

Gender and racial differences in nonalcoholic fatty liver disease

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Received November 15, 2013 Revised: December 14, 2013

Accepted: April 9, 2014

Published online: May 27, 2014

Abstract

Due to the worldwide epidemic of obesity, nonalcoholic fatty liver disease (NAFLD) has become the most common cause of elevated liver enzymes. NAFLD represents a spectrum of liver injury ranging from simple steatosis to nonalcoholic steatohepatitis (NASH) which may progress to advanced fibrosis and cirrhosis. Individuals with NAFLD, especially those with metabolic syndrome, have higher overall mortality, cardiovascular mortality, and liver-related mortality compared with the general population. According to the population-based studies, NAFLD and NASH are more prevalent in males and in Hispanics. Both the gender and racial ethnic differences in NAFLD and NASH are likely attributed to interaction between environmental, behavioral, and genetic factors. Using genome-wide association studies, several genetic variants have been identified to be associated with NAFLD/NASH. However, these variants account for only a small amount of variation in hepatic steatosis among ethnic groups and may serve as modifiers of the natural history of NAFLD. Alternatively, these variants may not be the causative variants but simply markers representing a larger body of genetic variations. In this article, we provide a concise review of the gender and racial differences in the prevalence of NAFLD and NASH

in adults. We also discuss the possible mechanisms for these disparities.

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Key words: Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis; Race; Gender; Prevalence; Genetic polymorphism

Core tip: According to the population-based studies, nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are more prevalent in males and in Hispanics. Both the gender and racial ethnic differences in NAFLD and NASH are likely attributed to interaction between environmental, behavioral, and genetic factors. In this article, we provide a concise review of the gender and racial differences in the prevalence of NAFLD and NASH in adults. We also discuss the possible mechanisms for these disparities.

Pan JJ, Fallon MB. Gender and racial differences in nonalcoholic fatty liver disease. *World J Hepatol* 2014; 6(5): 274-283 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v6/i5/274.htm> DOI: <http://dx.doi.org/10.4254/wjh.v6.i5.274>

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is highly associated with obesity and insulin resistance (IR) and represents a spectrum of liver injury ranging from simple steatosis with a more benign course to nonalcoholic steatohepatitis (NASH) which may progress to advanced fibrosis and cirrhosis^[1,2]. According to the National Health and Nutrition Examination Survey (NHANES), 33.8% and 23.7% of the United States (US) adults are obese and have metabolic syndrome, respectively^[3,4]. Due to the worldwide epidemic of obesity, NAFLD has become the most common cause of elevated liver enzymes with

Table 1 Prevalence rates of nonalcoholic fatty liver disease from population-based studies

Ref.	Study population	n	Definition of NAFLD	Prevalence of NAFLD				
				Overall	NHW	Hispanic	NHB	Others
Ruhl <i>et al</i> ^[11]	NHANES III (1988-1994)	5724	ALT ¹	2.8%	2.6%	8.4%	1.9%	3.1%
Clark <i>et al</i> ^[12]	NHANES III (1988-1994)	15676	ALT or AST ²	5.4%	4.8%	9.9%	4.2%	
Browning <i>et al</i> ^[13]	Dallas Heart Study	2287	MRS ³	31%	33%	45%	24%	
Ioannou <i>et al</i> ^[15]	NHANES (1999-2002)	6823	ALT or AST ⁴	8.1%				
Younossi <i>et al</i> ^[17]	NHANES III (1988-1994)	11613	Ultrasound	18.8%				
Lazo <i>et al</i> ^[18]	NHANES III (1988-1994)	12454	Ultrasound	19%	17.8%	24.1%	13.5%	
Schneider <i>et al</i> ^[19]	NHANES III (1988-1994)	9675	Ultrasound		12.5%	21.2%	11.6%	
Smits <i>et al</i> ^[20]	NHANES III (1988-1994)	3846	Ultrasound	30.2%	29.8%	39.4%	23.1%	
Liangpunsakul <i>et al</i> ^[22]	NHANES III (1988-1994)	4376	ALT ²	4.5%				

¹ALT > 43 U/L; ²ALT > 40 U/L and AST > 37 U/L for men; ALT and AST > 31 U/L for women; ³Hepatic triglyceride content > 5.5%; ⁴ALT > 43 U/L or AST > 40 U/L. NHANES: National Health and Nutrition Examination Survey; NAFLD: Nonalcoholic fatty liver disease; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; MRS: Magnetic resonance spectroscopy; NHW: Non-Hispanic whites; NHB: Non-Hispanic blacks.

prevalence rates ranging from 2.8% to 46%^[5,6]. Individuals with NAFLD and NASH, especially those with metabolic syndrome, have higher overall mortality, cardiovascular mortality, and liver-related mortality compared with the general population^[7-9]. Liver cirrhosis secondary to NAFLD is now the second most common indication for liver transplantation in obese patients^[10].

Among different racial and ethnic populations in the US, Hispanics (predominantly of Mexican origin) are at particular risk for NAFLD and tend to have a more aggressive disease course^[11-20]. Hispanics accounted for nearly 50% of the US population growth from 2000 to 2010 and are projected to reach 30% of the US population within the next three decades^[21]. Given the increasing prevalence and the expected growth in the Hispanic population, NAFLD poses a huge threat to the US health care system.

In this article, we provide a concise review of the gender and racial differences in the prevalence of NAFLD and NASH in adults. We also discuss the possible mechanisms for the racial/ethnic disparities, with a special focus on the Hispanics.

PREVALENCE OF NAFLD IN GENERAL POPULATIONS

The prevalence of NAFLD varies depending on the study population and the diagnostic tool used to determine the condition. The prevalence rates of NAFLD in the US based on population-based studies are summarized in Table 1. Most of these studies were based on the third NHANES (1988-1994) data. Defined as elevated alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), NAFLD was prevalent in 2.8%-5.4% of the US population^[11,12,22]. From 1999 to 2002, the prevalence of NAFLD in the US further increased to 8.1%^[15]. The differences of the prevalence between the two periods could be due to differences in assay methodology. Serum specimens were initially frozen after collection and then thawed prior to assay during the earlier period (1988-1994) whereas sera were only refrigerated before testing during the later time (1999-2002). Freezing

serum specimens to -20 °C has been shown to lead to a 46% loss of ALT activity, whereas refrigerating serum specimens to 4 °C only led to a 6% loss^[23]. Therefore, more individuals could have been falsely stratified as having normal liver enzymes and hence lower prevalence of NAFLD in the earlier period. On the other hand, true differences may exist as there was an increase in the prevalence of predictors for elevated ALT such as higher body mass index (BMI) and waist circumference between the periods 1988-1994 and 1999-2002^[15]. Nevertheless, studies relying on elevated liver enzymes probably underestimate the true prevalence of NAFLD as normal ALT level provides little diagnostic or prognostic value when assessing persons for NAFLD. In the Dallas Heart Study, 79% of the subjects with hepatic steatosis had normal ALT levels (defined as ALT ≤ 40 U/L for men and ≤ 31 U/L for women)^[13].

Using ultrasonography as the diagnostic tool for NAFLD, recent studies reported prevalence rates of 18.8%-30.2% in the US (Table 1)^[17-20]. Ultrasonography has been used in two studies to assess the prevalence of hepatic steatosis in non-US populations. The first study performed 25 years ago reported that fatty liver was found in 14% of the population in Okinawa, Japan^[24]. The second study reported that NAFLD was present in 20% of the residents who live in Northern Italy (the Dionysos study)^[25]. The lower prevalence of hepatic steatosis found in the Japanese study likely reflects the low frequency or absence of obese or diabetic subjects in the study cohort^[13]. Despite being more sensitive than liver enzymes for the detection of NAFLD, ultrasonography has its own limitation due to a low sensitivity for detection of mild hepatic steatosis (less than 30%)^[26]. Therefore, ultrasonography also likely underestimates the true prevalence of NAFLD in general populations. Using a more sensitive magnetic resonance spectroscopy technique for measuring fat content, 31% of the participants in the Dallas Heart Study had hepatic steatosis, defined as hepatic triglyceride content greater than 5.5%^[13].

NAFLD occurs in non-obese and non-overweight (defined as BMI < 25 kg/m²) persons as well. Based on the third NHANES data, 7% of the lean individuals have

Table 2 Gender difference in the prevalence of nonalcoholic fatty liver disease from population-based studies

Ref.	Study population	n	Definition of NAFLD	Prevalence of NAFLD	
				Men	Women
Ruhl <i>et al</i> ^[11]	NHANES III (1988-1994)	5724	ALT ¹	4.3%	1.6%
Clark <i>et al</i> ^[12]	NHANES III (1988-1994)	15676	ALT or AST ²	5.7%	4.6%
Browning <i>et al</i> ^[13]	Dallas Heart Study	734 ⁵	MRS ³	42%	24%
Ioannou <i>et al</i> ^[15]	NHANES (1999-2002)	6823	ALT or AST ⁴	13.4% ⁶	4.5% ⁶
Lazo <i>et al</i> ^[18]	NHANES III (1988-1994)	12454	Ultrasound	20.2%	15.8%
Schneider <i>et al</i> ^[19]	NHANES III (1988-1994)	4037 ⁵	Ultrasound	15%	10.1%

¹ALT > 43 U/L; ²ALT > 40 U/L and AST > 37 U/L for men; ALT and AST > 31 U/L for women; ³Hepatic triglyceride content > 5.5%; ⁴ALT > 43 U/L or AST > 40 U/L; ⁵Non-Hispanic white only; ⁶Not adjusted for alcohol consumption or hepatitis C antibody status. NHANES: National Health and Nutrition Examination Survey; NAFLD: Nonalcoholic fatty liver disease; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; MRS: Magnetic resonance spectroscopy.

NAFLD compared to 28% of the overweight-obese population^[17]. In the Dionysos study, hepatic steatosis on ultrasound was present in 16% of the non-obese participants^[27]. In a Japanese study, ultrasonographic fatty liver was found in 11.2% of non-obese persons during voluntary health check-up^[28].

PREVALENCE OF NASH IN GENERAL POPULATIONS

Liver biopsy is the current suboptimal standard for the diagnosis and staging of NASH, but invasiveness and cost preclude its use as a screening tool in general populations^[29]. The population prevalence of NASH has therefore been difficult to establish since it is unethical to biopsy asymptomatic persons in the community. Among 351 apparently nonalcoholic patients, a Canadian autopsy study from the late 1980s found that NASH was present in 2.7% of lean patients and in 18.5% of markedly obese patients^[30]. More recently, two Asian studies reported similar prevalence of NASH in 1.1%-2.2% of living donors before liver transplantation^[31,32]. Based on the third NHANES data, 2.6% of the US population have NASH defined as the presence of moderate-severe hepatic steatosis by ultrasound and elevated aminotransferases in the presence of type 2 diabetes or IR^[17].

GENDER DIFFERENCE IN THE PREVALENCE OF NAFLD

Some old studies reported that women were at higher risk for NAFLD, but these studies were not population based and were subject to potential ascertainment bias^[11]. Based on the third NHANES data, most of the studies reported that NAFLD is significantly more prevalent in men than in women (Table 2). However after dichotomizing individuals into lean and overweight-obese groups, Younossi *et al*^[17] reported that the lean NAFLD cohort was more commonly female. Using data from 698 patients from the well characterized NASH Clinical Research Network (CRN), patients with biopsy proven NASH were more likely to be female than male in a roughly 2:1 ratio; possibly reflecting a higher disease

burden in women or, alternatively, sex differences among those pursuing and receiving healthcare^[33]. Together, these findings highlight uncertainties regarding the influence of gender on NAFLD.

A number of mechanisms may contribute to gender differences in the prevalence of NAFLD.

The role of IR, which is closely associated with NAFLD^[1,2], remains controversial. Ruhl *et al*^[11] reported that NAFLD was more prevalent in men than in women (4.3% *vs* 1.6%, respectively), a finding essentially explained by the higher waist-to-hip circumference (WHR) ratio in men. WHR is correlated with visceral adipose tissue (VAT) and visceral adiposity is associated with both peripheral and hepatic IR^[34,35]. In another study using the same database but different cohort size, Clark *et al*^[12] also reported that men have higher prevalence of NAFLD than women (5.7% *vs* 4.6%, respectively), although there was no significant difference in either gender in IR as calculated by homeostasis model assessment (HOMA) or exercise level. Moreover, in the Dallas Heart Study, non-Hispanic white men had an approximately 2-fold higher prevalence of hepatic steatosis than white women. Differences in body weight or insulin sensitivity measured by HOMA did not explain these sex differences.

Alcohol use is another possible explanation for gender differences in NAFLD. In the Dallas Heart Study, white men who reported moderate ethanol intake had a significantly higher prevalence of hepatic steatosis than female counterparts (42% *vs* 20%, $P = 0.03$). In fact, moderate alcohol intake was associated with an decrease in the prevalence of hepatic steatosis in women^[13]. Similarly, Schneider *et al*^[19] reported that non-Hispanic white men, who were more likely to be self-defined as "low current drinkers" (men ≤ 2 drinks/d; women ≤ 1 drink/d), had a significantly higher prevalence of NAFLD than non-Hispanic white women (15% *vs* 10.1%, respectively), even after adjusting for BMI and waist circumference. Finally, in adult members of the Kaiser Permanente Medical Care Program in California, NAFLD was 3.5 times more common in Asian men than in Asian women ($P = 0.016$). There was no significant difference in BMI (> 28 kg/m²), diabetes mellitus, dyslipidemia, or current alcohol use between Asian men and women, but 68% of Asian men were previous drinkers, compared with 17% of Asian

women ($P < 0.02$)^[14]. Together, these studies suggest an effect of alcohol consumption on gender differences in the prevalence of NAFLD. Whether differences in hepatic metabolism of alcohol between men and women also contribute to the gender difference in not fully defined^[19].

Other factors, including lifestyle and sex hormone may also influence the gender difference in the prevalence of NAFLD. In one study, individuals with NAFLD had similar degrees of IR and obesity to those without, but males with NAFLD consumed more non-diet soda on a weekly basis (54.4% *vs* 34%, $P = 0.037$)^[16]. Another recent study showed that prevalence of NAFLD was similar in pre- and intrapubertal boys and higher in the postpubertal groups (51.2%), whereas in girls NAFLD was most common in the intrapubertal group (25.2%) and lower in the postpubertal group (12.2%)^[36].

RACIAL/ETHNIC DIFFERENCES IN NAFLD AND NASH

Despite using different diagnostic tools, US population-based studies all found that Hispanics have the highest and non-Hispanic blacks have the lowest prevalence of NAFLD (Table 1). Echoing the racial/ethnic differences in the NAFLD prevalence, Younossi *et al*^[17] recently reported that NASH was independently associated with being Hispanic [odds ratio (OR), 1.72; 95%CI: 1.28-2.33] and inversely associated with being African-American (OR, 0.52; 95%CI: 0.34-0.78). Each of these studies is limited by the fact that NASH was diagnosed by imaging and/or biochemical criteria rather than by histology.

Single center studies show that ethnicity may also influence NAFLD histology. For instance, African Americans were found to have less steatosis than whites. Asians and Hispanics showed higher grades of ballooning and Mallory bodies, respectively, than whites and other ethnicities combined^[37]. Williams *et al*^[16] also reported a significantly higher prevalence of NASH in Hispanics than Caucasians (19.4% *vs* 9.7%, $P = 0.03$) although comparison of demographics such as BMI between different ethnic groups were not available in this study. However, Kallwitz *et al*^[38] found no significant differences in hepatic steatosis, NASH, or liver fibrosis (\geq F2) between morbidly obese Hispanic and non-Hispanic white patients receiving bariatric surgery. Similar to the other reports, morbidly obese African American patients had a lower rate of NAFLD, NASH and less fibrosis than non-Hispanic whites and Hispanics. Moreover, in a NASH CRN study consisting mainly of Caucasian subjects (82%), subjects of Hispanic ethnicity overall had lower fibrosis scores and less advanced fibrosis^[33]. Finally, in an analysis restricted to 3082 individuals with normal weight (BMI 18.5-24.9 kg/m²), Schneider *et al*^[19] found no significant racial differences in the fully adjusted logistic regression model for NAFLD; however, Mexican Americans remained significantly more likely to have NAFLD with elevated aminotransferases (OR, 3.4; 95%CI: 1.29-7.18). This finding was confirmed in a prospective study where

overweight or obese Hispanics and Caucasians had similar hepatic or adipose tissue IR and severity of NASH by histology when matched for major clinical variables, in particular for total body fat^[39]. These findings suggest that a component of the higher prevalence of NAFLD and NASH observed in Hispanics may be attributed to differences in the frequency of major clinical variables such as components of metabolic syndrome or diabetes that influence the development of NAFLD.

MECHANISMS FOR THE RACIAL/ETHNIC DIFFERENCES IN NAFLD AND NASH

A number of potential factors have been implicated in racial and ethnic differences in NAFLD. These include differences in lifestyle, IR, distribution of adiposity and genetics. These factors are not mutually exclusive and may occur and act in concert.

Lifestyle

According to the “two hit” theory, steatohepatitis development requires a double hit, the first producing steatosis, and the second a source of oxidative stress capable of initiating significant lipid peroxidation^[40]. Dietary habits may promote steatohepatitis directly by modulating hepatic triglyceride accumulation and antioxidant metabolism as well as indirectly by affecting insulin sensitivity and postprandial triglyceride metabolism^[41]. Several studies have reported that different racial and ethnic groups have substantial differences in their diet. In an early US population-based study (1987 National Health Interview Survey), Hispanics reported higher energy and carbohydrate intakes and a lower percentage of energy from fat than blacks or whites (35.6%, 38.4%, and 38.7% of energy from fat for Hispanics, blacks, and whites, respectively). Whites had lower cholesterol intake than the other two groups, and blacks had a higher intake of sweets^[42]. According to the San Antonio heart study published almost 20 years ago, when data were pooled across socioeconomic groups, Mexican Americans consumed more carbohydrate, saturated fat, and cholesterol, and less linoleic acid than Anglo Americans. However, there were no ethnic differences in total fat, saturated fat, or carbohydrate consumption when compared within a given socioeconomic status^[43]. Data from the Stanford Five-City Project showed that low educated white adults consumed significantly more fat as measured by percentage of calories from total fat (37.7% *vs* 33.3%) and saturated fat (13.7% *vs* 11.8%), and consumed significantly less dietary carbohydrate (45.5% *vs* 49.7%) and fiber (17.1 g *vs* 26 g) than Hispanic adults. Interestingly, a graded relationship was found between acculturation and dietary measures, where more acculturated Hispanics (English-speaking) were intermediate between less acculturated Hispanics (Spanish-speaking) and whites in their dietary intake^[44].

Common theme in these studies is that Hispanics consume more carbohydrates than other ethnic groups.

The role of excess carbohydrate intake in NASH has been shown in at least two other studies^[45,46]. In the first study of a small series of Japanese adults, individuals with histology proven NASH had a higher intake of simple carbohydrates than those with simple steatosis^[44]. In the second study from the NASH CRN, Hispanics with NASH had higher carbohydrate intake compared to non-Hispanic whites with NASH^[45]. In addition to high carbohydrate diet, NASH is also associated with a low intake of zinc and lower ratio of intake of polyunsaturated fatty acid to saturated fatty acid^[44].

Analysis of the NASH CRN data further showed that patients with NAFLD ate at fast-food restaurants (≥ 1 per week) more often (70.9% *vs* 60.5%, $P = 0.049$) and exercised (≥ 30 min per week) less frequently (56.3% *vs* 68.9%, $P = 0.02$) than their non-NAFLD counterparts. However, racial differences in these two measures was not studied^[16]. A recent study based on the NHANES data reported that sedentary individuals had a significantly higher prevalence of NAFLD independent of other risk factors^[18]. In a small series of 37 patients, Krasnoff *et al*^[47] reported that patients with NAFLD of differing histological severity have suboptimal cardiorespiratory fitness, muscle strength, body composition, and physical activity participation. These findings establish the association between physical inactivity and NAFLD and support the current recommendation of regular exercise for patients with the condition.

IR

Several US and non-US population-based studies have shown that NAFLD is highly associated with central obesity, IR, and components of metabolic syndrome (high triglyceride, low high-density-lipoprotein cholesterol, hyperglycemia, and hypertension)^[11-13,15,18,22,25,48]. NAFLD has therefore been suggested to be a hepatic feature of the metabolic syndrome^[49]. However, Smits *et al*^[20] recently challenged this popular notion. In their study, NAFLD was strongly related to the different components of the metabolic syndrome. However, adding hepatic steatosis to a mathematical model containing the traditional components of the metabolic syndrome did not improve goodness of fit and if anything resulted in a decrease in model fit. They thus concluded that NAFLD is not an independent additional component or manifestation of the metabolic syndrome.

In addition to being a lipid storage compartment, adipose tissue is also an endocrine organ^[50]. Adipose tissue IR plays key role in the development of metabolic and histological abnormalities of obese patients with NAFLD. Liver steatosis was rare in metabolically healthy obese subjects with normal adipose tissue insulin sensitivity. Compared to patients without steatosis, patients with NAFLD were insulin resistant at the level of adipose tissue, liver, and skeletal muscle. Metabolic parameters, hepatic IR, and liver fibrosis but not necroinflammation deteriorated as adipose tissue IR worsened^[51]. The coincident occurrence of hepatic steatosis and IR has led to the

hypothesis that excess triglyceride in liver causes IR^[52]. This notion was challenged by a recent study by Lomonaco *et al*^[39]. In that study, liver fat was slightly, but not significantly, higher in Hispanic than Caucasian patients. This slightly higher liver fat content was not associated with worse hepatic or adipose tissue IR^[39].

As shown in Table 1, Hispanics have a higher prevalence and blacks have a lower prevalence of NAFLD than whites. According to the data from the third NHANES, both black and Mexican American women had higher cardiovascular disease risk factors such as hypertension, physical inactivity, higher BMI and diabetes than white women of comparable socioeconomic status^[53]. While the higher prevalence of hepatic steatosis in Hispanics can be explained by the high prevalence of obesity and IR in this population, the lower prevalence of hepatic steatosis in blacks cannot be explained by the same reason. In the Insulin Resistance Atherosclerosis Study, African Americans were more insulin resistant than Hispanics. Hispanics however had higher prevalence of NAFLD than African Americans (24% *vs* 10%)^[54]. Therefore an IR paradox may exist^[55]. It has been hypothesized that differences in NAFLD and NASH by race may result from differences in the distribution of adiposity (*e.g.*, subcutaneous *vs* visceral) or differences in triglycerides because blacks have relatively less VAT and lower triglycerides than Hispanics^[19,56]. In addition, African Americans may be more resistant to both the accretion of triglyceride in the abdominal visceral compartment (adipose tissue and liver) and hypertriglyceridemia associated with IR^[55].

Distribution of adiposity

Several studies have reported racial differences in the distribution of adiposity, especially in women. In a small study of age- and weight-matched healthy women (8 black and 10 white), black women had 23% less VAT as measured by computed tomography (CT) than white women. In addition, black women had significantly lower plasma glucose and triglycerides and significantly higher plasma high-density-lipoprotein cholesterol^[57]. Based on the Dallas Heart Study data, blacks had less intraperitoneal fat as measured by magnetic resonance imaging and more lower extremity fat than their Hispanic and Caucasian counterparts, despite controlling for age and total adiposity. In that study, the prevalence of IR was similar between blacks and Hispanics who had the highest levels of intraperitoneal fat and liver fat. Furthermore, insulin levels and HOMA values were the highest and serum triglyceride levels were lowest among blacks after controlling for intraperitoneal fat^[55]. In a prospective study of healthy sedentary women, Casas *et al*^[58] found that Hispanic women had greater total adiposity than white women, which was primarily the result of higher percentage fat and fat mass in the trunk. Within the trunk region, abdominal and subscapular skinfold thicknesses were 30%-40% significantly greater in the Hispanic women. Total fat-free mass was slightly but significantly lower in the Hispanic women primarily due to a smaller fat-free

mass in the trunk region. In a study involving healthy subjects, Asians despite of having lower BMI had more upper-body subcutaneous fat as measured by dual-photon absorptiometry than did whites. The magnitude of differences between the two races was greater in females than in males^[59]. A later study with a smaller cohort reported that Asian American premenopausal women had higher VAT than European American women, after adjusting for age and total body fat. There was a significant age by race interaction such that race differences in VAT were more evident over the age of 30 years. No differences in VAT could be detected between Asian American and European American men, even after adjusting for potential covariates^[60]. Visceral adiposity has been reported to be associated with both peripheral and hepatic IR, independent of gender, in diabetic patients^[35]. Visceral fat has also been shown as an important site for interleukin-6 secretion and provides a potential mechanistic link between visceral fat and systemic inflammation in people with abdominal obesity^[61]. Inflammatory activation within metabolic tissues such as white adipose tissue, liver, and skeletal muscle potentiates IR and metabolic disease^[62].

Together, these results support that differences in distribution of adiposity may influence racial differences in the prevalence of NAFLD and NASH.

Genetic variations

Caldwell *et al.*^[63] previously proposed that obesity and IR are often “essential but not sufficient” in the development of NAFLD given the variable prevalence of steatosis in different ancestry groups. They further suggested a genetic basis for the variable presence of steatosis in the metabolic syndrome. Possible mechanisms to explain this variation include differences in hepatic fatty acid-binding protein (influencing fatty acid import to the liver), in the activity of microsomal triglyceride transfer protein (influencing *de novo* fat synthesis), or in other compensatory mechanisms that are active in insulin-resistant patients without steatosis. The findings of familial clustering of NAFLD and NASH suggest a hereditary component for the conditions. Struben *et al.*^[64] retrospectively examined 8 index patients who had either NASH with or without cirrhosis or cryptogenic cirrhosis and 10 of their relatives from 8 kindreds. They found that co-existence of NASH and/or cryptogenic cirrhosis in 7 of 8 kindreds studied. Willner *et al.*^[65] reviewed 90 patients with NASH and found that 16 (18%) of the patients came from 9 families with NASH. Two generations were involved in 6 families and siblings were involved in the other 3 families. Notably, cirrhosis was observed in 7 of these 9 families. A small case series from Japan reported 3 families each with 2 members with biopsy-proven NASH^[66]. By studying overweight children with and without biopsy-proven NAFLD and their families, Schwimmer *et al.*^[67] reported that fatty liver was significantly more common in siblings (59% *vs* 17%) and parents (78% *vs* 37%) of children with NAFLD than those without NAFLD. In addition to genetic basis, sharing common environmental factors

and/or lifestyles could be alternative explanations for the familial nature of NAFLD and NASH.

In the landmark study from the Dallas Heart Study, Romeo *et al.*^[68] first reported that the rs738409[G] allele in patatin-like phospholipase domain-containing 3 (*PNPLA3*) gene was strongly associated with hepatic fat content even after adjustment for BMI, diabetes status, ethanol use, as well as ancestry. The variant is a cytosine to guanine substitution that changes codon 148 from isoleucine to methionine (I148M). Hepatic fat content was more than twofold higher in the G allele homozygotes than in noncarriers. The frequencies of the G allele were concordant with the relative prevalence of NAFLD in the three ancestry groups; the highest frequency of allele was in Hispanics (0.49), with lower frequencies observed in European Americans (0.23) and African Americans (0.17). In the Dallas Heart Study, rs738409(G) was significantly associated with ALT and AST levels only in Hispanics. Interestingly, rs738409(G) was not associated with BMI or indices of insulin sensitivity such as fasting plasma glucose and insulin concentrations or HOMA. Furthermore, *PNPLA3* genotype was not associated with concentrations of triglyceride, total cholesterol, high-density-lipoprotein cholesterol or low-density-lipoprotein cholesterol. Another variant of the *PNPLA3* [rs6006460(T), encoding S453I] was found to be associated with lower hepatic fat in African Americans. Regression analysis indicated that these two sequence variations accounted for 72% of the observed ancestry-related differences in hepatic fat content in the Dallas Heart Study.

Similar to the Dallas Heart Study, Wagenknecht *et al.*^[69] also found a higher frequency of *PNPLA3* rs738409(G) in Hispanics in a large US minority cohort (843 Hispanic Americans and 371 African Americans) study. The G allele was two times more common in Hispanic Americans than in African Americans (40% *vs* 19%), consistent with the greater prevalence of NAFLD in Hispanic Americans (24% *vs* 9%). The G allele was also associated with elevated ALT and AST but not metabolic phenotypes in both Hispanic- and African Americans. However, unlike the Dallas Heart Study, the *PNPLA3* genotype could only explain 4.4% of variation in liver fat content in Hispanic Americans and 5.6% in African Americans. Even with adjustment for the *PNPLA3* variation, a significant ethnic disparity in liver fat content persisted. It was therefore suggested that *PNPLA3* does not explain the unusually high prevalence of NAFLD in Hispanic Americans.

The *PNPLA3* genotype is associated with hepatic fat content and aminotransferase in non-US populations as well. In a Finnish study, 291 individuals were genotyped and had liver fat measured by magnetic resonance spectroscopy. The G allele was associated with increased liver fat content and AST independently of age, sex, and BMI. *PNPLA3* expression in the liver was positively related to obesity and to liver fat content in persons who were not morbidly obese (BMI < 40 kg/m²)^[70]. In another study, 678 obese (mean BMI = 41 kg/m²) Italians were genotyped for the *PNPLA3* variant. It was found that ALT

and AST were significantly higher in carriers of the G allele; 50% of the individuals homozygous for the G allele had elevated ALT (> 40 U/L) compared with 25% of the carriers of two C alleles, whereas 30% of the heterozygotes had elevated ALT. Glucose tolerance and insulin sensitivity were similar in all three genotypes^[71]. In a Latin American study, 172 Argentinians with NAFLD defined by ultrasonographic steatosis and 94 controls were genotyped. Similar to the previous reports, rs738409[G] was significantly associated with NAFLD, independent of age, sex, BMI, and HOMA index. Patients with CC genotype had a lower histologic steatosis score (14.9% ± 3.9%) in comparison with the CG genotype (26.3% ± 3.5%) and GG genotype (33.3% ± 4%) ($P < 0.005$). Similar to the previous US minority cohort study^[69], the *PNPLA3* genotype could only account for a small amount (5.3%) of the total variation in hepatic steatosis^[72].

The *PNPLA3* genotype exerts a strong influence not only on liver fat accumulation but also on the susceptibility of a more aggressive disease course. A recent meta-analysis of 16 studies concluded that the GG homozygotes had 3.24-fold greater risk of higher necroinflammatory scores and 3.2-fold greater risk of developing fibrosis when compared with the CC homozygotes (data from 1739 and 2251 individuals, respectively). NASH was more frequently observed in the GG than the CC homozygotes (OR, 3.488; 95%CI: 1.859-6.454; data from 2124 patients). In the meta-analysis, a negative correlation between the male proportion in the studied population and the effect of rs738409 on liver fat content was observed, suggesting that a sexual dimorphism might be involved in the effect of the single nucleotide polymorphism (SNP) on NAFLD development. The rs738409 GG genotype versus CC genotype was associated with a 28% increase in ALT levels. The *PNPLA3* rs738409 was therefore proposed as a strong modifier of the natural history of NAFLD^[73].

In addition to *PNPLA3*, the Genetics in Obesity-related Liver Disease (GOLD) Consortium studied 7176 individuals of European ancestry and identified genetic variants in or near three novel loci [neurocan gene *NCAN* (rs2228603), glucokinase regulatory protein gene *GCKR* (rs780094), and lysophospholipase-like 1 gene *LYPLAL1* (s12137855)] that were associated with both increasing CT hepatic steatosis and histologic NAFLD. The genetic variant in or near glycogen binding subunit of protein phosphatase 1 gene *PPP1R3B* (rs4240624) was associated with CT steatosis but not histologic NAFLD. Variants at these 5 loci exhibited distinct patterns of association with serum lipids, as well as glycemic and anthropometric traits. Specifically variants in or near *NCAN*, *GCKR*, and *PPP1R3B* associated with altered serum lipid levels, whereas those in or near *LYPLAL1* and *PNPLA3* did not. Variants near *GCKR* and *PPP1R3B* also affected glycemic traits. These findings suggest development of hepatic steatosis, NASH/fibrosis, or abnormalities in metabolic traits are probably influenced by different metabolic pathways and may provide new insights that into

how obesity can lead to metabolic complications in some but not all individuals^[74]. The observed genetic variants in European ancestry individuals were recently characterized in a multi-cohort study of African- ($n = 3124$) and Hispanic Americans ($n = 849$)^[75]. In that study, variants in or near *PNPLA3*, *NCAN*, *GCKR*, *PPP1R3B* in African Americans and *PNPLA3* and *PPP1R3B* in Hispanic Americans were significantly associated with CT hepatic steatosis. *LYPLAL1* was not significantly associated with hepatic steatosis in either African- or Hispanic Americans despite comparable allele frequencies. The association of *NCAN* with hepatic steatosis was in an opposite direction in Hispanic Americans, suggesting it would have a small protective effect in this population. The allele frequency and effect size of each variant varied across ancestries. For example, the effect size of *PNPLA3* rs738409 was similar across the ancestries and the frequency of the G allele was higher in Hispanics. The effect size of *PPP1R3B* rs4240624 was twice in European ancestry individuals than other ancestries, whereas its frequency was roughly the same across the three ethnic groups. *GCKR* rs780094 had the same effect across ancestries but its frequency in African Americans was half of that in European ancestry individuals and Hispanic Americans, which were about equal^[75].

Finally, in a recent multi-ethnic ($n = 4804$) study from the third NHANES, Hernaez *et al*^[76] attempted to replicate the findings of the GOLD Consortium. Similar to the previous report by Palmer *et al*^[75], the G allele of *PNPLA3* rs738409 was more prevalent in Mexican Americans than non-Hispanic whites and blacks. However, the T allele of *GCKR* rs780094 and the A allele of *PPP1R3B* rs4240624 were more common in non-Hispanic whites than the other two ethnic groups. In contrast to the GOLD Consortium, several discrepancies were noted. First of all, the *PNPLA3* variant was associated with hepatic steatosis diagnosed by ultrasonography only among Mexican Americans. Secondly, *NCAN* and *PPP1R3B* regions were associated with hepatic steatosis only in non-Hispanic whites. Thirdly, neither *LYPLAL1* nor *GCKR* were associated with hepatic steatosis in the third NHANES population. Fourthly, *PNPLA3* and *GCKR* were the only variants associated with elevated ALT (> 30 U/L in men and > 19 U/L in women) and the association in non-Hispanic whites only^[76]. In an editorial comment, Browning called for the following considerations when interpreting the data of Hernaez *et al*^[76]. The true prevalence of fatty liver in the study population might be higher than reported and/or that some individuals might have been mistakenly classified as having NAFLD since ultrasound is not as sensitive or specific for hepatic steatosis as other imaging modalities. In addition, the study appears to be underpowered to examine associations across ethnic/racial groups, especially for SNPs with a low allelic frequency. If underpowered, the analysis would be prone to false-negative results^[77].

Variants in other genes such as cytochrome P450 2E1^[78] and apolipoprotein C3^[79] have been reported to be

implicated in NAFLD. To provide a detailed review of other genetic variants in NAFLD is beyond the scope of this review.

CONCLUSION

According to the population-based studies, NAFLD and NASH are more prevalent in males and in Hispanics. The gender differences in NAFLD and NASH can be probably explained by gender disparities in body fat distribution, lifestyle, and sex hormone metabolism. The racial/ethnic differences in NAFLD and NASH are likely attributed to interaction between environmental, behavioral, and genetic factors. Despite having similar or worse insulin sensitivity, non-Hispanic blacks are less likely to have NAFLD/NASH than non-Hispanic whites and Hispanics. Racial differences in body fat distribution and lipid metabolism may explain the IR paradox. By using genome-wide association study, several SNPs have been identified to be associated with NAFLD/NASH. These genetic variants however only account for a small amount of variation in hepatic steatosis among ethnic groups and may serve as modifiers of the natural history of NAFLD. As suggested by Browning^[77], these trait-associated SNPs may not be the causative genetic variants but simply tags representing a larger body of SNPs. Further study is required to define how these variants alter normal physiology and/or identify the functional genetic variant in the haplotype block represented by the SNP^[77].

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