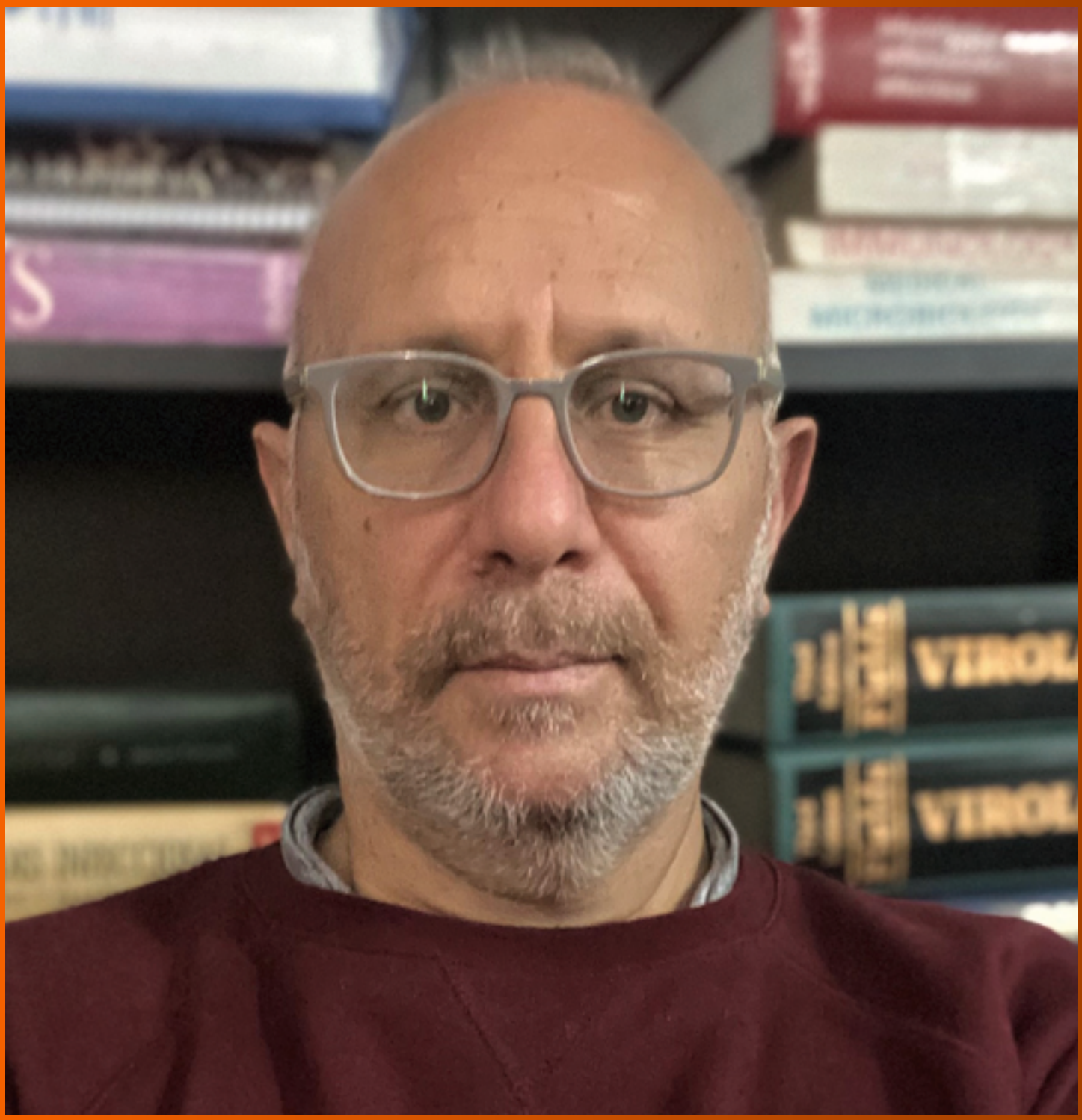
ISSN 1948-5182 (online)

World Journal of *Hepatology*

World J Hepatol 2021 July 27; 13(7): 717-829



Published by Baishideng Publishing Group Inc

World Journal of Hepatology

Contents

Monthly Volume 13 Number 7 July 27, 2021

EDITORIAL

717 Current state of medical tourism involving liver transplantation-the risk of infections and potential complications

Neupane R, Taweesedt PT, Anjum H, Surani S

OPINION REVIEW

723 Hepatitis E virus in professionally exposed: A reason for concern?

Mrzljak A, Balen I, Barbic L, Ilic M, Vilibic-Cavlek T

REVIEW

731 Clinical algorithms for the prevention of variceal bleeding and rebleeding in patients with liver cirrhosis

Pfisterer N, Unger LW, Reiberger T

747 Liver injury associated with drug intake during pregnancy

Kamath P, Kamath A, Ullal SD

MINIREVIEWS

763 Racial differences in prevalence and severity of non-alcoholic fatty liver disease

Bonacini M, Kassamali F, Kari S, Lopez Barrera N, Kohla M

774 Torsion of spleen and portal hypertension: Pathophysiology and clinical implications

Jha AK, Bhagwat S, Dayal VM, Suchismita A

781 Impact of coronavirus disease 2019 on prevention and elimination strategies for hepatitis B and hepatitis C

Rehman ST, Rehman H, Abid S

ORIGINAL ARTICLE

Retrospective Study

790 Prevalence and risk factors of steatosis and advanced fibrosis using transient elastography in the United States' adolescent population

Atsawarungruangkit A, Elfanagely Y, Pan J, Anderson K, Scharfen J, Promrat K

SYSTEMATIC REVIEWS

804 Safety of liver resection in patients receiving antithrombotic therapy: A systematic review of the literature

Fujikawa T

World Journal of Hepatology

Monthly Volume 13 Number 7 July 27, 2021

Contents

META-ANALYSIS

815 Effects of intragastric balloon placement in metabolic dysfunction-associated fatty liver disease: A systematic review and meta-analysis

de Freitas Júnior JR, Ribeiro IB, de Moura DTH, Sagae VMT, de Souza GMV, de Oliveira GHP, Sánchez-Luna SA, de Souza TF, de Moura ETH, de Oliveira CPMS, Bernardo WM, de Moura EGH

World Journal of Hepatology

Monthly Volume 13 Number 7 July 27, 2021

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Hepatology*, Jorge Quarleri, PhD, Adjunct Professor of Microbiology, Research Scientist, Institute of Biomedical Research on Retrovirus and Aids, School of Medicine, University of Buenos Aires (UBA)-National Scientific and Technical Research Council (CONICET), Buenos Aires C1121ABG, Argentina. quarleri@fmed.uba.ar

AIMS AND SCOPE

The primary aim of *World Journal of Hepatology* (*WJH*, *World J Hepatol*) is to provide scholars and readers from various fields of hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

INDEXING/ABSTRACTING

The *WJH* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database. The 2021 edition of Journal Citation Reports® cites the 2020 Journal Citation Indicator (JCI) for *WJH* as 0.61. The *WJH*'s CiteScore for 2020 is 5.6 and Scopus CiteScore rank 2020: Hepatology is 24/62.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Li-Li Wang*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Xiang Li*.

NAME OF JOURNAL
World Journal of Hepatology

ISSN
ISSN 1948-5182 (online)

LAUNCH DATE
October 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Nikolaos Pyrsopoulos, Ke-Qin Hu, Koo Jeong Kang

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-5182/editorialboard.htm

PUBLICATION DATE
July 27, 2021

COPYRIGHT
© 2021 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

© 2021 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Hepatology

Submit a Manuscript: https://www.f6publishing.com

World J Hepatol 2021 July 27; 13(7): 763-773

DOI: 10.4254/wjh.v13.i7.763

ISSN 1948-5182 (online)

MINIREVIEWS

Racial differences in prevalence and severity of non-alcoholic fatty liver disease

Maurizio Bonacini, Farah Kassamali, Swathi Kari, Nieves Lopez Barrera, Mohamed Kohla

ORCID number: Maurizio Bonacini 0000-0002-4460-2367; Farah Kassamali 0000-0001-5808-7143; Swathi Kari 0000-0001-6671-7301; Nieves Lopez Barrera 0000-0002-3591-3040; Mohamed Kohla 0000-0001-9570-4796.

Author contributions: Bonacini M and Kassamali F did the main literature review; all authors reviewed and rewrote the manuscript to address the reviewers questions.

Conflict-of-interest statement: Authors report no conflict-of-interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Maurizio Bonacini, Department of Gastroenterology and Hepatology, California Pacific Medical Center, California Pacific Medical Center, San Francisco, CA 94115, United States

Farah Kassamali, Department of Gastroenterology and Hepatology, California Pacific Medical Center, San Francisco, CA 94115, United States

Swathi Kari, Department of Internal Medicine, St. Mary's medical Center, San Francisco, CA 94117, United States

Nieves Lopez Barrera, Quest Clinical Research, San Francisco, CA 94115, United States

Mohamed Kohla, Department of Hepatology, National Liver Institute, Menoufiya University, Shibin Al Kom 32511, Menoufiya, Egypt

Corresponding author: Maurizio Bonacini, AGAF, MD, Associate Professor, Staff Physician, Department of Gastroenterology and Hepatology, California Pacific Medical Center, California Pacific Medical Center, 2333 Buchanan Street, San Francisco, CA 94115, United States. bonacim08@gmail.com

Abstract

The aim of this review is to assess the evidence regarding racial differences in the prevalence and severity of nonalcoholic fatty liver disease (NAFLD). We reviewed the published literature that reported prevalence, severity, and genetic associations of NAFLD in different ethnic groups. The metabolic syndrome (MetS) has been associated with NAFLD, but each component of the MetS is present in various races in different percentages and their effect on NAFLD appears to be dissimilar. An elevated triglyceride (TG) level seems to have the strongest association with NAFLD. The latter is more prevalent in Hispanic patients; Blacks have lower TG levels and a lower NAFLD prevalence, compared to Caucasians or Hispanics. The severity of liver fibrosis is lower in some, but not all biopsy-based studies of Black patients. No study has evaluated the severity of liver disease controlling for the individual components of MetS, especially TG. Important racial differences in the prevalence of selected genetic polymorphisms, particularly PNPLA-3 and MBOAT7 have been documented, together with their effects on the prevalence of liver steatosis and fibrosis. Data on overall and liver mortality have found no significant differences according to race/ethnicity, with the possible exception of one paper reporting lower cirrhosis mortality in Black patients. We conclude that NAFLD is more prevalent in Hispanics and less in Blacks. This is supported by differences in key genetic polymorphisms associated with hepatic

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: United States

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: January 4, 2021
Peer-review started: January 4, 2021
First decision: January 25, 2021
Revised: April 8, 2021
Accepted: July 7, 2021
Article in press: July 7, 2021
Published online: July 27, 2021

P-Reviewer: Sitkin S
S-Editor: Gao CC
L-Editor: A
P-Editor: Li X

fat storage. However, there is presently insufficient evidence to firmly conclude that race, per se, plays a role in the development of liver fibrosis and its complications. Further studies, appropriately controlled for diet, exercise, and individual MetS parameters are needed.

Key Words: Race; Ethnicity; Nonalcoholic fatty liver disease; Fatty liver disease; Metabolic syndrome

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Nonalcoholic fatty liver disease is one of the most common diagnoses made in a Gastroenterology practice. The prevalence and severity of nonalcoholic fatty liver disease in different ethnic groups need to be evaluated by controlling for the individual variables of the metabolic syndrome. This is because these variables are different in various ethnicities.

Citation: Bonacini M, Kassamali F, Kari S, Lopez Barrera N, Kohla M. Racial differences in prevalence and severity of non-alcoholic fatty liver disease. *World J Hepatol* 2021; 13(7): 763-773
URL: https://www.wjgnet.com/1948-5182/full/v13/i7/763.htm
DOI: https://dx.doi.org/10.4254/wjh.v13.i7.763

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is one of the most common diagnoses made in a gastroenterology practice. Several articles suggested differences in the prevalence and severity of liver disease according to patient race/ethnicity. If such differences were proven, this would have an important impact on resource allocation to decrease health disparities. Thus, it is imperative that the available literature be critically reviewed and existing knowledge gaps, if any, identified.

RACE AND NAFLD

Definitions

NAFLD is a condition marked by excess fat storage accounting for > 5% of the liver's volume in the absence of known alcohol abuse[1]. The latter is usually defined as the use of > 20 g alcohol/day for women and > 30 g/d for men[2], although lower limits have been used[3]. No study addressing race differences has verified absence of alcohol by testing hair for alcohol or using blood phosphatidylethanol levels[4,5]. The diagnosis is usually inferred by imaging studies, typically an ultrasound showing increased hepatic echogenicity[6,7]. Elevated alanine aminotransferase (ALT) in the absence of known competing causes has also been accepted as "suspected NAFLD" [7]. It is also crucial to differentiate primary *vs* secondary causes (medications, genetic or nutritional disorders); however only approximately 12% of studies excluded the latter[8].

We accepted the authors' race classification, which was typically based upon self-reporting. We recognize that race and ethnicity are "constructs that have no clearcut definition"[9]. It is important to keep in mind that Hispanics and Asians include significantly heterogeneous sub-populations[3,7,9].

Since Asians are underrepresented in most United States studies, this review will focus on Blacks (or African-Americans), Hispanics (or Latinos) and Whites (or Caucasians).

For the purpose of this paper, we will accept that the alcohol history is accurate, that a compatible ultrasound and/or elevated transaminases in the appropriate clinical setting are reasonable diagnostic tools, and that all reported cases are primary NAFLD.

Specific aim

To assess the strength of evidence suggesting that race-ethnicity in adults is associated with not only prevalence, but also with severity and prognosis of NAFLD.

Methods

We queried the PubMed English language database using the following keywords in the title or abstract: "fatty liver", "nonalcoholic fatty liver disease", "NAFLD", "liver or hepatic steatosis", "steatohepatitis" AND "race" or "ethnicity". We eliminated articles including alcoholic liver disease or HIV infected patients. We restricted this narrative review to adult populations.

Prevalence of NAFLD by race/ethnicity

The prevalence of NAFLD is reported to be highest in the Middle East (32%) and South America (31%), followed by Asia (27%), and Europe (23%)[10,11]. In Africa and India, the prevalence of NAFLD is approximately 9% of the population[12,13].

The most recent estimate places the United States prevalence of NAFLD at about 32%[14]. The United States is unique due to its mix of various races and ethnicities, while maintaining relative homogeneity in terms of geography and alimentary patterns. Therefore, it seems like an optimal population to study to uncover potential racial differences in disease.

A recent meta-analysis[8] shows that in population-based cohorts (*i.e.*, not high-risk patient groups such as diabetics) 23% of Hispanics have NAFLD, *vs* 14% of Caucasians, and 13% of African Americans. These percentages translate into a higher relative risk (RR) for Hispanics being diagnosed with NAFLD (RR = 1.5), and lower for African/Americans (RR = 0.7) compared to Whites[8]. If one focuses on patient subgroups that are at high risk for NAFLD, these differences become smaller (Hispanics RR = 1.2 and African-American RR = 0.8) but remain significant[8]. Interestingly, a NHANES based study[6], not included in the above meta-analysis, also found that Hispanics have a RR for NAFLD of 1.7 and African-American a RR of 0.8 compared to Whites: however when restricted to 'never drinkers', those differences are no longer significant, implying that small amounts of alcohol may have different effects on different races[6]. Thus, despite higher rates of HTN and insulin resistance, African-Americans have a lower prevalence of NAFLD[1,6,15-18].

There is relatively little written about Asian patients other that the prevalence may be about 25% in Asia[19], but may be lower in US-residing Asians, where NAFLD is noted in 20%[14]. A summary of the estimated prevalence of NAFLD in the United States is shown in Table 1.

Prevalence of the metabolic syndrome by race/ethnicity

Contributors to the rising worldwide prevalence of NAFLD include non-modifiable factors like genetics, but also modifiable variables such as diet and lifestyle choices[7,21,22]. Identifying, quantifying and controlling for these factors will be useful to establish whether some groups may be at higher risk, and therefore help allocate resources to mitigate those differences[23].

Diet and exercise has been found to be different in different ethnic groups. Asians have better diets (measured with an adapted healthy eating index) than Caucasians who in turn have better diet scores than Latinos and Blacks[21]. In Hawaii, however, intake of fruits and vegetables was lowest in Japanese-Americans compared to Filipinos or Native Hawaiians[22]. Yet, it is not clear whether a better diet score necessarily translates into a lower NAFLD risk[21,22]; and if so, by how much.

Similarly, exercise habits appear to be different, highest in Caucasians and lowest in Asians[9,22]. This is important because exercise decreases intrahepatic fat by MRI, even in the absence of weight loss[24]. Unfortunately, in articles focusing on NAFLD, these potentially important variables have not been adjusted for.

Metabolic syndrome (MetS) is accepted as the major association with NAFLD. MetS is defined by the presence of 3 or more out of 5 criteria: Increased fasting glucose, central obesity/waist circumference, low high-density lipoprotein (HDL), elevated triglycerides (TG), and elevated arterial pressure. Meeting this definition is associated with future development of diabetes type 2 (DM) and cardiovascular disease (CVD)[23]. There are differences in the prevalence of MetS according to race ethnicity, in non-institutionalized adult individuals living in the United States. A recent assessment shows that the prevalence of MetS was 35% in Whites, 30% in Blacks, followed by Hispanics (termed "Mexican Americans") (29%)[15]. No increased prevalence was noted in the Latino population surveyed[15]. A United States military study looked at the incidence of MetS (by ICD-10 codes), and found the highest was in Pacific-

Table 1 Estimated prevalence of nonalcoholic fatty liver disease in the general United States population (three main Race-ethnicities)

Ref.	Whites			Blacks			Hispanics		
	No.	Denom	Percentage	No.	Denom	Percentage	No.	Denom	Percentage
Rich *et al*[8]	24454	200510	0.12	3625	54790	0.07	5125	40591	0.13
Kallwitz *et al*[7]							1691	9342	0.18
Zou *et al*[14]	2229	4341	0.51	538	2833	0.19	1686	3886	0.43
Lim *et al*[20]	82	400	0.2	49	297	0.16	180	377	0.48
Foster *et al*[16]	189	1244	0.15	106	992	0.10	208	775	0.27
Total	26954	206495	0.13	4318	58912	0.07	8890	54971	0.16

Islanders, and the lowest in White personnel[25].

However, there are 3 important problems with MetS as a dichotomous variable. First, individual components of the MetS have a different distribution among races, elevated TG being more common in Latinos and White males and abnormal waist circumference in Blacks and White females[23]. In fact, the low TG levels in Blacks have been called "the TG paradox"[26]. Thus, African American patients have a higher body mass index (BMI) and similar prevalence of DM, yet they display a better lipid profile and therefore are less likely to have MetS compared to Hispanics (Table 2)[17]. The prevalence of DM is lowest in Whites (12%) and similar in Asians (19%), Blacks (20%) and Hispanics (22%)[18]. The latter group showed major heterogeneity, South American patients having less DM (12%) compared to other Latino groups[18].

Second, a diagnosis of MetS predicts the development of DM or CV disease differently in different races. For example, in patients with MetS, rates of incident DM are highest in Black males and females (17%) and lowest in white women (8%); whereas the rate of development of CVD is highest in White men (25%) and lowest in Black women (6%)[23]. Third, the association between individual MetS variables and NAFLD is not the same. In a recent study from China (Asian patients), NAFLD patients had higher levels of each of the 5 MetS parameters *vs* controls. However, when a multivariable analysis was run, adjusted for age and sex, the strongest association was with an elevated TG; the prevalence of NAFLD in the highest and lowest TG quartile was 50% *vs* 5 %[27]. Therefore a *z*-score, where the MetS is measured on a continuous scale (from -1 to +4) has been developed and shown to predict the development of diabetes and CVD better than the binary MetS[23]. When controlled for the z-score, Black individuals have double the rate of DM and higher rates of hypertension *vs* whites[16,23]. There are no data assessing the prevalence and severity of NAFLD, in patients matched by the *z*-score.

Fat distribution/obesity

Lean NAFLD (*i.e.*, with normal BMI) is found in as many as 5% of those with NAFLD in the United States[14] and this subgroup has a 65% chance of being metabolically abnormal, *i.e.*, fulfilling criteria for MetS[28]. On the other hand, overweight and obese NAFLD patients have a correspondingly higher chance of having MetS, 92% and 95%, respectively. Lean NAFLD seems more common in Asians *vs* other ethnic groups[14,20]. Elevated TG appears to be the commonality in patients with NAFLD, independent from BMI[17,27,28].

Patterns of visceral and liver fat depositions show ethnic differences and may contribute to the prevalence and severity of NAFLD. Total adiposity, measured by DEXA and MRI to account for visceral, liver and truncal fat was found to be highest in Japanese Americans and lowest in African Americans[17]. Interestingly, women had lower visceral fat area than men, except in the Japanese American group[20]. African-American adolescents have less visceral fat than either Hispanics or Whites[29].

A study using transient elastography and controlled attenuation parameter estimated hepatic steatosis and fibrosis in 2000 Korean patients. Obese (*i.e.*, BMI 25 or greater) but metabolically healthy (no MetS) individuals had greater liver steatosis and fibrosis than non-obese patients[30]. However, in the non-obese group, those with MetS, had higher steatosis estimates but similar fibrosis to those without MetS. BMI rather than MetS was the variable independently associated ($P < 0.001$) with both steatosis and fibrosis[30]. The Dallas heart study quantified visceral fat percentage by MRI in the general population: unfortunately, 3% to 8% of the individuals reported alcohol intake levels exceeding those used to define NAFLD[1]. The findings were that

Table 2 Prevalence of metabolic syndrome and its components in African Americans *vs* Hispanics[17]

	AA	H	*P* value
Percentage MetS	19	33	< 0.0001
% Diabetes	17	17	NS
Mean HDL	53	47	< 0.0001
Mean TG	107	160	< 0.0001
Mean BMI	31	29	0.008

AA: African Americans; H: Hispanics; MetS: Metabolic syndrome; HDL: High-density lipoprotein (mg%); TG: Triglyceride (mg%); BMI: Body mass index.

male Hispanic and White individuals had similar risk (42% to 45%) of having hepatic steatosis greater than 5.5 g TG per 100 g of liver tissue, much higher compared to Black males (23%). Women, both White and Black, had lower rates of abnormal hepatic steatosis (24%) compared to Latinas (45%). The fact that Blacks had higher HTN and Insulin resistance rates, but lower circulating TG levels, suggests racial and genetic differences in intrahepatic TG storage[1,16,20,31].

Genetics

Pathways of lipolysis or lipogenesis (MBOAT7, PNPLA3, TM6SF2,) are some of the genetic polymorphisms that have been linked to NAFLD prevalence and its severity [16,32-34].

In individuals of European descent, a T mutation in the MBOAT7 gene (rs641738) has been associated with severity of NAFLD in those with TT homozygosity[34]. Even the presence of one T polymorphism was associated with a small [odds ratio (OR) = 1.3] but significant risk of biopsy-proven F2, F3 or F4 fibrosis[34]. However, the association between the PNLPA3 G allele and F2-F4 was stronger (OR = 1.6)[34].

The PNPLA3 gene controls hepatic VLDL excretion, likely leading to hepatic TG accumulation; it may also sensitize the liver to environmental stressors, thus contributing to elevated transaminase levels in the presence of obesity[2]. The G allele mutation (rs738409), termed I148M (*vs* CC wild type) is a single-nucleotide polymorphism (SNP), which increases the risk of fat accumulation in the liver and thus NAFLD four-fold[17,32,33]. The G allele was found to be more frequent in Hispanics (40%) compared to Africans and Europeans (both 15%). In those with GG alleles, the risk of having NAFLD was similar in Asians and Caucasians (3-fold) and Hispanics (4-fold) but was much higher in Black patients (9-fold) compared to those with wild type genotype[35].

Within the United States population, the PNPLA3-G allele had a significant association with a non-invasive estimate of liver fibrosis, the FIB-4 score[7], but in one study this association was not clear (Table 3)[3]. The GG homozygosity has also been associated with a 5-fold increase in HCC risk[33]. A recent study from Sicily confirmed that the G allele (either heterozygous or homozygous) was associated with more advanced liver fibrosis[36]. In patients with stage 3 and 4 fibrosis, the G allele was associated with more liver decompensation, HCC and liver related death, despite a relatively small total number of patients followed (n = 471)[36]. Interestingly, 2/3 patients had the G allele and almost a quarter was homozygous GG[36].

In Hispanics with American ancestry (Mexican-, Central-, and South American), the frequency of PNPLA3-G is higher than in those of European or Afro-Caribbean background[3]. A small study in Hmong patients suggests that some Asian subpopulations have high rates of the G SNP and thus may have increased risk for NAFLD[37]. These findings underscore the existence of distinct and potentially relevant subpopulations within a traditional race/ethnicity group.

A minor allele (rs58542926) in transmembrane 6 superfamily member 2 (TM6SF2) was associated with hepatic TG content measured by magnetic resonance spectroscopy, in the Dallas Heart Study[1]. The C to T polymorphism decreases VLDL excretion, thus increasing TG concentration in the liver[33]. In addition, this TM6SF2 polymorphism was noted to increase the risk for hepatic fibrosis independent of age, obesity, diabetes, and PNPLA3 genotype[38]. On the other hand, the TM6SF2-T allele mutation E167K had similar low frequencies between Hispanics[3] and those from European ancestry and had a strong association with ALT levels[15].

Table 3 Percentage of patients with the *PNPLA3* G allele polymorphism and FIB-4 > 2.67[3]

	% PNPLA3-G allele	% Suspected NAFLD	% FIB-4 > 2.67
Mexican American	52	21	0.4
South American	51	20	0.3
Central American	48	23	0.9
Puerto-Rican	35	16	2.0
Cuban	28	16	1.8
Dominican	22	13	0.5

NAFLD: Nonalcoholic fatty liver disease.

NAFLD, liver fibrosis and liver complications

Several studies assessed metabolic factors associated with varying histopathological severity of NAFLD. There is agreement that the degree of steatosis is proportional to the number of elements of the MetS[7,16,20,32,39,40]. Additionally, one study showed that the MetS was associated with significantly greater risk of liver fibrosis stage 3 or 4 (33% *vs* 15% in those without MetS) and necroinflammation (61% *vs* 44%)[39]. The same study showed that in patients with NASH, 88% had MetS compared to 67% of those with simple fatty liver[39].

NAFLD is more prevalent in Hispanics[6,15,18,31], but the significance of this finding is debatable, as fibrosis is the only histological variable consistently associated with liver mortality[41]. While mortality in NAFLD patients is chiefly associated with cardiovascular events[42,43], it would be useful to tease out whether race independently affects the development of cirrhosis, and therefore liver mortality.

The fact that there is a relationship between elements of MetS and liver steatosis, inflammation and fibrosis[23,39] means that studies comparing liver disease severity between races must be controlled for the 5 MetS variables, keeping in mind that each may be more predictive in specific races.

The multi-ethnic cohort[44] looked at a United States population enriched with Asian minorities. The results showed that NAFLD was the most common cause of chronic liver disease in Japanese Americans (64% of those with liver disease) followed by Hawaiians (58%), Latinos (46%), Whites (41%) and Blacks (39%). When looking at the percentage of patients who had NAFLD-related cirrhosis (by ICD-9 codes) by race, the percentages were 4% (Japanese), 3.1% (Latinos), 1.7% (Whites) and 1.5% (Blacks)[44].

Dulai *et al*[42] reviewed 5 studies that assessed baseline liver fibrosis (mostly by biopsy) in patients with NAFLD or NASH. At baseline these 5 studies showed that most (67%) of patients had stage 0/1 fibrosis; 14% had F2; 12% F3 and 7% cirrhosis. Mortality was mainly cardiovascular related (about 40%) followed by cancer (20%) and liver disease (10%)[43]. There were no details comparing races within each study. In fact, one study had only Asians[45] and another 88% Whites[34]. A Canadian study did not mention race or ethnicity[46]. While baseline advanced fibrosis stage (F3/4) varied from 27% in Asians[45] to 12% in Whites[43], the percentages of MetS was also different (63% *vs* 33% respectively).

Within NAFLD, however, NASH on liver biopsy is less common in African-Americans (57%), but not significantly, *vs* Caucasians (73%)[47].

A recent meta-analysis[8] noted that 11 studies assessed stage of fibrosis (mostly by biopsy) in NAFLD and had data on race. The pooled proportion of patients with NAFLD and significant fibrosis (stages 3 and 4) was 19.5% [95% confidence interval (CI): 18.1-20.9]. The percentages were numerically highest in Whites (22.3%) and Hispanics (19.6%) and lowest among Blacks (13.1%). However, differences were not statistically significant for Whites *vs* Hispanics (RR 1.02, 95%CI: 0.94-1.11), and borderline significant for Whites *vs* Blacks (RR = 1.10, 95%CI: 1.00-1.22)[8]. A later paper showed that morbidly obese Black patients (mean BMI > 45) had lower % of NASH (4%) and lower % of fibrosis stages 3 and 4 (1.4%) *vs* Whites (17% and 9% respectively). The 2 groups had similar percentages of DM and hypertension[48]. A retrospective but well detailed study based on liver biopsy found advanced fibrosis (F3/F4) in 16% Caucasians *vs* 2.6% Blacks, despite the fact that the latter had greater BMI and higher DM rates. However, their lipid profile was healthier than Caucasians[49].

The most recent NHANES (1999-2016) evaluation[14] used the US Fatty Liver Index to define NAFLD and two noninvasive marker (FIB-4 and NAFLD Fibrosis Score) to assess advanced liver fibrosis (*i.e.*, stages 3 and 4). The results show that Latinos and Whites had higher likelihood of NAFLD (43% and 33%, respectively), *vs* Asians (20%) and African Americans (19%). Overall, mortality was associated with DM2 and FIB-4 but not race, and was higher in lean or overweight patients *vs* obese[14].

Interestingly, a work by Lomonaco *et al*[50] found that, when metabolic factors are controlled for, hepatic steatosis, inflammation and fibrosis scores (all by histology) were similar between Caucasians and Hispanics. A study assessing biopsy-confirmed NASH and comparing Latinos and Whites reported that the former were younger, had increased carbohydrate intake, and had a lower prevalence of hypertension[31]. However, while there were numerical different rates of F3/F4 (Whites and Blacks 30%, Asians 28% and Latinos 23%) these were not significant. Multivariable analysis identified only age, female gender, HTN and abnormal HOMA-IR as significantly associated with advanced fibrosis, but not race[31].

The preponderance of evidence shows that while Latinos have more NAFLD, they don't have significantly higher rates of advanced fibrosis. Studies based on liver biopsy, except one[31] have shown Black patients to have less fibrosis[8,49]. However, adequate controlling for the variables of the MetS has not been done.

NAFLD is associated with the development of hepatocellular carcinoma (HCC). One report demonstrated that patients with NAFLD have a 10-fold higher chance of developing HCC compared to controls[51]. The overall risk of HCC in NAFLD was low (estimated 0.02/100 patient-years), and it was higher in older (> 65 years) Hispanics and lower in Blacks: these subgroups were not matched by MetS risk[51].

Finding racial differences in mortality (especially liver mortality) in patients with fatty liver requires evaluation of a very large database. A NHANES analysis (1988-1994), looked at (mostly) NAFLD patients and found a correlation between high estimated liver fibrosis (by non invasive tests such as FIB-4) with mortality (both all cause and liver-related) up to 2006[52]. Unfortunately, liver mortality represented only 3% of the total mortality, so there were too few endpoints to make inferences about racial associations[52]. A review of total United States mortality captured in the latest National Vital Statistics (NVSS) database, showed that Hispanics with a diagnosis of NAFLD have lower mortality than Caucasians, although in both groups the trend is towards increased mortality the past 10 years: there was no attempt to adjust the data for underlying metabolic disease[53]. In 2016, the NIAAA issued a report on liver cirrhosis mortality. The age-adjusted mortality rates for cirrhosis "without mention of alcohol" were 50% lower in Blacks *vs* whites, but NAFLD codes were not specifically reported[54]. However, a paper looking at hospital charges, length of stay and mortality in non-Federal Community hospitals across the United States, showed that mortality was not statistically different across races in patients admitted with a NAFLD diagnosis[55].

More data on race-specific cirrhosis, HCC and mortality rate in patients with NAFLD are needed.

Response to therapy

There is considerably less data on racial responses to therapy for NAFLD. To date, this includes mainly weight loss strategies, including bariatric surgery.

Vilar-Gomez *et al*[56] published a small but well-designed study enrolling Cuban patients. They histologically documented decreased liver fibrosis (45% of patients) and resolution of NASH (90% of patients) when a 10% or greater weight loss was achieved [56]. The latter endpoint was noted in 10% of patients, all of them Cuban. However, diet and exercise may be beneficial to decrease liver steatosis in the absence of weight loss[24].

Behavioral therapy resulted in a maximum weight loss of 5 kg in Black patients, significantly less than 13 kg in Whites[57]. Metformin for one year significantly increased HDL-cholesterol (by 1-2 mg/dL) in White and Black patients: In Hispanics the HDL declined by approximately 1 mg/dL[58]. Lorcaserin lead to a placebo-adjusted weight loss of 3.2 kg, 2.7 kg and 1.4 kg in Whites, Blacks and Hispanics respectively[59]. Semaglutide as an injection for DM control showed minor changes in weight in different races[60].

A study in 3268 patients (1561 Hispanics, 660 Blacks, and 1047 Whites) examined the percentage of excess weight loss (EWL) after Roux-en-Y gastric bypass or adjustable gastric band placement[61]. EWL differed by ethnicity (-53% in Hispanics, -50% in Whites and -43% in Blacks), at 6 months post-operatively. These differences persisted at 1 and 2 years after surgery (-69%, -69% and -58%, respectively)[61]. A prior meta-analysis, looking at the percentage of EWL (between 12 and 24 mo post-

operatively) confirmed an average of 8% lower weight loss in Blacks compared to Whites[62].

In the future, large phase 3 studies using new NASH medications may uncover possible racial differences in baseline histology, and clinical liver outcomes. Those studies will have prospectively collected metabolic data, permitting investigators to assess risk by race, controlled for variables of the MetS[23].

CONCLUSION

In conclusion, there is convincing evidence that the prevalence of NAFLD depends on genetics and the prevalence of the MetS. Its individual components impact fatty liver differently in different populations. Socio-economic, dietary and lifestyle differences may also explain reported racial differences but have not been thoroughly studied in the NAFLD arena. In the United States, NAFLD and NASH seem more prevalent in Hispanics, however most studies have not been controlled for the individual variables of MetS, and this may have overestimated racial differences. African Americans have a lower prevalence of hypertriglyceridemia and this contributes to their lower prevalence of NAFLD despite higher rates of hypertension and DM. Fibrosis scores seem similar in Whites and Latinos: In most biopsy studies, Blacks have shown lower hepatic inflammation and fibrosis levels. There is no evidence that NAFLD mortality is higher in Latinos, and it may be lower in Blacks. We believe that there is presently insufficient evidence to confidently conclude that race, per se, plays a role in the development of the complications of NAFLD. Further studies, appropriately controlled for diet, exercise, and MetS parameters are needed.

REFERENCES

1 **Browning JD**, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, Grundy SM, Hobbs HH. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology* 2004; **40**: 1387-1395 [PMID: 15565570 DOI: 10.1002/hep.20466]

2 **Anstee QM**, Day CP. The genetics of NAFLD. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 645-655 [PMID: 24061205 DOI: 10.1038/nrgastro.2013.182]

3 **Kallwitz ER**, Tayo BO, Kuniholm MH, Cai J, Daviglus M, Cooper RS, Cotler SJ. American Ancestry Is a Risk Factor for Suspected Nonalcoholic Fatty Liver Disease in Hispanic/Latino Adults. *Clin Gastroenterol Hepatol* 2019; **17**: 2301-2309 [PMID: 30743004 DOI: 10.1016/j.cgh.2019.02.007]

4 **Lees R**, Kingston R, Williams TM, Henderson G, Lingford-Hughes A, Hickman M. Comparison of ethyl glucuronide in hair with self-reported alcohol consumption. *Alcohol Alcohol* 2012; **47**: 267-272 [PMID: 22336766 DOI: 10.1093/alcalc/ags010]

5 **Viel G**, Boscolo-Berto R, Cecchetto G, Fais P, Nalesso A, Ferrara SD. Phosphatidylethanol in blood as a marker of chronic alcohol use: a systematic review and meta-analysis. *Int J Mol Sci* 2012; **13**: 14788-14812 [PMID: 23203094 DOI: 10.3390/ijms131114788]

6 **Schneider AL**, Lazo M, Selvin E, Clark JM. Racial differences in nonalcoholic fatty liver disease in the U.S. population. *Obesity (Silver Spring)* 2014; **22**: 292-299 [PMID: 23512725 DOI: 10.1002/oby.20426]

7 **Kallwitz ER**, Daviglus ML, Allison MA, Emory KT, Zhao L, Kuniholm MH, Chen J, Gouskova N, Pirzada A, Talavera GA, Youngblood ME, Cotler SJ. Prevalence of suspected nonalcoholic fatty liver disease in Hispanic/Latino individuals differs by heritage. *Clin Gastroenterol Hepatol* 2015; **13**: 569-576 [PMID: 25218670 DOI: 10.1016/j.cgh.2014.08.037]

8 **Rich NE**, Oji S, Mufti AR, Browning JD, Parikh ND, Odewole M, Mayo H, Singal AG. Racial and Ethnic Disparities in Nonalcoholic Fatty Liver Disease Prevalence, Severity, and Outcomes in the United States: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2018; **16**: 198-210.e2 [PMID: 28970148 DOI: 10.1016/j.cgh.2017.09.041]

9 **Lear SA**, Gasevic D. Ethnicity and Metabolic Syndrome: Implications for Assessment, Management and Prevention. *Nutrients* 2019; **12** [PMID: 31861719 DOI: 10.3390/nu12010015]

10 **Loomba R**, Sanyal AJ. The global NAFLD epidemic. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 686-690 [PMID: 24042449 DOI: 10.1038/nrgastro.2013.171]

11 **Ong JP**, Younossi ZM. Epidemiology and natural history of NAFLD and NASH. *Clin Liver Dis* 2007; **11**: 1-16, vii [PMID: 17544968 DOI: 10.1016/j.cld.2007.02.009]

12 **Onyekwere CA**, Ogbera AO, Balogun BO. Non-alcoholic fatty liver disease and the metabolic syndrome in an urban hospital serving an African community. *Ann Hepatol* 2011; **10**: 119-124 [PMID: 21502672]

13 **Kalra S**, Vithalani M, Gulati G, Kulkarni CM, Kadam Y, Pallivathukkal J, Das B, Sahay R, Modi KD. Study of prevalence of nonalcoholic fatty liver disease (NAFLD) in type 2 diabetes patients in India (SPRINT). *J Assoc Physicians India* 2013; **61**: 448-453 [PMID: 24772746]

14 **Zou B**, Yeo YH, Nguyen VH, Cheung R, Ingelsson E, Nguyen MH. Prevalence, characteristics and mortality outcomes of obese, nonobese and lean NAFLD in the United States, 1999-2016. *J Intern Med* 2020; **288**: 139-151 [PMID: 32319718 DOI: 10.1111/joim.13069]

15 **Moore JX**, Chaudhary N, Akinyemiju T. Metabolic Syndrome Prevalence by Race/Ethnicity and Sex in the United States, National Health and Nutrition Examination Survey, 1988-2012. *Prev Chronic Dis* 2017; **14**: E24 [PMID: 28301314 DOI: 10.5888/pcd14.160287]

16 **Foster T**, Anania FA, Li D, Katz R, Budoff M. The prevalence and clinical correlates of nonalcoholic fatty liver disease (NAFLD) in African Americans: the multiethnic study of atherosclerosis (MESA). *Dig Dis Sci* 2013; **58**: 2392-2398 [PMID: 23546700 DOI: 10.1007/s10620-013-2652-7]

17 **Wagenknecht LE**, Scherzinger AL, Stamm ER, Hanley AJ, Norris JM, Chen YD, Bryer-Ash M, Haffner SM, Rotter JI. Correlates and heritability of nonalcoholic fatty liver disease in a minority cohort. *Obesity (Silver Spring)* 2009; **17**: 1240-1246 [PMID: 19584882 DOI: 10.1038/oby.2009.4]

18 **Cheng YJ**, Kanaya AM, Araneta MRG, Saydah SH, Kahn HS, Gregg EW, Fujimoto WY, Imperatore G. Prevalence of Diabetes by Race and Ethnicity in the United States, 2011-2016. *JAMA* 2019; **322**: 2389-2398 [PMID: 31860047 DOI: 10.1001/jama.2019.19365]

19 **Wong VW**, Chan WK, Chitturi S, Chawla Y, Dan YY, Duseja A, Fan J, Goh KL, Hamaguchi M, Hashimoto E, Kim SU, Lesmana LA, Lin YC, Liu CJ, Ni YH, Sollano J, Wong SK, Wong GL, Chan HL, Farrell G. Asia-Pacific Working Party on Non-alcoholic Fatty Liver Disease guidelines 2017-Part 1: Definition, risk factors and assessment. *J Gastroenterol Hepatol* 2018; **33**: 70-85 [PMID: 28670712 DOI: 10.1111/jgh.13857]

20 **Lim U**, Monroe KR, Buchthal S, Fan B, Cheng I, Kristal BS, Lampe JW, Hullar MA, Franke AA, Stram DO, Wilkens LR, Shepherd J, Ernst T, Le Marchand L. Propensity for Intra-abdominal and Hepatic Adiposity Varies Among Ethnic Groups. *Gastroenterology* 2019; **156**: 966-975.e10 [PMID: 30445012 DOI: 10.1053/j.gastro.2018.11.021]

21 **Rodriguez LA**, Jin Y, Talegawkar SA, Otto MCO, Kandula NR, Herrington DM, Kanaya AM. Differences in Diet Quality among Multiple US Racial/Ethnic Groups from the Mediators of Atherosclerosis in South Asians Living in America (MASALA) Study and the Multi-Ethnic Study of Atherosclerosis (MESA). *J Nutr* 2020; **150**: 1509-1515 [PMID: 32133497 DOI: 10.1093/jn/nxaa050]

22 **Yoshida H**, Maddock JE. Relationship Between Health Behaviors and Obesity in a Sample of Hawai'i's 4 Most Populous Ethnicities. *Hawaii J Health Soc Welf* 2020; **79**: 104-111 [PMID: 32328581]

23 **Gurka MJ**, Golden SH, Musani SK, Sims M, Vishnu A, Guo Y, Cardel M, Pearson TA, DeBoer MD. Independent associations between a metabolic syndrome severity score and future diabetes by sex and race: the Atherosclerosis Risk In Communities Study and Jackson Heart Study. *Diabetologia* 2017; **60**: 1261-1270 [PMID: 28378033 DOI: 10.1007/s00125-017-4267-6]

24 **Golabi P**, Locklear CT, Austin P, Afdhal S, Byrns M, Gerber L, Younossi ZM. Effectiveness of exercise in hepatic fat mobilization in non-alcoholic fatty liver disease: Systematic review. *World J Gastroenterol* 2016; **22**: 6318-6327 [PMID: 27468220 DOI: 10.3748/wjg.v22.i27.6318]

25 **Williams VF**, Oh GT, Stahlman S. Incidence and prevalence of the metabolic syndrome using ICD-9 and ICD-10 diagnostic codes, active component, U.S. Armed Forces, 2002-2017. *MSMR* 2018; **25**: 20-25 [PMID: 30620612]

26 **Yu SS**, Castillo DC, Courville AB, Sumner AE. The triglyceride paradox in people of African descent. *Metab Syndr Relat Disord* 2012; **10**: 77-82 [PMID: 22224930 DOI: 10.1089/met.2011.0108]

27 **Fan N**, Peng L, Xia Z, Zhang L, Song Z, Wang Y, Peng Y. Triglycerides to high-density lipoprotein cholesterol ratio as a surrogate for nonalcoholic fatty liver disease: a cross-sectional study. *Lipids Health Dis* 2019; **18**: 39 [PMID: 30711017 DOI: 10.1186/s12944-019-0986-7]

28 **Golabi P**, Paik J, Arshad T, Afendy M, Venkatesan C, Younossi Z. Factors associated with mortality in lean, overweight and obese non-alcoholic fatty liver disease. *Hepatology* 2019; **70**: A22

29 **Agbim U**, Carr RM, Pickett-Blakely O, Dagogo-Jack S. Ethnic Disparities in Adiposity: Focus on Non-alcoholic Fatty Liver Disease, Visceral, and Generalized Obesity. *Curr Obes Rep* 2019; **8**: 243-254 [PMID: 31144261 DOI: 10.1007/s13679-019-00349-x]

30 **Huh JH**, Kim KJ, Kim SU, Han SH, Han KH, Cha BS, Chung CH, Lee BW. Obesity is more closely related with hepatic steatosis and fibrosis measured by transient elastography than metabolic health status. *Metabolism* 2017; **66**: 23-31 [PMID: 27923446 DOI: 10.1016/j.metabol.2016.10.003]

31 **Bambha K**, Belt P, Abraham M, Wilson LA, Pabst M, Ferrell L, Unalp-Arida A, Bass N; Nonalcoholic Steatohepatitis Clinical Research Network Research Group. Ethnicity and nonalcoholic fatty liver disease. *Hepatology* 2012; **55**: 769-780 [PMID: 21987488 DOI: 10.1002/hep.24726]

32 **Lee SW**, Lee TY, Yang SS, Peng YC, Yeh HZ, Chang CS. The association of non-alcoholic fatty liver disease and metabolic syndrome in a Chinese population. *Hepatobiliary Pancreat Dis Int* 2017; **16**: 176-180 [PMID: 28381382 DOI: 10.1016/s1499-3872(16)60132-7]

33 **Del Campo JA**, Gallego-Durán R, Gallego P, Grande L. Genetic and Epigenetic Regulation in Nonalcoholic Fatty Liver Disease (NAFLD). *Int J Mol Sci* 2018; **19** [PMID: 29562725 DOI: 10.3390/ijms19030911]

34 **Mancina RM**, Dongiovanni P, Petta S, Pingitore P, Meroni M, Rametta R, Borén J, Montalcini T, Pujia A, Wiklund O, Hindy G, Spagnuolo R, Motta BM, Pipitone RM, Craxì A, Fargion S, Nobili V, Käkelä P, Kärjä V, Männistö V, Pihlajamäki J, Reilly DF, Castro-Perez J, Kozlitina J, Valenti L, Romeo S. The MBOAT7-TMC4 Variant rs641738 Increases Risk of Nonalcoholic Fatty Liver Disease in Individuals of European Descent. *Gastroenterology* 2016; **150**: 1219-1230.e6 [PMID: 26850495 DOI: 10.1053/j.gastro.2016.01.032]

35 **Sookoian S**, Pirola CJ. Genetic predisposition in nonalcoholic fatty liver disease. *Clin Mol Hepatol* 2017; **23**: 1-12 [PMID: 28268262 DOI: 10.3350/cmh.2016.0109]

36 **Grimaudo S**, Pipitone RM, Pennisi G, Celsa C, Cammà C, Di Marco V, Barcellona MR, Boemi R, Enea M, Giannetti A, Spatola F, Marchesini G, Craxì A, Petta S. Association Between PNPLA3 rs738409 C>G Variant and Liver-Related Outcomes in Patients With Nonalcoholic Fatty Liver Disease. *Clin Gastroenterol Hepatol* 2020; **18**: 935-944.e3 [PMID: 31419571 DOI: 10.1016/j.cgh.2019.08.011]

37 **Tepper CG**, Dang JHT, Stewart SL, Fang DM, Wong KA, Liu SY, Davis RR, Dao DY, Gregg JP, Török NJ, Chen MS Jr. High frequency of the PNPLA3 rs738409 [G] single-nucleotide polymorphism in Hmong individuals as a potential basis for a predisposition to chronic liver disease. *Cancer* 2018; **124** Suppl 7: 1583-1589 [PMID: 29578593 DOI: 10.1002/cncr.31122]

38 **Liu YL**, Reeves HL, Burt AD, Tiniakos D, McPherson S, Leathart JB, Allison ME, Alexander GJ, Piguet AC, Anty R, Donaldson P, Aithal GP, Francque S, Van Gaal L, Clement K, Ratziu V, Dufour JF, Day CP, Daly AK, Anstee QM. TM6SF2 rs58542926 influences hepatic fibrosis progression in patients with non-alcoholic fatty liver disease. *Nat Commun* 2014; **5**: 4309 [PMID: 24978903 DOI: 10.1038/ncomms5309]

39 **Marchesini G**, Bugianesi E, Forlani G, Cerrelli F, Lenzi M, Manini R, Natale S, Vanni E, Villanova N, Melchionda N, Rizzetto M. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. *Hepatology* 2003; **37**: 917-923 [PMID: 12668987 DOI: 10.1053/jhep.2003.50161]

40 **Kim D**, Kim WR, Kim HJ, Therneau TM. Association between noninvasive fibrosis markers and mortality among adults with nonalcoholic fatty liver disease in the United States. *Hepatology* 2013; **57**: 1357-1365 [PMID: 23175136 DOI: 10.1002/hep.26156]

41 **Ekstedt M**, Hagström H, Nasr P, Fredrikson M, Stål P, Kechagias S, Hultcrantz R. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. *Hepatology* 2015; **61**: 1547-1554 [PMID: 25125077 DOI: 10.1002/hep.27368]

42 **Dulai PS**, Singh S, Patel J, Soni M, Prokop LJ, Younossi Z, Sebastiani G, Ekstedt M, Hagstrom H, Nasr P, Stal P, Wong VW, Kechagias S, Hultcrantz R, Loomba R. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. *Hepatology* 2017; **65**: 1557-1565 [PMID: 28130788 DOI: 10.1002/hep.29085]

43 **Angulo P**, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, Mills PR, Keach JC, Lafferty HD, Stahler A, Haflidadottir S, Bendtsen F. Liver Fibrosis, but No Other Histologic Features, Is Associated With Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease. *Gastroenterology* 2015; **149**: 389-97.e10 [PMID: 25935633 DOI: 10.1053/j.gastro.2015.04.043]

44 **Setiawan VW**, Stram DO, Porcel J, Lu SC, Le Marchand L, Noureddin M. Prevalence of chronic liver disease and cirrhosis by underlying cause in understudied ethnic groups: The multiethnic cohort. *Hepatology* 2016; **64**: 1969-1977 [PMID: 27301913 DOI: 10.1002/hep.28677]

45 **Leung JC**, Loong TC, Wei JL, Wong GL, Chan AW, Choi PC, Shu SS, Chim AM, Chan HL, Wong VW. Histological severity and clinical outcomes of nonalcoholic fatty liver disease in nonobese patients. *Hepatology* 2017; **65**: 54-64 [PMID: 27339817 DOI: 10.1002/hep.28697]

46 **Sebastiani G**, Alshaalan R, Wong P, Rubino M, Salman A, Metrakos P, Deschenes M, Ghali P. Prognostic Value of Non-Invasive Fibrosis and Steatosis Tools, Hepatic Venous Pressure Gradient (HVPG) and Histology in Nonalcoholic Steatohepatitis. *PLoS One* 2015; **10**: e0128774 [PMID: 26083565 DOI: 10.1371/journal.pone.0128774]

47 **Bril F**, Portillo-Sanchez P, Liu IC, Kalavalapalli S, Dayton K, Cusi K. Clinical and Histologic Characterization of Nonalcoholic Steatohepatitis in African American Patients. *Diabetes Care* 2018; **41**: 187-192 [PMID: 29133343 DOI: 10.2337/dc17-1349]

48 **Browning MG**, Khoraki J, DeAntonio JH, Mazzini G, Mangino MJ, Siddiqui MS, Wolfe LG, Campos GM. Protective effect of black relative to white race against non-alcoholic fatty liver disease in patients with severe obesity, independent of type 2 diabetes. *Int J Obes (Lond)* 2018; **42**: 926-929 [PMID: 29437160 DOI: 10.1038/ijo.2017.309]

49 **Satapathy SK**, Marella HK, Heda RP, Ganguli S, Kirthi Reddy Y, Podila PSB, Clark I, Maliakkal B. African Americans have a distinct clinical and histologic profile with lower prevalence of NASH and advanced fibrosis relative to Caucasians. *Eur J Gastroenterol Hepatol* 2021; **33**: 388-398 [PMID: 32317586 DOI: 10.1097/MEG.0000000000001735]

50 **Lomonaco R**, Ortiz-Lopez C, Orsak B, Finch J, Webb A, Bril F, Louden C, Tio F, Cusi K. Role of ethnicity in overweight and obese patients with nonalcoholic steatohepatitis. *Hepatology* 2011; **54**: 837-845 [PMID: 21674556 DOI: 10.1002/hep.24483]

51 **Kanwal F**, Kramer JR, Mapakshi S, Natarajan Y, Chayanupatkul M, Richardson PA, Li L, Desiderio R, Thrift AP, Asch SM, Chu J, El-Serag HB. Risk of Hepatocellular Cancer in Patients With Non-Alcoholic Fatty Liver Disease. *Gastroenterology* 2018; **155**: 1828-1837.e2 [PMID: 30144434 DOI: 10.1053/j.gastro.2018.08.024]

52 **Unalp-Arida A**, Ruhl CE. Liver fibrosis scores predict liver disease mortality in the United States population. *Hepatology* 2017; **66**: 84-95 [PMID: 28195363 DOI: 10.1002/hep.29113]

53 **Kim D**, Li AA, Perumpail RB, Cholankeril G, Gonzalez SA, Kim W, Ahmed A. Disparate Trends in Mortality of Etiology-Specific Chronic Liver Diseases Among Hispanic Subpopulations. *Clin Gastroenterol Hepatol* 2019; **17**: 1607-1615.e2 [PMID: 30391436 DOI: 10.1016/j.cgh.2018.10.045]

54 **Yoon H**, Chen CM. Surveillance Report #105. Liver cirrhosis mortality in the United States: national, state, and regional trends, 2000-2013. National Institute on Alcohol Abuse and Alcoholism

2016: 1-69

55 **Adejumo AC**, Samuel GO, Adegbala OM, Adejumo KL, Ojelabi O, Akanbi O, Ogundipe OA, Pani L. Prevalence, trends, outcomes, and disparities in hospitalizations for nonalcoholic fatty liver disease in the United States. *Ann Gastroenterol* 2019; **32**: 504-513 [PMID: 31474798 DOI: 10.20524/aog.2019.0402]

56 **Vilar-Gomez E**, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, Friedman SL, Diago M, Romero-Gomez M. Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis. *Gastroenterology* 2015; **149**: 367-78.e5; quiz e14 [PMID: 25865049 DOI: 10.1053/j.gastro.2015.04.005]

57 **Goode RW**, Styn MA, Mendez DD, Gary-Webb TL. African Americans in Standard Behavioral Treatment for Obesity, 2001-2015: What Have We Learned? *West J Nurs Res* 2017; **39**: 1045-1069 [PMID: 28322668 DOI: 10.1177/0193945917692115]

58 **Zhang C**, Gao F, Luo H, Zhang CT, Zhang R. Differential response in levels of high-density lipoprotein cholesterol to one-year metformin treatment in prediabetic patients by race/ethnicity. *Cardiovasc Diabetol* 2015; **14**: 79 [PMID: 26068179 DOI: 10.1186/s12933-015-0240-1]

59 **Egan BM**, White K. Weight Loss Pharmacotherapy: Brief Summary of the Clinical Literature and Comments on Racial Differences. *Ethn Dis* 2015; **25**: 511-514 [PMID: 26675365 DOI: 10.18865/ed.25.4.511]

60 **DeSouza C**, Cariou B, Garg S, Lausvig N, Navarria A, Fonseca V. Efficacy and Safety of Semaglutide for Type 2 Diabetes by Race and Ethnicity: A Post Hoc Analysis of the SUSTAIN Trials. *J Clin Endocrinol Metab* 2020; **105** [PMID: 31769496 DOI: 10.1210/clinem/dgz072]

61 **Khorgami Z**, Arheart KL, Zhang C, Messiah SE, de la Cruz-Muñoz N. Effect of ethnicity on weight loss after bariatric surgery. *Obes Surg* 2015; **25**: 769-776 [PMID: 25430619 DOI: 10.1007/s11695-014-1474-9]

62 **Admiraal WM**, Celik F, Gerdes VE, Dallal RM, Hoekstra JB, Holleman F. Ethnic differences in weight loss and diabetes remission after bariatric surgery: a meta-analysis. *Diabetes Care* 2012; **35**: 1951-1958 [PMID: 22923683 DOI: 10.2337/dc12-0260]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2021 Baishideng Publishing Group Inc. All rights reserved.