the NIH Quality Assessment Tool for Observational Cohort and Cross-sectional Studies, which rates observational studies on a 14-point scale based on study sample appropriateness, comparability of study groups, and adequacy of assessing exposure and outcomes.

Data Synthesis and Statistical Analysis

For each study, a risk ratio for each study outcome of interest was calculated according to race/ethnicity (White vs. Black and White vs. Hispanic). Data for other racial/ethnic groups, e.g. Asians, were limited by small sample sizes and not included in analyses. We first

evaluated NAFLD prevalence in population-based and high-risk cohorts. Cohorts were deemed high-risk if they predominantly included patients with obesity (e.g., patients undergoing bariatric surgery), diabetes, or history of chronic liver disease. We next evaluated NAFLD severity, as assessed by two measures: 1) presence of NASH, the progressive form of NAFLD that can lead to cirrhosis and cirrhosis-related complications, and 2) presence of advanced (stage F3–F4) fibrosis. Although some studies reported components of NAFLD activity score (NAS) including degree of inflammation and steatosis, an insufficient number reported racial/ethnic differences in composite NAS to include as a severity measure. Finally, we evaluated NAFLD prognosis, including liver-related and all-cause mortality. Association between NAFLD and cardiovascular outcomes has been described elsewhere and not evaluated in this study⁸.

For each study outcome of interest, point estimates and 95% confidence intervals were calculated using the adjusted Wald method. We calculated pooled risk ratio estimates for NAFLD prevalence and severity using the DerSimonian and Laird method for a random effects model. Heterogeneity was evaluated graphically by examining forest plots and statistically using the inconsistency index (I^2 statistic). I^2 values >75% are consistent with high heterogeneity, and values between 50–75% are considered moderate heterogeneity. When there were concerns for heterogeneity, sensitivity analyses, in which one study was removed at a time, were performed to evaluate for undue influence of a single study. Publication bias was evaluated graphically by funnel plot analysis and statistically using Egger's test. An asymmetric funnel plot suggests possibility of small studies not being published. All data analysis was performed using Stata 14.2 (StataCorp, College Station, TX, USA).

RESULTS

Literature Search

The search strategy yielded 7,921 potentially relevant citations. After removing 1,893 duplicate citations there were 6,028 unique citations. After initial review, 2,428 titles met inclusion criteria, and abstracts were reviewed. Of 351 publications that underwent full text review, 46 met inclusion criteria. Fourteen studies contained overlapping data from NHANES, so we selected the most inclusive studies representing patients from non-overlapping NHANES cohorts ($n=2$)^{9,10}. We also excluded an additional study only reporting prevalence for racial/ethnic minority patients but not Whites, as risk ratios comparing minority populations to the index white population could not be calculated¹¹. Searches of meeting abstracts yielded 3 abstracts with sufficient data for inclusion, and recursive literature searches revealed 1 additional article meeting inclusion criteria, for a total of 34 studies. Agreement between reviewers for final study inclusion exceeded 90%. Supplemental Figure 1 represents a flow diagram depicting study selection.

Study Characteristics

We identified 34 studies, with a total of 368,569 patients, characterizing racial/ethnic disparities in NAFLD prevalence, severity or prognosis. Studies had racial/ethnic diversity including 216,501 (58.7%) Whites, 57,412 (15.6%) Blacks, 43,737 (11.9%) Hispanics, 10,

100 (2.7%) Asians, and 40,819 (11.1%) “other” race/ethnicity. All included studies reported races/ethnicities as mutually exclusive categories. Of included studies, 17 (n=350,076) characterized disparities in NAFLD prevalence, 18 (n=16,083) in NAFLD severity, and 6 (n=15,187) reported disparities in NAFLD prognosis; seven studies reported disparities in more than one study outcome. Six studies focused on White-Black disparities and did not include data for Hispanics, while one study focused on White-Hispanic disparities and did not include data for Blacks^{12–18}. Of NAFLD prevalence studies, 9 were conducted among population-based cohorts and 8 were conducted in high-risk cohorts. Of NAFLD severity studies, 10 evaluated presence of NASH and 11 characterized fibrosis staging. There were fewer studies of NAFLD prognosis including two full publications and 4 meeting abstracts, and reporting of outcomes was not standardized among available studies. We found no evidence of publication bias for NAFLD prevalence or severity by Egger’s test ($p>0.05$ for each) or funnel plot inspection.

NAFLD Prevalence in Population-Based Cohorts

Nine studies (n=343,393) assessed NAFLD prevalence in population-based cohorts (Table 1)^{9,10,12,13,16,19–22}. NAFLD diagnosis was determined by presence of steatosis on ultrasound (n=3), steatosis per MR spectroscopy (n=2), steatosis on CT (n=2), elevated aminotransferases alone (n=1), and ICD-9 codes (n=1). Four studies required exclusion of other liver diseases to make a NAFLD diagnosis; however, only one required histologic confirmation.²²

NAFLD prevalence ranged widely from 6.6% to 46.0% between studies, with a pooled prevalence of 11.2% (95% CI 11.1–11.3%). Compared to Whites, Hispanics had higher risk of NAFLD with a pooled RR of 1.36 (95% CI 1.08–1.73), and Blacks had lower risk of NAFLD with a pooled RR of 0.68 (95% CI 0.54–0.84). There was significant heterogeneity ($I^2>90\%$) in both comparisons; on visual inspection of Forest plots, the study by Reddy was an outlier.²⁰ This study was conducted among hospitalized patients and NAFLD diagnosis was based on ICD-9 codes, which have low accuracy, so it was excluded in sensitivity analyses. After removing this study, pooled NAFLD prevalence was 15.1% (95% CI 14.8–15.5%). NAFLD prevalence was highest in Hispanics (22.9%, 95% CI 21.6–24.1%), intermediate in Whites (14.4%, 95% CI 14.0–14.8%), and lowest in Blacks (13.0%, 95% CI 12.2–13.9%). Compared to Whites, the pooled RR of NAFLD in Hispanics was 1.47 (95% CI 1.35–1.61), and I^2 decreased to 41% (Figure 1A); the pooled RR of NAFLD in Blacks compared to Whites was 0.74 (95% CI 0.69–0.80), and I^2 decreased to 0% (Figure 1B).

NAFLD Prevalence in High-Risk Cohorts

Eight studies (n=6,683) assessed NAFLD prevalence in high-risk cohorts (Table 1)^{14,15,17,18,23–26}. NAFLD diagnosis was ascertained using intraoperative liver biopsy (n=5), MR spectroscopy (n=2), and history/ICD-9 codes (n=1), with only one study requiring histologic confirmation.

NAFLD prevalence ranged from 51.7% to 89.1%, with a pooled prevalence of 55.7% (95% CI 54.5–56.9%). NAFLD prevalence was 55.5% (95% CI 52.6–57.4%) among Whites, 48.8% (95% CI 46.3–51.3%) among Hispanics, and 47.6% (95% CI 44.2–51.1%) among

Blacks. NAFLD prevalence among other races/ethnicities, including Asians, was evaluated in few studies but appeared high at 62.9%. Risk of NAFLD in Hispanics among high-risk patients was not significantly different than Whites, with a pooled RR of 1.10 (95% CI 0.96–1.27), although there was moderate heterogeneity ($I^2 > 70\%$). Studies by Chen and Kallwitz were outliers on visual inspection of Forest plots. There was not clinical heterogeneity justifying exclusion of Chen; however, Kallwitz was the only study to use intraoperative biopsy. On sensitivity analyses, we found a pooled RR of 1.26, 95%CI 1.09–1.46 ($I^2 = 94\%$) if the Chen study was excluded and a pooled RR of 1.16, 95%CI 1.03–1.33 ($I^2 = 25\%$) if the Kallwitz study was excluded (Figure 1A).

Blacks had lower risk of NAFLD than Whites in high-risk patients, with a pooled RR of 0.85 (95% CI 0.75–0.97). There was moderate heterogeneity ($I^2 > 50\%$) and studies by Brill and Setiawan were outliers on visual inspection of Forest plots. Both studies used non-invasive means to define NAFLD – MR spectroscopy and ICD-9 codes, respectively – whereas remaining studies used liver biopsy. On sensitivity analysis removing all 3 studies defining NAFLD non-invasively, the pooled RR was 0.78 (95%CI 0.67–0.91), and I^2 decreased to 47% (Figure 1B).

NAFLD Severity

Eighteen studies ($n=16,083$) addressed racial/ethnic differences in NAFLD severity (Table 2)^{10,14,18,22,23,27–39}. Among 10 studies that evaluated presence of NASH among NAFLD patients, pooled NASH prevalence was 31.4% (95%CI 30.1–32.7%). NASH prevalence was highest in Hispanics (45.4%, 95% CI 40.7–50.2%), intermediate in Whites (32.2%, 95% CI 30.7–33.7%), and lowest in Blacks (20.3%, 95% CI 16.8–24.2%). The pooled RR of NASH in Hispanics compared to Whites was 1.24 (95%CI 1.02–1.52), with moderate heterogeneity ($I^2 > 50\%$). The study by Brill was an outlier on visual inspection of Forest plots; however, there was not clinical heterogeneity justifying exclusion. The study by Younossi did not appear to be an outlier but was the only study to define NASH using liver enzymes instead of histology. On sensitivity analyses, we found a pooled RR of 1.30, 95%CI 1.05–1.63 ($I^2 = 63\%$) if the study by Brill was excluded and pooled RR of 1.09, 95%CI 0.98–1.21 ($I^2 = 4\%$) if the study by Younossi was excluded (Figure 2A). The pooled RR of NASH in Blacks compared to Whites was 0.72 (95%CI 0.60–0.87), with minimal heterogeneity ($I^2 < 20\%$) (Figure 2B).

Among 11 studies assessing stage of fibrosis, pooled proportion of NAFLD patients with significant fibrosis (stage F3–F4) was 19.5% (95%CI 18.1–20.9%). Significant fibrosis proportions were numerically highest in Whites (22.3%, 95% CI 20.5–24.2%) and Hispanics (19.6%, 95% CI 16.0–23.0%) and lowest among Blacks (13.1%, 95% CI 8.9–18.2%); however differences were not statistically significant (Whites vs. Blacks: RR of 1.10, 95% CI 1.00–1.22; Whites vs. Hispanics: RR 1.02, 95%CI 0.94–1.11).

NAFLD Prognosis

Six studies assessed racial/ethnic differences in prognosis among NAFLD patients (Table 3)^{30,40–44}. All studies were retrospective and outcomes included progression to cirrhosis, development of HCC, liver-related mortality, and all-cause mortality. Heterogeneity of

outcomes precluded pooling of data. One study reported Hispanics had higher odds of developing cirrhosis (OR 2.7, 95%CI 1.2–5.8) and HCC (OR 2.5, 95%CI 1.1–5.5) compared to Whites, although another study found no significant difference in cirrhosis proportions between Hispanics and Whites (6.7% vs. 5.6%, $p=0.65$). Studies on liver-related and all-cause mortality also reported discordant results. Younossi and colleagues reported significantly higher hazards of all-cause mortality among Blacks than Whites (HR 1.36, 95%CI 1.03–1.78) and lower hazards among other racial/ethnic minorities including Hispanics compared to Whites (HR 0.65, 95%CI 0.43–0.96). In contrast, another study reported non-significant higher hazards of liver-related and all-cause mortality among whites than racial/ethnic minorities and another reported no differences in all-cause mortality between racial/ethnic groups.

Quality Assessment

Quality assessment of studies is provided in Table 4. Four studies had quality scores <5 , 17 had a score of 5–7, and 13 studies had quality scores >7 . Three of the four studies with quality scores <5 were abstracts. Most studies had appropriate cohort selection, including representativeness of the at-risk cohort. The most common limitation observed was cross-sectional study design (27 of 34 studies), which precluded the exposure being measured prior to outcome, sufficient time frame, repeated measurements of the exposure over time, and loss to follow-up reporting. Although outcomes were clearly defined and valid in most studies, ascertainment method for those outcomes varied. Some studies used imaging including ultrasound, CT, or MRI for NAFLD prevalence, whereas others used liver enzymes, which have lower sensitivity for NAFLD ascertainment. Similarly, most studies assessed NAFLD severity via histology although some studies used less reliable methods such as imaging and/or liver enzymes. Finally, several studies used large administrative databases, e.g. NHANES, which have inherent limitations, including missing or incomplete data on diagnosis of NAFLD thus increasing risk of ascertainment bias.

DISCUSSION

While NAFLD prevalence varied widely among studies, particularly in population-based cohorts, our systematic review highlights NAFLD is very common in the United States. We found nearly 1 in 6 of all Americans and 1 in 2 high-risk individuals have NAFLD. NAFLD prevalence appeared highest among Hispanics and lowest among Blacks, although differences were less marked in high-risk cohorts than population-based cohorts. Among patients with NAFLD, risk of NASH is greatest in Hispanics and lowest in Blacks; however, the proportion with advanced fibrosis did not significantly differ between racial/ethnic groups. Data are discordant regarding the presence of racial/ethnic disparities in NAFLD-related prognosis such as progression to cirrhosis and/or mortality. To the best of our knowledge, this is the first systematic review to quantify racial/ethnic differences in NAFLD prevalence, severity, and prognosis. These data provide insight into where in the NAFLD-to-NASH cirrhosis continuum disparities start to arise and suggest determinants of each step may differ.

Our findings reflect the wide variation in NAFLD prevalence among studies, particularly in population-based cohorts, ranging from 6.6% to 46.0%. Prevalence appeared to depend on method of NAFLD diagnosis, with highest prevalence reported in studies using ultrasound or MR spectroscopy. As expected, NAFLD prevalence was higher in high-risk cohorts than population-based cohorts, with approximately 50% of patients with obesity or diabetes having NAFLD, independent of race/ethnicity. Despite variation in reported prevalences, observed racial/ethnic disparities were fairly consistent across studies. The highest NAFLD burden was evident among Hispanics, the fastest growing demographic in the United States. Population-based studies suggest nearly 1 in 4 Hispanics have NAFLD compared to only approximately 1 in 10 blacks. However, differences in prevalence were less marked in high-risk cohorts, suggesting differences in prevalence may be, in part, driven by the differential distribution of underlying risk factors including obesity and diabetes. These data are important to consider when determining targets for NAFLD screening in the general population and for determining pre-test likelihood of NAFLD in the differential diagnosis for patients with aminotransferase elevations. Development and validation of accurate predictive models, including factors such as age, race/ethnicity, and metabolic syndrome features, may help target NAFLD screening to those at highest risk.

Among patients with NAFLD, nearly 30% had evidence of NASH and nearly 20% had evidence of advanced fibrosis (stage F3–F4), underscoring the high potential for NAFLD-related morbidity and need for effective treatment strategies. Currently, lifestyle modifications remain the cornerstone of NASH therapy and while there are no currently widely available pharmacologic therapies, a number of novel drugs are in development. Given the widespread burden of NAFLD in the U.S., it may not be feasible to identify all at-risk persons. It may be more cost-effective to concentrate efforts on identifying patients who are most likely to develop adverse consequences of NASH (including cirrhosis, portal hypertensive complications, and HCC) and those who would derive most benefit from early preventative and therapeutic interventions. These patients would also need to be closely monitored for development of cirrhosis, at which time measures such as HCC surveillance and varices screening should be implemented.

It is unclear from current literature if NAFLD-related severity and prognosis differs between racial/ethnic groups. Although Hispanic NAFLD patients were more likely to have NASH than their counterparts, presence of advanced fibrosis did not differ between racial/ethnic groups and data characterizing prognosis were discordant. These data highlight the need for further research in areas of NASH severity and prognosis, as current data are sparse and inconsistently reported.

Although several studies have described racial/ethnic and socioeconomic disparities, further studies are needed to characterize precisely *why* these disparities exist. While NAFLD disease burden is related to metabolic syndrome components such as obesity, diabetes, and dyslipidemia, NAFLD risk extends beyond environmental factors. For example, diabetes and obesity are both more common among Blacks compared to Whites; however, the latter group has significantly higher risk of NAFLD^{2,45}. Cultural and socioeconomic factors are also likely implicated including dietary and exercise habits, access to health care, and allostatic load experienced by those living in poverty. Prior studies have demonstrated genetic risk

factors play a large role in NAFLD. In particular, single nucleotide polymorphisms in *PNPLA3*, *TM6SF2* and *MBOAT* have unequal distributions across races/ethnicities which contributes to the observed differences in NAFLD prevalence^{46–48}. For instance, the I148M variant in *PNPLA3* is strongly associated with hepatic fat content, and occurs most frequently in Hispanics (49%) compared to non-Hispanic Whites (23%) and Blacks (17%)⁴⁶. Additionally, recent studies have demonstrated polymorphisms in *PNPLA3* are frequent in Asian Indians with NAFLD, which is likely contributing to the increasing prevalence of NAFLD in this population.⁴⁹ Though genetic factors are clearly implicated, further studies are needed to characterize the relative contribution of genetic and environmental factors toward NAFLD pathogenesis to help inform risk stratification and future prevention efforts. Additionally, it is possible mechanisms for NAFLD progression differ from mechanisms that lead to development of NAFLD. Our study supports this hypothesis, as racial/ethnic disparities are less apparent for NAFLD severity and prognosis than prevalence, though the paucity of data on disparities in NAFLD prognosis should be noted. Although some genetic factors such as polymorphisms in *PNPLA3* are also associated with NAFLD severity and prognosis⁵⁰, it is unclear if this is true for other genetic factors such as *TM6SF2* or environmental factors.

Studies in our meta-analysis have several inherent limitations given the complexity of racial/ethnic health disparities. First, data on race and ethnicity is self-reported and may not be collected reliably. Second, differences between racial groups may be difficult to interpret, as there may be as much genetic heterogeneity within races as between races. One particular challenge becoming more common over time is the classification of multi-ethnic individuals, who are often forced into a single category. Finally, race and socioeconomic status are often highly correlated, complicating interpretation of observed disparities in health outcomes. Racial/ethnic differences in some health outcomes can be mitigated, or even disappear, if adequately adjusting for socioeconomic status; however, this can often be difficult, particularly for retrospective analyses. Additional limitations of the NAFLD-related literature are worth acknowledging. First, most included studies in our analysis were cross-sectional with limitations in study quality. There was also heterogeneity in method of NAFLD diagnosis; some studies used liver histology or MR spectroscopy, while others used ICD-9 codes and laboratory tests which may underestimate or overestimate NAFLD prevalence. Additionally, while the NAFLD Activity Score (NAS) is the most accepted measure of NASH severity, racial/ethnic differences in NAS scores were rarely reported. Finally, there were little data on other underrepresented minority groups such as Asian/Pacific Islanders and Native Americans.

While awaiting effective NAFLD chemoprevention and treatment, our meta-analysis provides important data characterizing NAFLD disparities. Our study highlights NAFLD is common in the U.S., with nearly 1 in 6 of all Americans and 1 in 2 high-risk individuals having NAFLD. There are notable racial and ethnic disparities in NAFLD prevalence and severity, with the highest burden in Hispanics and lowest in Blacks. Few studies have evaluated racial/ethnic differences in NAFLD prognosis, with discordant results, demonstrating the need for further research in this area. Studies are also needed to identify determinants of NAFLD disparities, which would be the first crucial step to identify

appropriate intervention targets to reduce racial/ethnic disparities and improve NAFLD morbidity and mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AASLD	American Association for the Study of Liver Disease
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
HCC	Hepatocellular carcinoma
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
MBOAT	Membrane-bound O-acyl transferase
NAFLD	Nonalcoholic fatty liver disease
NAS	NAFLD activity score
NASH	Nonalcoholic steatohepatitis
NIH	National Institute of Health
OR	Odds ratio
PNPLA3	Patatin-like phospholipase domain-containing protein 3
TM6SF2	Transmembrane 6 superfamily 2 human gene

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Figure 1.

A. NAFLD prevalence among Hispanics vs. Whites in population-based and high-risk cohorts

B. NAFLD prevalence among Blacks vs. Whites in population-based and high-risk cohorts

Figure 2.

A. Presence of NASH and advanced fibrosis among patients with NAFLD for Hispanics vs. Whites

B. Presence of NASH and advanced fibrosis among patients with NAFLD for Blacks vs. Whites

Table 1

Studies characterizing racial/ethnic disparities in NAFLD prevalence among U.S. patients

Prevalence (unselected cohort)						
Author/Year	Study Design	Cohort	Method of NAFLD diagnosis	n	n (white/black/Hispanic)	n NAFLD [overall prevalence]
Pirerdine, 2012 ¹⁷	Cross-sectional	Retrospective, NHANES 2001–2008	Aminotransferases	18550	13422 / 2061 / 2242	1782 [9.6%]
Browning, 2004 ³⁸	Cross-sectional	Prospective, Dallas Heart Study	MR spectroscopy	2240	734 / 1105 / 401	687 [30.7%]
Kim, 2013 ³²	Cross-sectional	Prospective, Study of Women's Health Across the Nation, Michigan site	Ultrasound	331	130 / 201 / 0	94 [28.3%]
Loomba, 2015 ³¹	Cross-sectional	Prospective, Twins in Southern California	MR spectroscopy	120	94 / 0 / 18	26 [21.7%]
North, 2012 ³⁵	Cross-sectional	Retrospective, NHLBI family heart study	CT	2,727	2221 / 506 / 0	181 [6.6%]
Reddy, 2013 ³⁹	Cross-sectional	Retrospective, Nationwide Inpatient Sample	ICD-9 codes	303,396	173,314 / 48,432 / 36,259	32,347 [10.7%]
Tison, 2015 ⁴⁰	Cross-sectional	Retrospective, MESA	CT	4088	1503 / 1233 / 955	706 [17.3%]
Williams, 2011 ⁴¹	Cross-sectional	Prospective, Brooke Army Medical Center patients	Ultrasound +/- biopsy	328	205 / 37 / 72	151 [46.0%]
Younossi, 2012 ²⁹	Cross-sectional	Retrospective, NHANES 1988–1994	Ultrasound +/- aminotransferases	11,613	8887 / 1215 / 644	2492 [21.5%]
Total				343393	200,510 / 54,790 / 40,591	38466 [11.2%]
Prevalence (high risk cohort)						
Author	Study Design	Cohort	Method of NAFLD diagnosis	n	n (white/black/Hispanic)	n NAFLD [overall prevalence]
Bril, 2014 ⁴²	Cross-sectional	Prospective, Diabetics/pre-diabetics	MR spectroscopy	93	31 / 31 / 31	71 [76.3%]
Chen, 2009 ⁴³	Cross-sectional	Prospective, Diabetics, patients with impaired glucose tolerance	MR spectroscopy	76	22 / 5 / 49	59 [77.6%]
Corey, 2013 ³⁶	Cross-sectional	Prospective, Obese undergoing weight loss surgery	Biopsy	159	107 / 52 / 0	110 [69.2%]
Garcia, 2015 ³⁷	Cross-sectional	Prospective, Obese women undergoing bariatric surgery	Biopsy	51	41 / 10 / 0	33 [64.7%]
Kallwitz, 2009 ⁴⁴	Cross-sectional	Prospective, Obese undergoing weight loss surgery	Biopsy	238	110 / 92 / 36	212 [89.1%]
Setiawan, 2016 ⁴⁵	Cross-sectional	Retrospective, Multiethnic cohort	ICD-9 codes	5783	1148 / 609 / 1442	2990 [51.7%]
						n NAFLD (white/black/Hispanic)
						22 / 25 / 24
						13 / 2 / 44
						85 / 25 / 0
						28 / 5 / 0
						105 / 73 / 34
						467 / 239 / 658

Prevalence (unselected cohort)							
Author/Year	Study Design	Cohort	Method of NAFLD diagnosis	n	n (white/black/Hispanic)	n NAFLD [overall prevalence]	n NAFLD (white/black/Hispanic)
Stepanova, 2010 ³⁴	Cross-sectional	Prospective, Obese undergoing weight loss surgery	Biopsy	94	73 / 21 / 0	81 [86.2%]	64 / 17 / 0
Solga, 2005 ³³	Cross-sectional	Prospective, Obese undergoing weight loss surgery	Biopsy	189	163 / 26 / 0	166 [87.8%]	149 / 17 / 0
Total				6683	1695 / 846 / 1558	3722 [55.7%]	933 / 403 / 760

Table 2
Studies characterizing racial/ethnic disparities in NAFLD severity among U.S. patients

Author/Year	Study Design	Retrospective/Prospective	Cohort	Method of NAFLD/NASH diagnosis	n
Bambha, 2012 ⁴⁶	Cross-sectional	Prospective	NASH CRN	Biopsy	1026
Bril, 2014 ⁴²	Cross-sectional	Prospective	Diabetics/pre-diabetics	MR spectroscopy, biopsy	93
Campos, 2008 ⁴⁷	Cross-sectional	Prospective	Obese undergoing weight loss surgery	Biopsy	200
Corbin, 2013 ⁴⁸	Cross-sectional	Prospective	Single center NAFLD registry	Biopsy	446
García, 2015 ³⁷	Cross-sectional	Prospective	Obese, non-diabetic women	Biopsy	51
Ha, 2016 ⁴⁹	Cohort	Retrospective	NAFLD patients at single center	Imaging, histology	460
Hossain, 2009 ⁵⁰	Cross-sectional	Prospective	NAFLD patients at single center	Biopsy	432
Kallwitz, 2009 ⁵¹	Cross-sectional	Retrospective	Obese undergoing weight loss surgery	Biopsy	238
Lomonaco, 2011 ⁵²	Cross-sectional	Prospective	Obese patients	Biopsy	152
Mohanty, 2009 ⁵³	Cross-sectional	Retrospective	Pts with “steatosis” on pathology	Biopsy	238
Nelson, 2007 ⁵⁴	Cross-sectional	Prospective	Multicenter cohort, NASH	Biopsy	126
Pimentel, 2016 ⁵⁵	Cross-sectional	Prospective	Single center NAFLD registry	Biopsy	183
Rafiq, 2009 ⁵⁶	Cohort	Retrospective	NAFLD registry (2 centers)	Biopsy	173
Solga, 2005 ³³	Cross-sectional	Prospective	Obese undergoing weight loss surgery	Biopsy	189
Tabibian, 2011 ⁵⁷	Cross-sectional	Retrospective	Single center NAFLD registry	Biopsy	90
Verna, 2015 ⁵⁸	Cross-sectional	Prospective	Single center NAFLD registry	Biopsy	45
Williams, 2011 ⁴¹	Cross-sectional	Prospective	Single center NAFLD registry	Biopsy	328
Younossi, 2012 ²⁹	Cross-sectional	Retrospective	NHANES 1988–1994	Ultrasound +/- aminotransferases	11613

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Table 3
Studies characterizing racial/ethnic disparities in NAFLD prognosis among U.S. patients

Author, Year	Study Design	Retrospective/Prospective	Cohort	n	Method of NAFLD/NASH diagnosis
De Martini, 2014 ⁵⁹	Cohort	Retrospective	Single center registry	626	Clinical criteria, biopsy
Ditah, 2014 ¹⁸	Cohort	Retrospective	NHANES III + mortality-linked files to National Death Registry	11,863	Ultrasound
Ha, 2016 ⁴⁹	Cohort	Retrospective	Single center NAFLD registry	460	Imaging, biopsy
Stepanova, 2013 ⁶⁰	Cohort	Retrospective	NAFLD databases (2 centers)	289	Biopsy
Yip, 2015 ⁶¹	Cohort	Retrospective	Single center registry	696	Biopsy
Younossi, 2013 ⁶²	Cohort	Retrospective	NHANES III + mortality-linked files to National Death Index	6,709	Ultrasound

Table 4

Quality assessment for all included studies

Prevalence Studies														
Author, year	1	2	3	4	5	6	7	8	9	10	11	12	13	14 Overall Score Outcomes assessed
Bierdine, 2012	*	*	*	*	no	no	no	no	*	no	*	*	NA	8 NAFLD
Younossi, 2012	*	*	*	*	no	no	no	NA	*	no	*	*	NA	NAFLD/NASH
Tison, 2015	*	*	*	*	no	no	no	*	*	no	*	*	NA	9 NAFLD
Browning, 2004	*	*	*	*	no	no	no	NA	*	no	*	NR	NA	6 HCTG
Williams, 2011	*	*	*	*	no	no	no	NA	*	no	*	NR	NA	7 NAFLD/NASH
Loomba, 2015	*	*	NA	*	*	no	no	NA	*	no	*	NR	NA	7 NAFLD
Kim, 2013	*	*	*	*	no	no	no	NA	*	no	*	*	NA	8 Hepatic steatosis
Reddy, 2013	*	*	NA	no	no	no	no	NA	no	no	no	NA	*	3 NAFLD
North, 2012	*	*	*	*	no	no	no	NA	*	no	*	*	NA	8 NAFLD
Bril, 2014	*	no	NR	NR	no	no	no	NA	NR	*	NR	NA	*	3 NAFLD
Chen, 2009	no	no	NR	NR	no	no	no	NA	*	no	*	NR	NA	2 NAFLD
Corey, 2013	*	*	*	*	no	no	no	NA	*	no	*	*	NA	8 NAFLD/NASH
Garcia, 2015	*	*	NR	*	no	no	no	*	*	no	*	no	NA	6 NAFLD/NASH
Kallwitz, 2009	*	*	*	*	no	no	no	NA	*	no	*	*	NA	8 NAFLD/NASH
Setiawan, 2016	*	*	NA	*	no	no	no	NA	*	no	*	NA	NA	5 NAFLD
Stepanova, 2010	*	*	*	*	no	no	no	NA	*	no	*	*	NA	7 NAFLD/NASH
Solga, 2005	*	*	*	*	no	no	no	NA	*	no	*	*	NA	8 NAFLD/NASH
Severity Studies														
Author, year	1	2	3	4	5	6	7	8	9	10	11	12	13	14 Overall Score Outcomes assessed
Younossi, 2012	*	*	*	*	no	no	no	NA	*	no	no	*	NA	7 NAFLD/NASH
Williams, 2011	*	*	*	*	no	no	no	NA	*	no	*	NR	NA	7 NAFLD/NASH
Bril, 2014	no	NR	NR	NR	no	no	no	NA	NR	no	*	NR	NA	3 NAFLD
Garcia, 2015	*	*	NR	*	no	no	no	*	*	no	*	no	NA	6 NAFLD/NASH
Kallwitz, 2009	*	*	*	*	no	no	no	NA	*	no	*	*	NA	8 NAFLD/NASH
Solga, 2005	*	*	*	*	no	no	no	NA	*	no	*	*	NA	8 NAFLD/NASH

Prevalence Studies																
Author, year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Overall Score	Outcomes assessed
Campos, 2008	*	*	*	*	*	no	no	NA	*	no	*	*	NA	*	8	NASH
Corbin, 2013	*	*	NR	no	*	no	no	NA	*	no	*	NR	NA	*	6	Degree of steatosis
Ha, 2016	*	*	NR	*	no	*	*	NA	*	no	*	NR	NR	NR	7	Progression to NASH, decompensation, HCC, all-cause mortality
Hossain, 2009	*	*	NR	*	no	no	no	NA	*	no	*	*	NA	*	7	Degree of fibrosis
Lomonaco, 2011	*	*	NR	*	no	no	no	NA	*	no	*	*	NA	no	6	NASH severity (histologic score)
Mohanty, 2009	*	*	NA	*	no	no	no	NA	*	no	*	*	NA	*	7	NASH severity
Nelson, 2007	*	*	NA	*	no	no	no	NA	*	no	*	no	NA	*	6	Degree of fibrosis
Pimentel, 2016	*	*	NA	*	no	no	no	NA	*	no	*	*	NA	*	7	NASH/non-NASH
Rafiq, 2009	*	*	NR	*	no	*	*	NA	*	no	*	NR	NR	NR	7	overall survival
Tabibian, 2011	*	*	*	*	no	no	no	NA	*	no	*	*	NA	*	8	NASH severity
Verna, 2015	*	*	NR	*	*	no	no	NA	*	no	*	*	NA	*	8	Fibrosis severity
Outcomes Studies																
Author, year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Overall Score	Outcomes assessed
Ha, 2016 [‡]	*	*	NR	*	no	*	*	NA	*	no	*	NR	NR	NR	7	15-year cumulative incidence of cirrhosis, HCC, all-cause mortality
De Martini, 2014 [‡]	*	*	NR	*	no	no	*	NA	NR	no	NR	NR	NA	*	5	Cirrhosis, HCC, liver transplantation
Ditah, 2014 [‡]	*	*	NA	*	no	*	*	NA	NR	NR	*	NR	NR	NR	6	All-cause mortality
Stepanova, 2013	*	*	NR	*	no	*	*	NA	*	no	*	NR	NR	*	8	Liver-related and all-cause mortality
Yip, 2015 [‡]	*	no	NR	NR	no	NR	NR	NA	*	NR	NR	NR	NR	*	3	Cirrhosis, HCC, liver transplantation
Younossi, 2013	*	*	NA	*	no	*	*	NA	*	no	*	no	NR	NR	7	Overall survival, Cardiac-specific mortality and Liver-specific mortality

Key: An asterisk (*) indicates that the study met criteria NA = Not applicable; NR = Not reported.

[‡] abstract only