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Review

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Racial and ethnic disparities in metabolic dysfunction-associated steatotic liver disease

Reeti Gulati[1], Cynthia A. Moylan[2,3], Julius Wilder[2], Kara Wegermann[2]

[1]Internal Medicine, Duke University Hospital, Durham, NC 27710, USA.
[2]Department of Medicine, Division of Gastroenterology and Hepatology, Duke University, Durham, NC 27710, USA.
[3]Department of Medicine, Durham Veterans Affairs Medical Center, Durham, NC 27710, USA.

Correspondence to: Dr. Reeti Gulati, Internal Medicine, Duke University Hospital, 2301 Erwin Rd, Durham, NC 27710, USA. E-mail: reeti.gulati@duke.edu

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) has an increasing prevalence, morbidity, and mortality both within the United States and globally. Here, we review newer evidence demonstrating racial and ethnic disparities that exist in the incidence of MASLD in the United States Many studies demonstrate that Hispanic populations have the highest prevalence of MASLD within the United States, followed by non-Hispanic White populations and then non-Hispanic Black populations. In addition, we present the latest research investigating specific factors that contribute to these disparities, including genetics, environmental exposures, diet, physical activity, and socioeconomic disparities. Finally, we discuss future directions and interventions needed to increase knowledge of racial and ethnic disparities in MASLD and reduce future disparities. The necessary strategies include increasing diversity and documentation of race and ethnicity in MASLD clinical studies, and increased screening and preventative health education for MASLD in vulnerable populations.

Keywords: Metabolic, fatty liver disease, non-alcoholic, racial, ethnic, disparities

INTRODUCTION

This narrative review covers disparities by race and ethnicity in metabolic dysfunction-associated steatotic liver disease (MASLD). We first present recent epidemiologic studies and then discuss potential

contributors.

MASLD describes the abnormal accumulation of fat in the liver in the presence of at least one of five cardiometabolic risk factors: (1) body mass index (BMI) ≥ 23 kg/m^2 or waist circumference ≥ 90 cm for male and ≥ 85 cm for female; (2) fasting serum glucose ≥ 100 mg/dL or type 2 diabetes or treatment for type 2 diabetes; (3) blood pressure ≥ 130/85 mmHg or antihypertensive treatment; (4) triglycerides ≥ 150 mg/dL or lipid-lowering treatment; or (5) high-density lipoprotein (HDL) cholesterol ≤ 40 mg/dL for male and ≤ 50 mg/dL for female or lipid-lowering treatment[1]. MASLD is an umbrella term for a spectrum of diseases ranging from simple steatosis, in which patients do not have significant liver inflammation or damage, to steatohepatitis (MASH), in which fat accumulation causes oxidative stress leading to inflammation. MASLD is the most common cause of chronic liver disease in the developed world[2]. The global prevalence of MASLD is estimated to be 30 percent, with the highest prevalence in the Middle East and North Africa (26.5 percent each)[3]. The incidence of MASLD is increasing due to the rising incidence of obesity and diabetes mellitus[4]. The NHANES 1999-2018 survey found that the prevalence of MASLD in young adults in the United States increased from 9.98% in 1999 to 19.49% in 2018[5]. Based on predictive modeling, MASLD prevalence is likely to increase from 83.1 million cases in 2015 to 110.9 million by 2030[6]. In the United States, MASLD-related cirrhosis is currently one of the leading indications for liver transplantation, and annual medical costs of MASLD in the United States are estimated to be approximately $103 billion ($1612.18 per patient)[2]. In addition, from 2010-2019, the global all-age, age-standardized deaths from liver cancer related to MASLD increased faster than liver cancer deaths related to other etiologies[3].

Given the staggering prevalence of MASLD, it is important to determine which populations are at greater risk for the development and progression of MASLD. Unfortunately, effective risk stratification tools do not yet exist due to the heterogeneity and unpredictability of the natural history of MASLD. However, disparities by race and ethnicity have been observed. In this review, we aim to describe epidemiologic data supporting these disparities, and explore several possible contributors. This analysis focuses on newer evidence when available. We use the term MASLD, a new nomenclature as of June 2023 for non-alcoholic fatty liver disease (NAFLD)[1]. An important caveat is that previous studies identified patients according to the NAFLD definition. There is a significant overlap between NAFLD and MASLD, with both diagnoses requiring the presence of hepatic steatosis[7,8]. In MASLD, the presence of at least one cardiometabolic risk factor is required for the diagnosis[1]. Implementing this definition, a study investigated 1,333 patients at Swedish university hospitals with confirmed NAFLD and found that only 4 patients (0.3%) did not meet the criteria for a diagnosis of MASLD[7]. Similarly, utilizing proton-magnetic resonance spectroscopy, Song *et al.* recently reported a minimal difference in the prevalence of NAFLD (25.6%) and MASLD (26.7%) in 1,106 random persons from Hong Kong[9]. Studies such as these support the idea that previous data collected on NAFLD can be extrapolated to MASLD, given the large overlap. However, multi-society guidelines recommend the use of the term MASLD[1].

We use the terms Black, Hispanic, Asian, and White to describe race and ethnicity, as these are commonly reported in the literature. However, these terms are vague and overlook substantial heterogeneity in ancestry within groups. Most studies discussing race and ethnicity disparities in MASLD rely on self-reported data, which is often incomplete or poorly elaborated[10]. Better inclusivity of observational studies and clinical trials, as well as granular reporting of race, ethnicity, and sociodemographic factors, will hopefully lead to a better understanding of disparities in the future.

EPIDEMIOLOGY OF MASLD BY RACIAL AND ETHNIC GROUP

Higher prevalence of MASLD in Hispanic individuals in the United States

In the United States, Hispanic individuals have the highest prevalence of MASLD, followed by non-Hispanic White individuals and then non-Hispanic Black individuals[2,11,12] [Table 1]. Browning *et al.* used magnetic resonance spectroscopy to analyze a diverse longitudinal cohort and found that Hispanic individuals had a higher prevalence of MASLD compared to non-Hispanic White individuals and non-Hispanic Black individuals (45% *vs.* 33% *vs.* 24%); this study also found Hispanic individuals to have a higher prevalence of obesity and insulin resistance[13]. Studies from 2018 and onwards have continued to support this finding. A systematic review and meta-analysis published in 2018 analyzed 34 studies with a total of 368,569 unique patients in the United States and found that MASLD prevalence was highest in Hispanic individuals, intermediate in non-Hispanic White individuals, and lowest in non-Hispanic Black individuals (22.9% *vs.* 14.4% *vs.* 13.0%)[14]. This study also found that among individuals with MASLD, the risk of MASH was highest in Hispanic individuals and lowest in non-Hispanic Black individuals. A systematic review published in 2021 that analyzed 20 articles (mostly from the United States) found that the prevalence of MASLD is higher among Hispanic individuals, followed by non-Hispanic White individuals and Asian individuals, and lastly, non-Hispanic Black individuals[15]. This study also found that Hispanic ethnicity is a risk factor for developing MASLD and that non-Hispanic Black individuals have lower odds of developing MASLD. Similarly, data from the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN) found that of patients with biopsy-proven MASLD, the frequency of MASH varied by race and ethnicity: 63% in Hispanic individuals, 62% in non-Hispanic White individuals, 52% in non-Hispanic Black individuals, and 52% in Asians[16]. A review paper that summarized published evidence for disease disparities in the United States found that within 19 disease entities, including metabolic disorders, cancers, inflammatory diseases, dermatologic disorders, and infectious diseases, the prevalence of the disease is found in modest excess within Hispanic populations compared to non-Hispanic White populations, with most notable differences found in MASLD, diabetes, and obesity[17]. In a study of ICD codes for MASLD in the National Inpatient Sample, Adejumo *et al.* found that the largest rate of increase of admissions with MASLD was found among Hispanic individuals at 107/100,000 hospitalizations/year compared to White individuals at 80/100,000 hospitalizations per year and Black individuals at 75/100,000 hospitalizations/year[18].

Higher prevalence of MASLD among Mexican-American populations

"Hispanic" is a blanket term for patients with ancestry from countries that speak Spanish, and overlooks significant heterogeneity in race, ethnicity, and numerous other factors that may contribute to health outcomes. Studies have found that within Hispanic populations in the United States, the prevalence of MASLD is higher in those of Mexican origin[12]. A study published in 2020 analyzed 4,538 adult participants from the National Health and Nutrition Examination Survey (NHANES) from 2011-2016 in the United States found that MASLD prevalence was highest among Mexican Americans (48.4%), and lowest among non-Hispanic Black individuals (8.0%) and Asians (18.1%)[19]. Another study utilizing NHANES data from 2017-2018 investigated 3,190 adults (categorized as normoglycemic, prediabetic, or diabetic) and found that Mexican American men had the highest prevalence of severe MASLD (defined as controlled attenuation parameter [CAP] score > 290 dB/m) in the normoglycemic and diabetic populations compared to non-Hispanic White, non-Hispanic Black, and other Hispanic groups[20]. Similarly, among females, Mexican-Americans had the highest prevalence of severe MASLD among normoglycemic individuals. The review from 2021 analyzing 20 articles mentioned above found that in the United States population, Mexican-Americans had the highest prevalence of MASLD, followed by non-Hispanic White individuals and non-Hispanic Black individuals (21.2% *vs.* 12.5% *vs.* 11.6%)[15].

Table 1. Epidemiology of MASLD by racial and ethnic group: summary of findings

Key finding	Sources
In the United States, Hispanic individuals have the highest prevalence of MASLD, followed by non-Hispanic White individuals and then non-Hispanic Black individuals	[2,11-15]
Of patients with biopsy-proven MASLD, the frequency of MASH varies by race and ethnicity with highest frequency in Hispanic individuals, then non-Hlispanic White individuals, and then non-Hispanic Black individuals and Asian individuals	[16]
The largest rate of increase of hospital admissions with MASLD was found amongst Hispanic individuals, followed by non-Hispanic White individuals andthen non Hispanic Black individuals	[18]
Within Hispanic populations in the United States, the prevalence of MASLD is higlher in those of Mexican origin	[12,15,19, 20]
Similar trends are found among young adults and adolescent populatiorns with Hispanic individuals having a significantly higher prevalence of MASLD than non Hispanic individuals	[21,22]
Non-Hispanic Black individuals are less likely to develop MASLD tthan non-Hispanic White individuals	[25,26]

MASH: Metabolic Dysfunction-associated Steatohepatitis; MASLD: Metabolic dysfunction-associated steatotic liver disease.

Racial and ethnic distribution of MASLD among younger populations

Similar disparities in the prevalence of MASLD exist in children and adolescents. Data from the National Health and Nutrition Examination Survey between 2007 and 2016, including 4,654 adolescents and young adults aged 12 to 29 years old, found that among all age groups, Hispanic individuals had a statistically significant higher prevalence of MASLD than non-Hispanic White individuals and non-Hispanic Black individuals (38.3% *vs.* 22.4% *vs.* 14.0% among young adults aged 25-29 for example)[21]. This study also reported an increase in the prevalence of MASLD among the 18-24-year-old age group between 2007-2016, which was felt to be partially driven by increases among young Hispanic men. A similar study analyzing 209 children and adolescents (age 7-21 years old) found that individuals of Central American heritage were over 3 times more likely than non-Hispanic individuals to have MASLD after adjusting for socioeconomic factors and health behaviors[22]. An autopsy study in New York City examined liver specimens of 582 children 2-19 years old who died of unexpected causes[23] and found the highest rates of MASLD among White and Hispanic children (8.3% and 7.9%) with non-Hispanic Black children having the lowest prevalence of MASLD (1%). A cross-sectional study of the National Inpatient Sample (NIS) from 2004 to 2018 investigated MASLD-associated hospitalizations among age groups 0-17 years old[24] and reported an increase in pediatric hospitalizations with an ICD code for MASLD, with the highest rates among Hispanic patients compared to non-Hispanic White patients and non-Hispanic Black patients.

Distribution of MASLD within non-Hispanic Black and Asian American populations

It is important to acknowledge that Black and Asian individuals within the United States also have ancestries from various countries within Africa and Asia, respectively. Specific ancestry thus likely impacts MASLD prevalence within these groups. “Black” is a blanket term for individuals whose origins are in any of the Black racial groups of Africa, but it is also broad and includes those of Caribbean descent if they identify as such. “Asian American” is a blanket term for patients with ancestry from any country in East Asia, Southeast Asia, or the Indian subcontinent including Cambodia, China, Bangladesh, India, Japan, Korea, Pakistan, Thailand, Vietnam, and many more. Given the lack of available data on MASLD variation within Black and Asian populations, we cannot provide a review of this topic but can provide a summary assessing these populations as a whole.

Substantial evidence supports that non-Hispanic Black individuals are less likely to develop MASLD than White individuals. For example, a study with 226 total individuals found that although the prevalence of type 2 diabetes mellitus was similar between the two groups, White individuals were significantly more likely than Black individuals to have biopsy-proven MASLD[25]. Interestingly, type 2 diabetes mellitus was associated with an increased risk of MASLD only in White individuals. A retrospective cohort study

published in 2022 investigated the electronic health records of 139,336 patients in the United States and found that the rate of MASLD diagnosis was higher in non-Hispanic White patients with metabolic syndrome compared to non-Hispanic Black patients with metabolic syndrome, particularly among females and patients aged 18-39 years and 40-59 years[26]. One study analyzing 134 subjects compared non-Hispanic Black individuals to non-Hispanic White individuals and found that while Black individuals had a lower intrahepatic triglyceride content, the prevalence of metabolic associated steatohepatitis (MASH) [formerly called non-alcoholic steatohepatitis (NASH)] was even among the two groups in patients who had MASLD[27]. This study showed that once MASLD develops, MASH develops as frequently and as severely in Black individuals as compared to White individuals with MASLD. The prevalence of MASLD has also been increasingly investigated among Asian American populations. Utilizing data from NHANES from 2011-2016, a study found Asian Americans to have a lower prevalence of MASLD than non-Hispanic White individuals (18.3% *vs.* 28.4%)[28].

Limitations of determining racial and ethnic distribution of MASLD

Several limitations affect the currently available evidence on the prevalence of MASLD in different racial and ethnic groups. Incomplete documentation is one factor. A meta-analysis published in 2020 investigated the inclusion of racial and ethnic minority groups in 38 North American clinical trials for MASLD from 2005 to 2019[10]. This study found that documentation of racial and ethnic demographic data occurred in less than half of the trials. More specifically, less than half of the trials (45%) included documentation regarding the participation of Hispanic individuals. When documentation does occur, it is generally self-reported race or ethnicity and often in less descriptive categories such as "Hispanic." Underrepresentation is also a significant problem in clinical trials. Of the total participants in all trials included in the study mentioned previously, only 11.6 percent were reported to be Hispanic. While the study did show that enrollment of Hispanic individuals increased over time (comparing trials from before and after 2015), enrollment lagged behind the percentage of Hispanic individuals in the US population. Black patients are even more poorly represented in clinical trials, as extensively documented in the literature from cardiology, oncology, and other fields. Another study that points towards limitations of our current epidemiology data of MASLD is a longitudinal observational study called TARGET-NASH published in 2021[29]. This study prospectively followed a cohort of 3,474 pediatric and adult patients with MASLD in the United States for 5 years. The study found that two-thirds of the patient population with MASLD did not have a liver biopsy, and those without a biopsy were more likely to be non-White, older, or have a normal ALT. Since a large amount of the existing literature on MASLD is derived from data from liver biopsies, this study brings up the concern that the reported epidemiology of MASLD may not be fully accurate as non-White patients may be less likely to have had a liver biopsy. Other limitations within studies determining the racial and ethnic distribution of MASLD include confounding factors such as sex, BMI, and other demographic characteristics. For example, in the study by Browning *et al.*, the prevalence of MASLD in Hispanic and White men was similar (45% *vs.* 42%), so the overall difference may be driven by Hispanic and White women (45% *vs.* 24%)[13]. Similarly, when matching subjects for BMI, a significant difference was not seen within insulin resistance or the presence of MASLD between Hispanic and White individuals[30]. Further research is needed to determine racial and ethnic incidence patterns without the influence of confounding factors.

Disparities in prognosis and detection of MASLD by racial and ethnic groups

Studies have demonstrated a poorer prognosis for Hispanic individuals with MASLD compared to others. Hispanic individuals in the United States experience the greatest burden of MASLD-related hepatocellular carcinoma (HCC) compared with other ethnicities[31,32]. Interestingly, United States-born Hispanic individuals are at a higher risk for MASLD-related HCC compared with non-United States-born Hispanic individuals[33]. On the contrary, foreign-born Asians are at a higher risk for MASLD-related HCC compared

with United States-born Asians. In addition, Hispanic and White patients are more likely to be diagnosed with cirrhosis at an age younger than 40 years compared to non-Hispanic Black patients[34]. A study utilizing the NIS analyzed all adult hospitalizations from 2016 to 2018 with MASH and found that non-Hispanic Black patients were less likely to have cirrhosis and liver disease-related complications, but had overall worse hospital mortality, longer lengths of stay, and higher hospital costs than White patients[35]. Multiple studies have been done investigating the significance of racial and ethnic disparities in patients undergoing liver transplantation for MASLD-related HCC. Couto *et al.* found that Hispanic patients were at increased risk for needing liver transplant for MASLD-related HCC, which may be attributed to Hispanic individuals with HCC having more co-morbidities such as diabetes and hypertension than non-Hispanic individuals with HCC[36]. It is important to note that while the impact of MASLD on certain populations' risks of other associated diseases such as colorectal cancer has been established thoroughly, there is a lack of research on these phenomena in certain racial and ethnic groups[37]. Further research is needed to determine whether MASLD impacts all populations similarly.

An additional limitation results from significant racial and ethnic disparity around the detection of MASLD. Although liver biopsy is the gold standard for diagnosis and assessment of the severity of MASLD, its use is limited due to its risks, invasiveness, and cost[38]. Due to this, many noninvasive clinical scores including MASLD fibrosis score (NFS), BARD, Fibrosis-4 (FIB-4), and aspartate aminotransferase-to-platelet ratio index (APRI) have been developed and are utilized regularly to predict advanced fibrosis in patients with MASLD. Some of these scores can efficiently use demographic and laboratory test information from patients to risk-stratify patients with MASLD and help guide clinical decision-making. A study published in 2021 investigated the performance of the NFS, BARD, FIB-4, and APRI in a predominantly Hispanic patient population and found that while the area under the receiver operating characteristic curve (AUROC) was similar for these scores in Hispanic and non-Hispanic White populations, they had uniformly lower negative predictive values among the Hispanic study population[38]. This study suggests that widely used non-invasive fibrosis scores may not accurately rule out advanced liver fibrosis in Hispanic populations, most likely due to differences in the underlying prevalence of disease. Studies have also found disparities in MASLD diagnostic markers for other ethnicities. De Silva *et al.* noted that NFS, APRI, FIB-4, and AST/ALT ratio were less sensitive for detecting advanced liver fibrosis in South Asian populations compared to White populations[39]. These studies highlight disparities in detecting and staging MASLD, which may contribute to our understanding of its epidemiology.

POTENTIAL CONTRIBUTORS OF RACIAL AND ETHNIC DISPARITIES IN MASLD

After recognizing the existence of racial and ethnic disparities in the prevalence, severity, and natural history of MASLD in the United States, an important next step in decreasing these disparities is discovering why they exist. Based on available evidence, racial and ethnic disparities in MASLD are likely multifactorial, resulting from genetics, environmental exposures, diet/physical activity, healthcare factors including access to primary care and sub-specialists, provider bias, and socioeconomic disparities, including those that influence health-promoting activities such as exercise [Figure 1] [Table 2]. While the relative contribution of each factor is unclear, they appear interconnected in promoting the development and progression of MASLD. The importance of each factor likely varies by race and ethnicity and over one's lifetime. The purpose of presenting various potential factors that contribute to these disparities within MASLD is to promote discussion regarding efforts and initiatives that can be made to decrease the burden of MASLD within specific populations that are at higher risk for the disease than others.

Contribution of genetics to racial and ethnic disparities within MASLD

Multiple genome-wide association studies (GWAS) have discovered and validated specific genetic

Table 2. Potential contributors of racial and ethnic disparities in MASLD: summary of findings

Key finding	Sources
The *PNPLA3* I148M allele is found most commonly in Hispaniic individuals, then European individuals, and then non-Hispanic Black individuals	[42,43]
Within Hispanic populations, the *PNPLA3* I148M allele is associiated with elevated levels of AST, ALT, FIB-4 score, and increased risk of MASLD	[44-48]
The frequency of the *PNPLA3* I148M allele varies among Hispanicc groups, with Mexican individuals having the highest frequency, followed by South Americans, Central Americans, Puerto Ricans, Cubans, and lastly Dominicans	[48]
Within Hispanic populations, low plasma concentrations of very long chain n-3 polyunsaturated fatty acids and very long chain saturated fatty acids are rongly associated with advanced liver fibrosis	[51,52]
There is a positive association between exposures including arsenic and mercury and risk of MASLD, with the highest exposure seen among Mexican Americans and those of Hispanic ethnicity	[58,59]
Behavioral risk factors, including high-fat, high-carbohydrate diet and sedentary behavior, are risk factors for all populations to develop MASLD,regardless of race and ethnicity	[5,63-66,71-76]
Socioeconomic factors, including income, education, and health insurance status, likely play a role in contributing to racial and ethnic disparities in MASLD	[80-84]

AST: aspartate aminotransferase; ALT: alanine aminotransferase; FIB-4: fibrosis-4 index; MASLD: Metabolic dysfunction-associated steatotic liver disease.

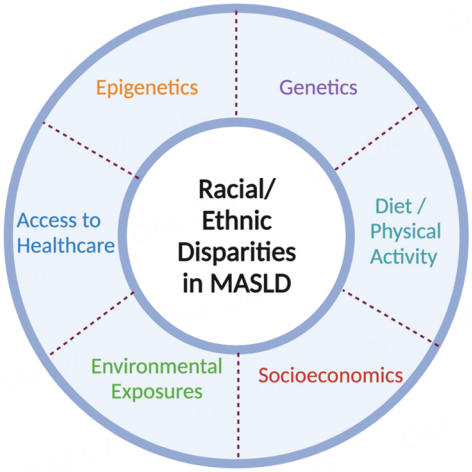

Figure 1. Current evidence supports that a variety of factors contribute to the racial and ethnic disparities in MASLD. This figure is not meant to be proportional - the relative contribution of each factor to one's risk for MASLD is unknown, and this likely varies by race and ethnicity, and also changes over one's lifetime.

polymorphisms associated with MASLD risk and progression. The most notable single nucleotide polymorphism (SNP) associated with MASLD is the gene that codes for *PNPLA3*. Patatin-like phospholipase domain-containing protein 3 regulates lipids in hepatocytes and stellate cells[40]. *PNPLA3*'s role within hepatocytes consists of hydrolyzing triglycerides and catalyzing the transfer of the polyunsaturated fatty acids from di- and tri-acylglycerols to phosphocholines, allowing it to assist with remodeling phospholipids of lipid droplets[41]. *PNPLA3* is typically degraded via ubiquitylation of lysine and thus becomes targeted for proteasomal degradation. In 2008, Romeo *et al.* conducted a GWAS of the Dallas Heart Study cohort and discovered an association between the SNP at rs738409 (also known as the G allele or I148M), which codes for guanine instead of cytosine and thus methionine in place of isoleucine, and MASLD independent of BMI, diabetes, and alcohol use. This I148M allele is less accessible for degradation by ubiquitylation and thus leads to increased retention of triglycerides and polyunsaturated fatty acid-enriched lipid droplets, which increases the accumulation of liver fat. In Romeo *et al.*, among the North American cohort of patients, the I148M allele was most common in Hispanic individuals, intermediate in

individuals of European descent, and least common in non-Hispanic Black individuals[42]. This same study found that another gene variant of *PNPLA3*, rs6006460, which results in the accumulation of less hepatic fat than average, was expressed in 10 percent of Black individuals compared to less than 1 percent in White or Hispanic individuals. Thus, this variant of *PNPLA3* may play a role in non-Hispanic Black populations having a lower observed prevalence of MASLD.

The 1,000 Genomes Project Study, published in 2015, utilized whole-genome sequencing in 2,504 individuals from 26 populations and found that the distribution of the *PNPLA3* I148M allele varies globally, with the M variant being most common in populations of Hispanic and East Asian ancestry[43]. Multiple studies support that the *PNPLA3* I148M allele (rs738409) variant is associated with increased levels of ALT, AST, and FIB-4 score in Hispanic individuals, including a study of 503 Hispanic adult participants from the Arizona Insulin Resistance (AIR) registry and a study published in 2023 of 8,739 adult Hispanic participants from the Bio*Me* biobank[44,45]. A study from 2019 specifically examined Mexican-American individuals and found that multiple variants of the *PNPLA3* gene including rs4823173, rs2896019, and rs228113 were associated with elevations in ALT and AST, thus highlighting a role for other variants of *PNPLA3*[46]. Rutledge *et al.* additionally found that of all the individuals, those with ancestry from Ecuador and Mexico had the highest outpatient ALT, AST, and FIB-4 values, and these were the same individuals who had the highest frequency of the *PNPLA3* I148M allele variant[45]. Walker *et al.* utilized an electronic health records dataset of more than 27,000 individuals with genetic data from a multiethnic biobank and found that the *PNPLA3* I148M allele variant was associated with increased risk of MASLD and earlier age of MASLD diagnosis, with both phenomena having the strongest effects within Hispanic individuals[47]. Thus, these studies confirm that Hispanic individuals with this variant are significantly vulnerable to MASLD.

A study published in 2019 utilized data from the Hispanic Community Health Study/Study of Hispanic individuals to investigate the association of MASLD-associated genetic variants and continental ancestry with suspected MASLD, which was defined by an unexplained increase in levels of aminotransferases and FIB-4 score[48]. Upon analyzing data from 9,432 Hispanic individuals from Chicago, Bronx, Miami, and San Diego, the study found that the *PNPLA3* I148M allele was an independent predictor of increased ALT levels in United States Hispanic individuals. Interestingly, the frequency of the *PNPLA3* I148M allele varied within Hispanic groups of specific nationalities, with Mexican individuals having the highest frequency (51.7%), followed by South American individuals (50.8%), Central American individuals (47.8%), Puerto Rican individuals (35.6%), Cuban individuals (28.5%), and lastly Dominican individuals (2.6%). Thus, this PNPLA3 I148M allele may play a role in explaining why among Hispanic individuals, those with Mexican ancestry have the highest incidence of MASLD. This same study also found that continental ancestry may play a role in an individual's risk for MASLD as well - American ancestry had a positive association with the level of ALT, whereas African and European ancestry were inversely associated with the level of ALT.

Recent research has also investigated the role of other genes in the high prevalence of MASLD within Hispanic populations. A study published in 2021 utilized a large multiethnic cohort to determine whether previously identified genetic variants associated with MASLD within White populations were also associated with MASLD within other ethnicities[49]. The study analyzed genes including *PNPLA3, TM6SF2, GATAD2A, GCKR, SUGP1, MBOAT7*, and others and found that the highest percentage of replication was found in Hispanic individuals (43%), followed by Japanese Americans (37%), and Native Hawaiians and non-Hispanic Black individuals (less than or equal to 10%). A study published in 2020 analyzed genotypes of the *HSD17B13* gene, an enzyme shown to be upregulated in individuals with MASLD, within 9,342 United States Hispanic individuals[50]. This study found that the loss-of-function rs72613567:TA allele was associated with lower rates of suspected MASLD and lower FIB-4 scores among Hispanic populations. In

addition, the study found that the rs72613567:TA allele was associated with lower rates of suspected MASLD in Hispanic individuals with the *PNPLA3* I148M allele. Rutledge *et al.* also investigated the role of *HSD17B13* in MASLD in Hispanic populations and found a similar trend where *HSD17B13* variants which were predicted to have loss-of-function were associated with reduced ALT, AST, and FIB-4 levels[45]. In fact, this study found that the same Hispanic individuals who had the highest outpatient ALT, AST, and FIB-4 levels and were found to have the highest frequency of the PNPLA3 G allele variant also had the lowest frequency of the *HSD17B13* variants predicted to have loss-of-function. The study concluded that the *HSD17B13* loss-of-function variants mitigated the increase in ALT that came about with the *PNPLA3* G allele, thus further supporting the protective role of HSD17B13 in Hispanic individuals with MASLD.

Studies investigating lipid profiles in Hispanic populations with MASLD

Recent genetic studies have dived into other potential genetic explanations for the higher incidence of MASLD within Hispanic populations. A study published in 2021, which analyzed plasma fatty acid concentrations in 116 Hispanic subjects from South Texas, found that low plasma concentrations of very long-chain n-3 polyunsaturated fatty acids and very-long-chain saturated fatty acids were strongly associated with advanced liver fibrosis in this population[51]. This finding was supported by a separate targeted lipidomic profiling study published in 2022 in Hispanic individuals and non-Hispanic White individuals with biopsy-confirmed MASLD[52]. The authors reported that MASLD is associated with diminished long-chain polyunsaturated fatty acids in Hispanic populations, along with lower lipoxygenase and higher soluble epoxide hydrolase activities in Hispanic individuals compared to non-Hispanic White individuals. Another study published in 2021 compared untargeted plasma metabolomics profiles for primary metabolism, complex lipids, choline, and related compounds between a group of Hispanic and White subjects[53]. This study found that independent of obesity, Hispanic individuals had higher plasma triglycerides, acylcarnitines, and free fatty acids. In addition, MASLD progression was associated with higher free fatty acids and lysophospholipids, greater hepatic triglyceride content, and higher plasma triglyceride concentrations in Hispanic individuals, thus suggesting more significant alterations in lipid metabolism in Hispanic individuals with MASLD progression. These studies each contribute to our current understanding of genetic factors associated with a higher risk of MASLD presence and severity.

Genetic studies investigating MASLD in pediatric populations

Recent research has also been conducted investigating genetic variants in pediatric populations with MASLD, and how these may vary among different ethnicities/races. A GWAS including 624,297 SNPs was performed in 234 Hispanic children (up to 18 years of age) with biopsy-proven MASLD in the Nonalcoholic Steatohepatitis Clinical Research Network Studies. The study found 10 SNPs associated with BMI z score, including 1 within *CAMK1D* which plays a role in liver gluconeogenesis. In addition, 9 novel variants were identified and associated with insulin resistance - 6 associated with HOMA-IR and 3 associated with HbA1c[54]. Other studies have investigated whether genetic variant trends found in adults are also seen in children. The rs626283 polymorphism in the *MBOAT7* gene has been associated with MASLD in adults, which is believed to be due to increased intrahepatic triglyceride content and inflammation. A study published in 2018 investigated this association within a multiethnic cohort of obese children and adolescents and found that this rs626283 variant in the *MBOAT7* gene was associated with MASLD in non-Hispanic White obese children and adolescents but not among Hispanic and Black children and youth, thus showing genetic variation at the pediatric level that does not exist at the adult level[55].

Studies have also started investigating the association between certain hormones and antibodies with MASLD in Hispanic pediatric populations. Since previous studies had found an association between elevated thyroid-stimulating hormone (TSH) levels and MASLD in non-Hispanic White children, a study was published in 2020 that investigated the association between elevated TSH and MASLD in Hispanic

children with biopsy-proven MASLD[56]. Multivariate analyses controlling for age, sex, and severity of obesity found a significant association between elevated TSH and MASLD. This association has been found in both pediatric and adult Hispanic and non-Hispanic populations; thus, this association does not currently appear to be race-specific. A study was published in 2022 that analyzed antinuclear antibody (ANA) status in 38 Hispanic children with a histologic diagnosis of MASLD[57]. The analysis found that in this population, a positive ANA result is associated with insulin resistance and lower HDL levels and thus concluded that ANA may be more indicative of pro-inflammatory activity of adipose tissue rather than an autoimmune hepatitis process. Although this association between ANA and insulin resistance was found, it cannot currently be assumed that the association is driven by race or ethnicity. Each of these studies contributes to understanding the pathogenesis of MASLD in Hispanic populations, a process that is likely to begin at an early age. Further research is needed to elucidate the nuances of how these hormones and antibodies influence the pathogenesis of MASLD within various populations.

Contribution of environmental exposures to increased predominance of MASLD

Although the exact mechanism is unknown, environmental exposures are believed to play a role in the pathogenesis of MASLD. More research has been conducted recently, including experiments among animals, identifying an association of exposures to mercury and arsenic with MASLD. Frediani *et al.* investigated 8518 multiethnic individuals from the National Health and Nutrition Survey (2005-2014) and found that there was a positive association between urinary arsenic exposure level and risk of MASLD among United States adolescents and adults, and interestingly, the association was the highest among Mexican Americans[58]. Similar effects have been found with other exposures. A study published in 2018 of 944 adolescents found that individuals with higher quartiles of exposure to bisphenol-A (BPA), a chemical used in plastic manufacturing, had an increased risk of suspected MASLD, especially those of Hispanic ethnicity[59]. One's risk of suspected MASLD was defined by meeting certain thresholds of ALT and BMI, and evidence of insulin resistance. On the other hand, Chen *et al.* analyzed data from 6,389 adolescents (12-17 years old) from the NHANES (1999-2014) and found a positive association between blood mercury exposure and risk of MASLD, which was highest among non-Hispanic White individuals[60]. Cadmium is another heavy metal exposure previously associated with MASLD[61]. A study from 2022 analyzing 423 soil samples from the southern United States found that as the percentage of non-White populations increased in an area, so did the concentration of metals in the soil including arsenic and cadmium, suggesting that populations of minority races and ethnicities have a greater risk of exposure to these metals[62]. These recent studies highlight a variety of environmental exposures that may play an important, yet underappreciated role in individuals developing MASLD, and different exposures may make certain populations more vulnerable to MASLD than others.

Contribution of health behavioral factors to predominance of MASLD

As the global incidence of obesity and diabetes mellitus increases, so does the global incidence of MASLD[4]. Obesity is a major risk factor for MASLD, and both body mass index and waist circumference have been shown to be positively correlated with the presence of MASLD and its progression[5,63]. It is well documented that patients with MASLD in their 40s to 60s are likely to be obese[64]. While the risk of obesity is multifactorial, specific behavioral risk factors among patients with MASLD, including fast food consumption, infrequent physical activity, and sedentariness, are associated with more obesity[65,66]. Several different diets have been implicated including diets high in fat and carbohydrates, which promote liver fat deposition via mechanisms including mitochondrial defects and endoplasmic reticulum and oxidative stress[67,68]. Consumption of red and processed meat and MASLD have been inversely related, while consumption of sugar-sweetened beverages is associated with a higher prevalence of MASLD, the presence of MASH, and a higher degree of fibrosis[69,70]. Regardless of race and ethnicity, these dietary behaviors increase one's risk of developing MASLD, but whether they impact one race or ethnicity more so than

others remains less well known.

Sedentary behavior among patients is not only associated with obesity, but also with MASLD, and this has been demonstrated in various populations[66]. Utilizing the 2007-2016 United States NHANES, Kim *et al.* included a group of 24,588 multiethnic individuals and found that sedentary behavior is an independent predictor of MASLD, and that physical activity of 150 minutes or more per week demonstrated 40 percent lower odds of MASLD[71]. Among a group of 2,892 multiethnic adults in the United States, with a 35.6% prevalence of MASLD, Heredia *et al.* found that high adherence to United States dietary recommendations and more physical activity were associated with reduced odds of MASLD[72]. In a separate study, Heredia *et al.* investigated Hispanic adults from the 2017-2018 NHANES and found that higher levels of physical activity were associated with a lower risk of MASLD[73]. Television viewing time was found to be independently associated with a higher fatty liver index in Finnish adults[74]. Similarly, device usage time, including computers and mobile devices, was found to be associated with increased odds of MASLD in Chinese adults[75]. Besides the obvious benefit of weight loss, physical activity and exercise reduce one's risk of MASLD by improving peripheral insulin sensitivity, increasing very-low-density-lipoprotein clearance which enables the liver to export triglycerides, and also by improving appetite control[76].

These behavioral risk factors, including high-fat, high-carbohydrate diet and sedentary behavior, are risk factors for all populations to develop MASLD, regardless of race and ethnicity. Understanding barriers to health-promoting behaviors, which include Mediterranean, high-protein, and low-carbohydrate diets and increased physical activity, in all populations vulnerable to MASLD will allow the design of targeted interventions.

Contribution of epigenetics to predominance of MASLD

Epigenetics have been found to play a significant role in the development of MASLD. There is increasing evidence that maternal pre-pregnancy obesity, diabetes, weight gain during pregnancy, and gestational diabetes are associated with greater amounts of fatty acids in the fetus and MASLD in childhood[77]. In addition, maternal and paternal obesity are associated with DNA methylation changes in newborn cord blood that are not seen in newborns of non-obese parents. Studies have found that maternal obesity, diabetes, or Western diet consumption leads to an unfavorable intrauterine environment in which hepatic mitochondrial function in the fetal liver is more vulnerable to damage[78]. These exposures can thus bring about fetal metabolic reprogramming via epigenetic mechanisms, which contribute to the risk of MASLD in the child's lifetime. The prevalence of gestational diabetes is two to three times higher in Hispanic populations than in the general population, which may contribute to an increased prevalence of MASLD in Hispanic populations[79]. Populations with obesity and gestational diabetes are more likely to influence their offspring's genes and increase their risk of developing obesity and metabolic syndrome as well. This contributes to a perpetual cycle as one generation increases the risk of MASLD in the next generation. Determining populations with these risk factors can help determine which populations are more vulnerable to MASLD developing within their offspring as well.

Contribution of socioeconomic disparities to racial and ethnic disparities in MASLD

Given how interconnected the risk of MASLD is to factors such as diet quality, time and energy for physical activity, and access to preventative healthcare as discussed above, it is therefore logical that socioeconomic disparities play a role in racial and ethnic disparities within MASLD. Data from the United States Centers for Disease Control and Prevention has previously found that within United States populations, higher socioeconomic status is associated with less obesity prevalence, and vice versa[80]. The same trend has been found specifically among Hispanic individuals, as higher household income and higher educational attainment are both associated with a lower risk of obesity and a greater chance of weight loss[81].

Giammarino *et al.* specifically investigated the relationship between socioeconomic deprivation and MASLD. After retrospectively reviewing the electronic medical records of 1,430 patients in a large tertiary healthcare network in New York, their analysis found a significant association between four or more socioeconomic parameters in predicting MASH[82]. The areas with socioeconomic factors found to predict MASH and associated with greater severity of MASH included areas with public healthcare versus private, higher percentage of foreign-born individuals, higher percentage without a car, and crowded housing units. This study found that areas with higher social deprivation index (SDI), i.e., more impoverished areas, had more Black and Hispanic populations. Poverty also increases one's risk of harmful exposures, including metals such as cadmium and arsenic that are associated with the development of MASLD as discussed previously. The study from 2023 analyzing 423 soil samples within the southern United States found that for every 10 percentiles of increase in poverty rank, the concentration of cadmium in the soil increased significantly by 4.7 percent[62]. Individuals' socioeconomics can increase their risk of harmful exposures and also distance them from healthy resources. A significant percentage of Hispanic individuals (15% *vs.* 11% of non-Hispanic White individuals) in the United States live in lower-income communities where the nearest grocery market can be up to 10 miles away. This may contribute to poor diet quality and the development of metabolic syndrome features and MASLD.

Significant disparities by race and ethnicity are seen in access to healthcare. The United States Census Bureau from 2022 revealed that Hispanic people in the United States have the highest uninsured rate in the nation at 17.7%, whereas non-Hispanic White people have an uninsured rate of 5.7%. A lack of health insurance can play a role in increasing one's risk for obesity and thus MASLD in a variety of ways, including lower utilization of preventative healthcare to reduce metabolic risk factors such as hypertension, diabetes mellitus, hyperlipidemia, lower utilization of bariatric surgery, and also lower use of weight-reducing medications[83]. In addition, studies in the past have shown that lack of health insurance may lead to increased weight gain as a side effect from older, less expensive medications due to not being able to use the newer, more expensive options[84]. Not only can lack of insurance affect one's risk of developing MASLD, but also one's prognosis with MASLD. Adejumo *et al.* investigated hospitalizations with ICD codes for MASLD from 2007-2014 in the United States and found that uninsured patients hospitalized with MASLD had higher mortality, longer length of stay, and poorer discharge disposition than the privately insured, thus implying that one's insurance status does impact their disease course[18].

CONCLUSION

Although it was previously known that racial and ethnic disparities exist within the distribution of MASLD, this narrative review shares recent literature that summarizes and elucidates these disparities. Recent studies show that within the United States, Hispanic populations have the highest incidence of MASLD and among Hispanic populations, those of Mexican origin have the greatest burden of MASLD. An increasing amount of research has also been conducted to determine why these disparities exist. What is clear is that there is not a single factor driving MASLD disparities but a variety of factors that contribute to increasing Hispanic individuals' risk for MASLD. These include genetics, environmental exposures, health behaviors, and socioeconomic disparities.

There are a variety of future steps to be taken to better understand and reduce these disparities. A major limitation of interpreting racial and ethnic disparities of MASLD reflects the lack of inclusion of diverse populations in observational, epidemiologic, and interventional trials in MASLD and the lack of appropriate race and ethnicity documentation. In addition, there are limitations to some of the standard diagnostic markers used for MASLD when it comes to certain races and ethnicities, thus inhibiting us from detecting MASLD accurately in individuals of all backgrounds. It is imperative that going forward, efforts be made to

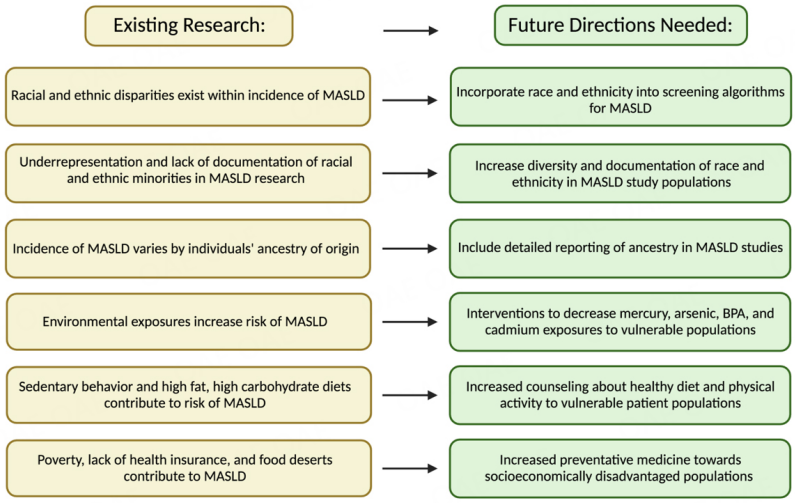

Figure 2. Current research demonstrates a variety of factors that contribute to the racial and ethnic disparities within MASLD. Future directions including further research, public health and environmental interventions, and increased preventative medicine are needed to help reduce these disparities.

ensure that research studies for MASLD include diverse study populations to accurately determine its incidence, severity, and prognosis among all races and ethnicities. In addition, developments need to be made in the specificity and sensitivity of diagnostic markers used for MASLD and advanced fibrosis for all races and ethnicities so that no diagnosis is missed. As our narrative review reflects, increasing evidence supports that not only does one's race and ethnicity affect the risk for MASLD, but so does one's ancestry of origin. The incidence of MASLD and the incidence of the PNPLA3 G allele within Hispanic individuals in the United States varies greatly depending on geography-specific ancestry. This is a growing field of research, but further research is needed to truly understand how a certain population's ancestry impacts their risk for MASLD, and the trends that exist within Hispanic populations of different ancestries. In addition, there is currently a lack of evidence about the ethnic variation of MASLD within Black and Asian populations, so the prevalence of MASLD within different ancestries needs to be studied within those populations as well. The detailed reporting of ancestry in clinical studies of MASLD would be an important first step.

Ultimately, the purpose of recognizing disparities is to help resolve the disparities. Since existing literature has recognized that Hispanic populations are at higher risk for MASLD and that various factors exist that contribute to their higher risk, future directions include developing interventions and strategies that not only help target these vulnerable populations for diagnosis but also for prevention and management [Figure 2]. Race and ethnicity should likely be factors in screening algorithms for MASLD. The genetic studies conducted are important in helping recognize which individuals are at higher risk for developing MASLD. Environmental interventions should be made to help protect populations who are exposed to substances such as mercury and BPA that increase their risk for MASLD. Public health interventions should be made for all populations to increase education to eat healthier diets (such as Mediterranean, high-protein, and low-carbohydrate diets) and be more physically active, as poor diets and sedentary behavior increase the risk of MASLD within all races and ethnicities. Such education should be designed in a way that centers on and values a population's cultural identity to ensure that it reaches Hispanic populations, given the burden of MASLD in this group. Lastly, preventative medicine should be applied especially among those who have socioeconomic disadvantages to reduce their metabolic risk factors.

DECLARATIONS

Authors' Contributions

Conducted literature review and writing of the manuscript: Gulati R
Contributed to the conception of the review and editing of the manuscript: Wegermann K
Contributed to the editing of the manuscript: Moylan CA, Wilder J

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Consent for Publication

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