Nonalcoholic Fatty Liver Disease and Associated Risk Factors in a Community-Based Sample of Mexican-Origin Adults

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The incidence of nonalcoholic fatty liver disease (NAFLD) is highest among Mexican-origin (MO) adults. Few studies have estimated the prevalence of NAFLD in this subpopulation, particularly by sex and age. We assessed the prevalence of NAFLD in a community sample of MO adults residing in a border region of southern Arizona and determined risk factors associated with NAFLD. A total of 307 MO adults (n = 194 women; n = 113 men) with overweight or obesity completed an in-person study visit, including vibration-controlled transient elastography (FibroScan) for the assessment of NAFLD status. A continuous attenuation parameter score of ≥288 dB/m (≥5% hepatic steatosis) indicated NAFLD status. Multivariable logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for NAFLD. We identified 155 participants (50%) with NAFLD, including 52% of women and 48% of men; there were no sex differences in steatosis (men, 287.8 dB/m; women, 288.4 dB/m). Sex, age, patatin-like phospholipase domain containing 3 (*PNPLA3*) risk allele carrier status, comorbidities, and cultural and behavioral variables were not associated with NAFLD status. There was some evidence for effect modification of body mass index (BMI) by sex ($P_{interaction}$ = 0.08). The estimated OR for an increase in BMI of 5 kg/m^2 was 3.36 (95% CI, 1.90, 5.91) for men and 1.92 (95% CI, 1.40, 2.64) for women. In post hoc analyses treating steatosis as a continuous variable in a linear regression, significant effect modification was found for BMI by sex ($P_{interaction}$ = 0.03), age (P = 0.05), and *PNPLA3* risk allele carrier status (P = 0.02). *Conclusion:* Lifestyle interventions to reduce body weight, with consideration of age and genetic risk status, are needed to stem the higher rates of NAFLD observed for MO populations. (*Hepatology Communications* 2022;6:1322-1335).

Nonalcoholic fatty liver disease (NAFLD) is the hepatic manifestation of metabolic syndrome that is defined as steatosis affecting ≥5% of hepatocytes not caused by excess alcohol intake, hepatitis B or C, autoimmune hepatitis, iron overload, drugs, or toxins.[1-3] It is estimated to affect approximately 20% (64 million) of the United States (US)

population each year, leading to annual medical costs exceeding $100 billion.[4] Although not all individuals with NAFLD progress to end-stage liver disease, nearly 30% are at greater risk for developing cirrhosis, portal hypertension, and hepatocellular carcinoma (HCC), making NAFLD an emerging risk factor for HCC that is projected to become the leading cause of

liver-related morbidity and mortality.[5] Additionally, NAFLD is the fastest growing indication for liver transplantation in the US, with rates projected to increase by 55% between years 2016 and 2030.[6]

The incidence of NAFLD is highest in Mexican-origin (MO) adults compared to all adults of Hispanic origin and all racial and ethnic subpopulations in the US. Population-based cohort studies have defined NAFLD using various assessment methodologies, and overall prevalence rates of NAFLD for Hispanics have ranged from 18.8% to 70.7%.[7-13] However, few population-based studies have focused specifically on MO populations and none in the border region of southern Arizona. Estimates from the National Health and Nutrition Examination Survey (NHANES) 2017-2018 using vibration-controlled transient elastography (VCTE) demonstrated Hispanic populations had a higher NAFLD prevalence (63.7% overall; men, 70.7%; women, 57.0%) compared with all women (48.8%) and other race or ethnicities (non-Hispanic White, 56.8%; non-Hispanic Black, 46.2%); however, no data were provided specifically for MO adults.[11] More recently, Shaheen et al.[13] estimated the prevalence of severe hepatic steatosis in NHANES 2017-2018 was highest among Mexican Americans (42.8%) compared to non-Hispanic Blacks (21.6%), non-Hispanic Whites (30.6%), and other Hispanics (27.6%); however, no estimates were provided for Mexican American men and women. Continued efforts to estimate the prevalence of NAFLD in MO populations, particularly by sex and age, are important to assess the magnitude and burden associated with this disease in a high-risk population underrepresented in the NAFLD literature.

Differences observed in the incidence of NAFLD by Hispanic heritage and sex have been attributed to a complex interaction of genetic, lifestyle, and environmental factors.[10] For example, MO adults have the highest rates of obesity and type 2 diabetes mellitus in the US, both of which are strongly associated with NAFLD.[12] Other primary lifestyle risk factors for NAFLD include physical inactivity and high levels of sugar-sweetened beverage consumption,[12,14-16] behaviors that are highly evidenced among MO men and women. Risk of NAFLD is further increased in MO adults by a greater frequency (up to 55%) of the rs738409 C/G variant in patatin-like phospholipase domain-containing 3 (*PNPLA3*), which confers a substantially greater susceptibility to NAFLD and HCC.[10,12,17] Estimates from a Mexican population suggests the frequency of the G risk allele is higher at 77%, including 54.5% for the GG genotype and 11% for the CC genotype.[18] This variant is reported to be the strongest common genetic variant associated with NAFLD severity and progression, accounting for 5.3% of total phenotypic variance.[19] The marked variation in lifestyle factors and underlying genetic risk for NAFLD by sex and Hispanic subpopulations

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warrants further investigation. Therefore, the purpose of this study was to 1) assess the prevalence of NAFLD in a community sample of MO adults residing in a border region of southern Arizona and 2) determine risk factors (e.g., lifestyle, acculturation, *PNPLA3* risk allele carrier status) associated with NAFLD in this study sample.

Participants and Methods

STUDY SAMPLE

To be eligible, participants must have self-identified as MO, been 18-64 years of age, had a body mass index (BMI) ≥ 25 kg/m², had the ability to provide informed consent, and had the ability to speak, read, and write in English and/or Spanish. Given that the risk of NAFLD is more prevalent at higher BMIs, we chose to limit our inclusion criteria to adults classified as overweight or obese. Individuals were excluded if they reported ongoing or recent alcohol consumption (≥21 standard drinks on average per week for men and ≥14 standard drinks on average per week for women); had a history of exposure to hepatotoxic drugs; were previously diagnosed with liver disease or liver cancer; had an active chronic gastrointestinal disorder (e.g., inflammatory bowel disease, ulcerative colitis, Crohn's disease, celiac disease); were taking any medication or supplement known to affect body composition; had uncontrolled vascular or metabolic disease (e.g., high blood pressure, type 2 diabetes); had any syndrome or disease known to affect body composition or fat distribution; participated in any structured exercise, nutrition, or weight-loss program within 6 months of recruitment; previously had bariatric surgery; or were currently pregnant or breastfeeding. These exclusion criteria were selected based on factors known to affect liver steatosis and fibrosis.[20] Detailed exclusion criteria can be found in Supporting Table S1.

In-person research activities took place at Arizona Liver Health in Tucson, AZ. All participants provided informed consent, and all study procedures were approved by the University of Arizona Institutional Review Board (IRB #1902380787). In addition, a Certificate of Confidentiality (CC-OD-19-293) was obtained due to the ethical considerations of our population (e.g., citizenship status) and the sensitive research information (genetics) collected.

RECRUITMENT

Recruitment efforts primarily targeted community-based settings that had demonstrated success in previous studies.[21-24] These included the Tucson Tanque Verde Swap Meet (an outdoor marketplace), the Consulate of Mexico in Tucson, churches, and community centers. Further, collaborations with stakeholders, health clinics, and media groups that serve Tucson's Hispanic community allowed for the use of community events and listserves to enhance recruitment efforts. Throughout recruitment efforts, an emphasis was placed largely on face-to-face recruitment, a strategy that has been shown to be particularly important when recruiting MO populations.[25] Recruitment took place in Tucson, AZ, between May 2019 and March 2020, with study visits occurring in an ongoing manner throughout this time period. All research activities were stopped March 14, 2020, due to the corona virus disease 2019 pandemic. The final analytic sample represents data for MO adults who completed all study procedures (n = 307), including 194 women and 113 men (Fig. 1). Notably, this sample size represents 76.8% of the study recruitment goal of 400 MO adults (200 women and 200 men).

STUDY PROCEDURES AND MEASURES

Following the signing of informed consent, participants completed a 60-90 minute in-person study visit, including anthropometric assessment, collection of a genetic sample, a VCTE (FibroScan) for the assessment of NAFLD status, and self-reported questionnaires related to demographics, acculturation, and lifestyle behaviors. Dietary recalls by telephone were completed after the in-person study visit. In-person study visits, self-reported questionnaires, and dietary recalls were completed in the participant's language of preference (English or Spanish). All questionnaires were reviewed in person with each participant by study staff during the in-person visit to ensure all questions were completed. All participants received a written summary of their anthropometric assessment and VCTE results along with a list of local health care providers should they choose to seek medical care or discuss the results of their FibroScan with a provider. At the end of the study visit, participants were compensated US $25 for their time and were
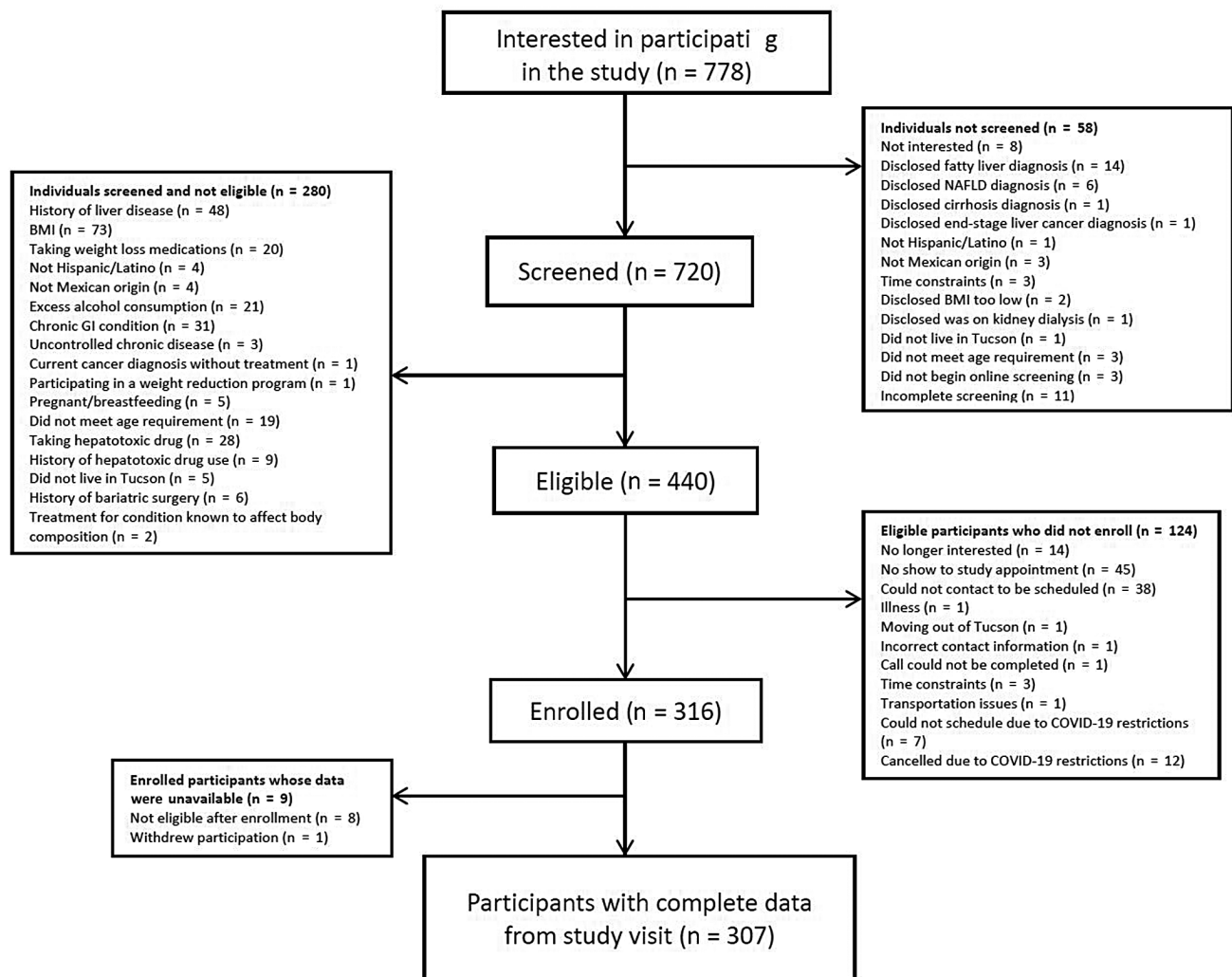
FIG. 1. Flow diagram for the recruitment of the study participants. Abbreviations: COVID-19, corona virus disease 2019; GI, gastrointestinal.

compensated an additional $25 following completion of dietary recalls.

ANTHROPOMETRICS

Standardized methods were used to collect participants' height, weight, and waist circumference.[26] The participant's height was measured without shoes, twice to the nearest 0.1 cm, using a wall-mounted stadiometer (ShorrBoard). A third measurement was taken if the two measurements differed by more than 0.5 cm. With shoes remaining off and the participant in street clothes, body weight was measured twice on a calibrated digital scale (Seca 876) to the nearest 0.1 kg. A third measurement was taken if the two measurements differed by more than 0.2 kg. The average of the two measurements that met the criteria for height and weight were used to calculate the BMI using body weight in kilograms divided by squared height in meters (kg/m^2). Two measurements of waist circumference directly at the umbilicus were measured to the nearest 0.1 cm by using a Gulick measuring tape. A third measurement was taken if the first two measurements differed by more than 2.0 cm, with the average of the two measurements closest to each other documented for data collection.

NAFLD ASSESSMENT

VCTE (FibroScan 502 Touch model; Echosens, Paris, France) was used to measure participants' liver steatosis and liver stiffness (a validated proxy for fibrosis).[27,28] The FibroScan is a 10-15-minute noninvasive technique that transmits prorogated shear waves within the liver by using M or XL probes. All participants were asked to fast for at least 3 hours before the scan, which was performed by a certified physician or technician who obtained a minimum of 10 measurements from each participant. The speed of the shear wave also provides liver stiffness measurements (LSMs) from the velocity of liver tissue microdisplacements induced by propagated shear waves. The device simultaneously calculated the median continuous attenuation parameter (CAP) and LSM values along with the interquartile range (IQR). CAP is measured in decibels per meter (dB/m), and values range from 100-400 dB/m, with higher values indicating higher amounts of liver fat. CAP measurements are considered valid when the IQR of CAP is <30 dB/m and 10 valid measurements are achieved.[27,29] A CAP score ≥288 dB/m (≥5% hepatic steatosis) indicated NAFLD status.[27] This threshold has been validated with our study population and is an acceptable strategy for the screening of NAFLD.[27] However, we also examined the following steatosis stages used in previous populations studies:[11,30] none (S0), CAP < 248 dB/m; mild (S1), CAP 248 to <268 dB/m (10%-33% steatosis); moderate (S2), 268 to <280 dB/m; and severe (S3), ≥280 dB/m (>66% steatosis). LSM measurements range from 1.5 kPa to 75 kPa, with higher values indicating more severe fibrosis. Fibrosis severity cut-off values used were <7.9 kPa (F0-F1), 7.9 to <8.8 kPa (F2), 8.8 to <11.7 kPa (F3), and ≥11.7 kPa (F4).[28] LSM values of 7.9 kPa or greater indicated significant fibrosis.[28] All participants were given the opportunity to review their VCTE results with a physician, one of whom was bilingual and bicultural.

GENOTYPING

Two buccal swabs (Whatman OmniSwab), one from each cheek, were collected from the study participants. After collection, the University of Arizona Genetics Core isolated genomic DNA, quantitated

it, and used it as the template in a TaqMan single-nucleotide polymorphism (SNP) genotyping assay. The genotype at the rs738409 SNP, located in codon 148 of *PNPLA3,* was then determined for each participant categorized as genotypes CC (no-risk alleles), CG (one-risk allele), and GG (two-risk alleles).

SELF-REPORTED QUESTIONNAIRES

A demographics questionnaire was administered to collect information regarding age, health status (diagnosed controlled hypertension or type 2 diabetes), marital status (married or live-in partner), employment status, annual household income, highest level of education completed, health insurance status, and primary language spoken at home. The validated Acculturation Rating Scale for Mexican-Americans–II was used to assess cultural orientation through a multidimensional approach.[31] The 30-item scale was used to assess the Anglo Orientation Subscale (AOS; 13 items) and the Mexican Orientation Subscale (MOS; 17 items). The items selected for each subscale were added and divided by the number of items on the MOS and AOS scales separately to obtain a raw score mean for each scale. This allowed acculturative types, such as traditional Mexican, integrated low bicultural, and integrated high bicultural, to be identified. In addition, place of birth was obtained from the participant's response to generation status. Those who self-identified as first generation (born in Mexico or other country besides the United States) were classified as foreign born. Physical activity was assessed using the validated Global Physical Activity Questionnaire (GPAQ).[32,33] The GPAQ was administered to participants by study staff using show cards in either English or Spanish to assist participants in completing the questionnaire accurately. The GPAQ provides minutes per week of leisure time physical activity (LTPA) calculated by responses to intensity type (moderate-vigorous), frequency (days/week), and duration (minutes). Lastly, sleep quality over the past month was assessed using the Pittsburgh Sleep Quality Index (PSQI).[34] The PSQI includes 19 self-rated items combined into seven component scores (sleep duration, sleep disturbance, sleep latency, daytime dysfunction due to sleepiness, sleep

efficiency, overall sleep quality, and sleep medication use). Component scores range from 0 to 3 points (0, no difficulty; 3, severe difficulty). The sum of the seven component scores results in the total global score with a range from 0 to 21 and a score of ≥5 indicating poor sleep quality.

DIETARY RECALLS

Dietary intake was assessed by three 24-hour dietary recalls on two weekdays and one weekend day, using the US Department of Agriculture Automated Multiple-Pass Method.[35] All recalls were administered by trained bilingual staff by telephone in the participant's preferred language. A food amounts booklet was provided to participants at the completion of the in-person study visit to assist in estimating portion sizes during the recalls. The nutrition data were analyzed by using the Nutrition Data System for Research, version 18.[36] Diet quality was assessed using the Healthy Eating Index (HEI)-2015, a diet quality index that has demonstrated validity and reliability for measuring alignment with the Dietary Guidelines for Americans.[37] The HEI-2015 includes 13 dietary components consisting of nine adequacy components and four moderation components. Each component was assigned a maximum of 5-10 points, with the total HEI score ranging from 0 to 100 points, with a higher score aligning with the dietary guidelines.[37] HEI-2015 has been used previously to assess diet quality and eating practices among Hispanic/Latino men and women.[38]

STATISTICAL METHODS

Summary statistics were used to describe the sample stratified by NAFLD status. Because physical activity was skewed, we used the median and IQR. We compared individuals with and without NAFLD by using t tests and chi-squared tests for continuous and categorical variables, respectively. Point-biserial correlation (continuous variables) and Kendall's tau correlation (categorical variables) were used to estimate the correlation between NAFLD and each of the variables. To investigate possible sex differences, we compared steatosis and fibrosis scores by sex using t tests as well as repeating our initial univariate tests by sex.

Multivariable logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for NAFLD and were specified *a priori*. Our base model (model 1) included *PNPLA3*, age, sex, BMI, and the interaction of BMI and sex, as there is evidence that each of these variables is a NAFLD risk factor and that the association with BMI may be modified by sex.[4,12] We chose BMI over waist circumference or weight by itself because of its strong association with NAFLD as well as its interpretability. We did not include waist circumference in the same model as BMI due to the high correlation between these variables. We then fit several other models: model 1 + comorbidities (diabetes, hypertension); model 1 + cultural variables (MOS, home language preference); model 1 + behavioral variables (LTPA, sleep quality, and HEI). We used the concordance index (c-index) to assess whether these added variables improved the fit of model 1. The c-index is a measure of goodness of fit for logistic models, with values close to 1 indicating good fit to the data. Although some genetic models assume a linear relationship (coded continuously as 0, 1, 2), we used *PNPLA3* as a categorical variable (CC, GC, CG) because descriptive statistics did not support a linear relationship. However, we also examined the *PNPLA3* genotype, assuming an additive/linear model. For self-reported questionnaire variables (MOS, PSQI, HEI-2015), we estimated ORs for an increase of 1 SD. Prevalence of NAFLD by sex was estimated from model 1. Prevalence and 95% CI of steatosis stage and fibrosis stage, with the same cutoffs as Zhang et al.,[11] were estimated.

The primary aim of this study was to estimate the prevalence of NAFLD, but we recognize that dichotomization of continuous variables can lead to decreased power and misclassification bias.[39] Therefore, we performed additional post hoc supporting analyses using hepatic steatosis score as a continuous variable using the covariates from model 1. All analyses were conducted in SAS, version 9.4 (Cary, NC).

Results

There were 307 participants, 155 (50%) of which were classified as having NAFLD (Table 1). Participants were mostly women (194, 63%), with a mean age of 44.5 years, BMI of 32.7 kg/m^2, weight of 88.9 kg, and waist circumference of 106.7 cm. Most participants were married or had a partner (222, 72.3%), were foreign born (214, 69.7%), preferred to

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF 307 MO MEN AND WOMEN (MAY 2019-MARCH 2020)

	Correlation with NAFLD*	No NAFLD (n = 152)	NAFLD (n = 155)	P Value[†]	Total (n = 307)
Liver steatosis (CAP; dB/m)	-	246.6 (30.3)	328.9 (28.8)	<0.0001	288.1 (50.6)
Liver fibrosis (kPa)	0.26	4.9 (1.2)	6.4 (3.7)	<0.0001	5.7 (2.8)
PNPLA3	0.08			0.18	
CC		42 (27.6)	38 (24.5)		80 (26.1)
CG		78 (51.3)	70 (45.2)		148 (48.2)
GG		32 (21.1)	47 (30.3)		79 (25.7)
Sex	0.04			0.47	
Female		93 (61.2)	101 (65.2)		113 (36.8)
Male		59 (38.8)	54 (34.8)		194 (63.2)
Age (years)	0.03	44.2 (11.7)	44.8 (10.7)	0.64	44.5 (11.2)
Age categories	0.03			0.58	
19-29		20 (13.2)	12 (7.7)		32 (10.4)
30-39		35 (23.0)	38 (24.5)		73 (23.8)
40-49		41 (27.0)	49 (31.6)		90 (29.3)
50-59		42 (27.6)	41 (26.5)		83 (27.0)
60-70		14 (9.2)	15 (9.7)		29 (9.5)
BMI (kg/m^2)	0.34	30.9 (4.1)	34.5 (5.7)	<0.0001	32.7 (5.3)
Weight (kg)	0.28	84.3 (13.6)	93.5 (17.9)	<0.0001	88.9 (16.6)
Waist circumference (cm)	0.36	101.9 (10.4)	111.3 (10.4)	<0.0001	106.7 (13.0)
Hypertension	0.03	29 (19.1)	33 (21.2)	0.63	62 (20.2)
Diabetes	0.07	12 (7.9)	19 (12.3)	0.20	31 (10.1)
Married/live-in partner	0.06	106 (69.7)	116 (74.8)	0.32	222 (72.3)
Employed	−0.10	115 (75.7)	103 (66.5)	0.08	218 (71.0)
Annual Household Income	−0.02			0.89	
<30K		76 (50.0)	81 (52.3)		157 (51.1)
30-60K		54 (35.5)	51 (32.9)		105 (34.2)
>60K		22 (14.5)	23 (14.8)		45 (14.7)
Education	−0.07			0.42	
Less than high school		40 (26.5)	50 (32.3)		90 (29.4)
High school or GED		32 (21.2)	70 (45.2)		67 (21.9)
Greater than high school		79 (52.3)	35 (22.6)		149 (48.7)
Health insurance	−0.05	94 (61.8)	89 (57.4)	0.43	183 (59.6)
Birthplace	0.07			0.21	
Foreign born		101 (66.5)	113 (72.9)		214 (69.7)
United States born		51(33.6)	42 (27.1)		93 (30.3)
Language at home	0.03			0.62	
Spanish		110 (72.4)	116 (74.8)		226 (73.6)
English		42 (27.6)	39 (25.2)		81 (26.4)
MOS (1-5)	−0.05	4.13 (0.62)	4.06 (0.66)	0.40	4.10 (0.64)
Acculturation	0.005			0.50	
Very Mexican oriented		78 (51.3)	73 (47.1)		151 (49.2)
Mexican oriented to approximately bicultural		40 (26.3)	48 (31.0)		88 (28.7)
Slightly Anglo bicultural		23 (15.1)	24 (15.5)		47 (15.3)
Strongly Anglo oriented		11 (7.2)	8 (5.2)		19 (6.2)
Very assimilated		0 (0)	2 (1.3)		2 (0.7)

TABLE 1. *Continued*

	Correlation with NAFLD*	No NAFLD (n = 152)	NAFLD (n = 155)	*P* Value[†]	Total (n = 307)
LTPA (hours/week; median, IQR)	0.03	1.5 (0, 3.0)	2.0 (0, 4.0)	0.34	1.6 (0, 3.5)
HEI (0-100)	0.008	55.7 (11.4)	55.9 (12.2)	0.90	55.8 (11.8)
Sleep (PSQI, 0-21)	0.003	6.0 (3.8)	6.0 (3.6)	0.97	296 (6.0)

Note: Values displayed are means (SD) of continuous variables and counts (%) of categorical variables unless otherwise noted. Missing data rates <1%, except for HEI (8%) and PSQI (4%).
Abbreviation: GED, General Educational Development.
*Point-biserial (continuous) and Kendall's tau (categorical). Steatosis not shown as this is how NAFLD is defined. Statistical significance for correlations was similar to *t* tests and chi-squared tests.
[†]*t* test (continuous) and chi-squared test (categorical).

TABLE 2. PREVALENCE OF STEATOSIS AND FIBROSIS STAGE IN 307 MO MEN AND WOMEN

Steatosis Stage by CAP	n (%)	95% CI for Prevalence
S0 (none): <248 dB/m	68 (22.2)	17.6, 22.7
S1 (mild): 248-267 dB/m	36 (11.7)	8.4, 15.9
S2 (moderate): 268-279 dB/m	30 (9.8)	9.8, 6.7
S3 (significant): ≥280 dB/m	173 (56.4)	50.6, 62.0
Fibrosis		
F0-F1 (<7.9 kPa)	271 (88.3)	84.1, 91.7
F2 (7.9 to <8.8 kPa)	15 (4.9)	2.8, 7.9
F3 (8.8 to <11.7 kPa)	15 (4.9)	2.8, 7.9
F4 (≥11.7 kPa)	6 (2.0)	0.7, 4.2

speak Spanish at home (226, 73.6%), had education of high school or less (157, 51.3%), were employed (218, 71.0%), and had an annual houshold income less than $30,000 per year (157, 51.1%). Median LTPA was 1.6 hours/week. The prevalence of S1, S2, and S3 steatosis stage by CAP were 36%, 30%, and 56.4%, respectively (Table 2). Nearly 12% of participants were identified as having significant fibrosis.

Statistically significant differences between individuals with and without NAFLD were found for BMI, weight, waist circumference, and liver fibrosis (P < 0.0001). When univariate analyses were repeated by sex, the same variables were significant but with slightly smaller differences for women (data not shown). No other variables were associated with NAFLD prevalence. The variables with highest correlation with NAFLD were waist circumference (r = 0.36), BMI (r = 0.34), weight (r = 0.28), and liver fibrosis (r = 0.26). All other correlations had magnitudes ≤0.1. There was no evidence of sex differences in steatosis (men, 287.8 dB/m; women, 288.4 dB/m) or fibrosis (men, 5.69 kPa; women, 5.56 kPa).

There was some evidence for effect modification of BMI by sex ($P_{interaction}$ = 0.08), particularly when considering the differences in effect size (Table 3). The estimated OR for an increase in BMI of 5 kg/m^2 was 3.36 (95% CI, 1.90, 5.91) for men and 1.92 (95% CI, 1.40, 2.64) for women. The estimated prevalence of NAFLD was 0.48 (95% CI, 0.44, 0.52) for men and 0.52 (95% CI, 0.50, 0.54) for women. Neither sex nor age were statistically significant, with an OR of 0.78 for women compared to men at a mean BMI of 32.7 kg/m^2 (95% CI, 0.44, 1.39) and an OR of 1.10 (95% CI, 0.98, 1.23) for each 5-year increase in age. *PNPLA3* genotype was also not statistically significant (P = 0.28), with an OR of 1.62 (95% CI, 0.82, 3.19) for GG compared to CC and 1.06 (95% CI, 0.59, 1.91) for CG compared to CC. Modeling *PNPLA3* genotype linearly did not show a statistically significant effect either. Including comorbidities, cultural variables or behavioral variables did not substantially improve the fit of the model, with c-indices 0.71-0.72. None of the added variables were statistically significant in any of the models, and estimates for BMI, sex, age, and *PNPLA3* were similar to those in model 1.

When steatosis was used as a continuous variable in a linear regression for post hoc supporting analyses, we found similar results but with increased power, as expected. We found significant effect modification of BMI by sex ($P_{interaction}$ = 0.03) as well as significant effects of age (P = 0.05) and *PNPLA3* (P = 0.02). An increase in BMI of 5 kg/m^2 resulted in an increase in steatosis of 42.2 dB/m (95% CI, 23.3, 61.0) for men but only 30.1 dB/m (95% CI, 21.1, 39.1) for

TABLE 3. FACTORS ASSOCIATED WITH NAFLD IN 307 MO MEN AND WOMEN

	Model 1: Age, Sex, BMI, BMI×Sex, *PNPLA3*	Model 1 + Comorbidities	Model 1 + Cultural Variables	Model 1 + Behavioral Variables
BMI (per 5 kg/m^2)	$P_{interaction}$ = 0.08*	$P_{interaction}$ = 0.08*	$P_{interaction}$ = 0.09*	$P_{interaction}$ = 0.13*
Male	3.40 (1.92, 6.00)	3.35 (1.90, 5.93)	3.44 (1.94, 6.01)	3.27 (1.84, 5.81)
Female	1.89 (1.38, 2.59)	1.90 (1.38, 2.60)	1.97 (1.42, 2.71)	1.98 (1.42, 2.75)
Sex (female vs. male, at mean BMI, 32.7 kg/m^2)	0.78 (0.44, 1.39)	0.80 (0.47, 1.38)	0.83 (0.48, 1.43)	0.84 (0.48, 1.47)
Age (per 5 years)	1.10 (0.98, 1.23)	1.10 (0.98, 1.24)	1.10 (0.98, 1.23)	1.09 (0.97, 1.22)
PNPLA3	P = 0.28	P = 0.32	P = 0.35	P = 0.17
CC	Reference	Reference	Reference	Reference
CG	1.06 (0.59, 1.91)	1.04 (0.57, 1.88)	1.08 (0.60, 1.96)	1.07 (0.58, 1.95)
GG	1.62 (0.82, 3.19)	1.57 (0.80, 3.11)	1.59 (0.80, 3.14)	1.80 (0.90, 3.60)
Diabetes		1.41 (0.60, 3.31)		
Hypertension		0.88 (0.45, 1.70)		
Language at home (Spanish vs. English)			1.90 (0.94, 3.82)	
MOS (per SD, 0.64)			0.89 (0.64, 1.21)	
LTPA (hours)				1.02 (0.95, 1.10)
Sleep quality (PSQI, per SD, 3.6)				0.94 (0.74, 1.21)
HEI (per SD, 11.4)				1.09 (0.84, 1.42)
c-index (0-1, larger is better)	0.712	0.714	0.722	0.717

Note: Values shown are ORs and 95% CIs.
*$P_{interaction}$ = P value for the BMI × sex term.

women. A 10-year increase in age was associated with an increase in steatosis of 4.7 dB/m (95% CI, 0.03, 9.4). Mean steatosis for individuals with the CC, CG, and GG genotypes was 280.9, 284.9, and 301.6 dB/m, respectively, with significant differences between CC versus GG and CG versus GG (see Fig. 2). In a linear model assuming an additive/linear genetic model controlling for age, sex, BMI, and sex by BMI interaction, we found a significant association of *PNPLA3* SNP with steatosis (beta = 9.5; 95% CI, 2.5, 16.6; P = 0.008).

Discussion

This study is among the first to use VCTE (FibroScan) to estimate the prevalence of NAFLD and to examine a comprehensive range of risk factors (comorbidities, behavioral, cultural, and genetic) in a community-based sample of MO adults. In a primarily Spanish-speaking, foreign-born study group residing in southern Arizona near the United States–Mexico border, the overall estimated prevalence of NAFLD was 50%. Women had a slightly higher prevalence of

NAFLD (52%) compared to men (48%); however, this difference was not statistically significant. There were significant differences in anthropometric measures (BMI, weight, waist circumference) and liver fibrosis for those identified with NAFLD compared to those without. However, there was no evidence of associations between NAFLD and comorbidities, cultural, and behavioral factors. In post hoc analyses, we did find a significant effect modification of BMI by sex (larger effect of BMI for men than women), age, and *PNPLA3* risk allele carrier status. Further, a significant association of the *PNPLA3* risk allele with steatosis was observed, particularly for individuals who were carriers of the GG genotype.

Overall, the prevalence rates of NAFLD observed in our study sample are higher than previous population-based studies. The Dallas Heart Study (DHS) was the first population-based study to examine NAFLD by race and ethnicity by using magnetic resonance (MR) spectroscopy.[7] In a sample of 401 Hispanics, including 172 men and 229 women, NAFLD was found to be significantly higher in Hispanics (45% for both men and women) compared to 33% in non-Hispanic Whites and 24% in non-Hispanic Blacks.[7] The
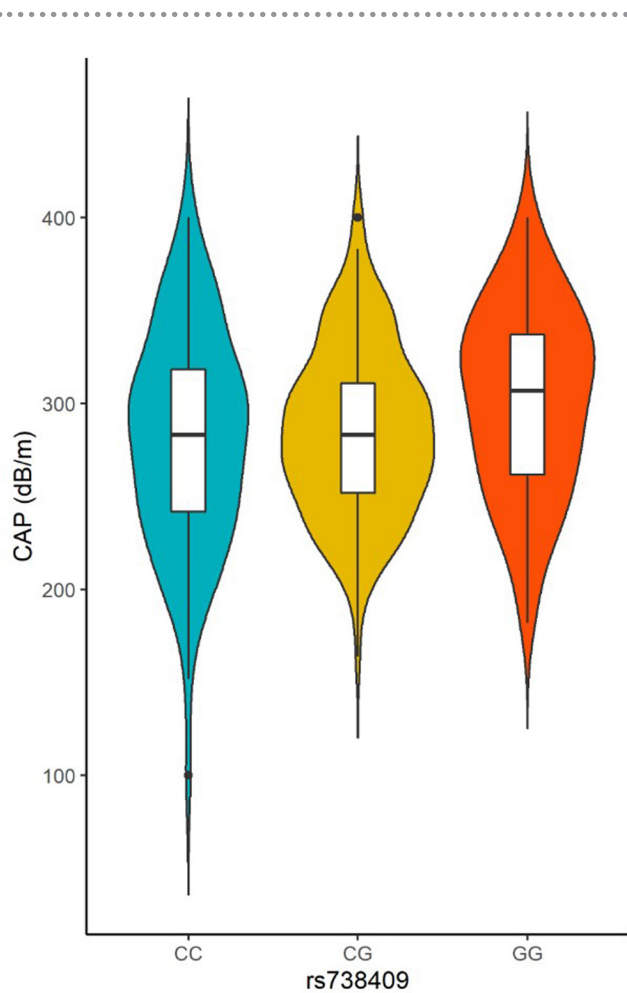
FIG. 2. Levels of liver steatosis (CAP; dB/m) among individuals with CC, CG, or GG genotypes of the *PNPLA3* rs738409 SNP. Violin plots show median value (horizontal line in middle), the first and third quartile (box), and first quartile – 1.5 IQR (lower whisker) and third quartile + 1.5 IQR (upper whisker). Colored area represents a kernel density estimation to show the distribution of the values.

authors attributed the higher prevalence of NAFLD in Hispanics to the higher prevalence of obesity and insulin resistance. Compared to our study sample, the DHS was a population based study; therefore, it is possible it was a more representative sample of individuals who enrolled due to general health concerns. In fact, Hispanic women and men in the DHS were on average 2 years younger and had lower BMIs (approximately 2 BMI units) compared to our study sample. In addition, the DHS used MR spectroscopy, a gold standard for noninvasive assessment of hepatic steatosis. Further, no data were reported specifically

for MO adults. These reasons could potentially explain the slightly lower NAFLD prevalence rates. Fleischman et al.[9] were the first to compare prevalence rates of NAFLD between U.S. Hispanic subpopulations, including Hispanics of MO and Hispanics of Caribbean origin (Dominican and Puerto Rican) in the Multi-Ethnic Study of Atherosclerosis (MESA). In a sample of 788 Hispanics (524 MO adults, 121 Dominicans, and 143 Puerto Ricans), cardiac computed tomography determined 33% (n = 179) of Hispanics of MO had NAFLD compared to 16% (n = 21) of Hispanics of Dominican origin and 18% (n = 25) of Hispanics of Puerto Rican origin.[9] Consistent with our findings, of the 179 Hispanics of MO identified with NAFLD, 52% (n = 93) were women and 48% (n = 86) were men.[9] When Fleischman et al.[9] examined predictors of NAFLD, including demographic, anthropomorphic, and physiologic characteristics, there were no significant differences across Hispanic subpopulations; however, when compared to each other, Hispanics of MO had significantly higher BMIs compared to Hispanics of Dominican origin. Notably, MO adults with NAFLD in our study sample had nearly identical BMIs as Hispanics of MO in MESA, yet they were almost 16 years younger and had a lower prevalence of comorbid conditions, such as hypertension and diabetes.

Within NHANES III (1988-1994), estimates of NAFLD assessed by ultrasonography for MO adults were 28.7% for MO women and 29.6% for MO men.[8,12] These estimates were higher in MO men with obesity, ranging from 48.6% to 59.5% for obese class I (BMI, 30-34.9 kg/m²) and class II (BMI, 35-39.9 kg/m²) categories.[8,12] Similar increases were observed for MO women (obese class I, 38.1%; obese class II, 52.2%). There were strong independent associations between diabetes or insulin resistance and dyslipidemia with NAFLD.[8] Further, sedentary individuals had a significantly higher prevalence of NAFLD independent of other risk factors.[8] Similar to our findings, no statistically significant interactions were found between age and sex or diabetes (comorbid condition) and BMI. However, we did find a clinically significant interaction between BMI and sex (when using NAFLD as the outcome) and a clinically and statistically significant interaction when using the continuous measure of steatosis. In the Hispanic Community Health Study/Study of Latinos (HCHS/SOL), levels of aminotransferase were used as a

surrogate biomarker to identify suspected NAFLD in a sample of 520 MO adults.[10] The overall prevalence of suspected NAFLD was 26% for MO men and 18.8% for MO women, an estimate much lower than previous studies. Notably, the HCHS/SOL study was the first to examine NAFLD based on levels of acculturation characterized by language use (e.g., Spanish language only, Spanish better than English, both equal, English better than Spanish, or English only). Similar to our findings, no behavioral (e.g., sleep disturbance, physical activity, or dietary carbohydrates) or cultural variables (e.g., acculturation) were directly associated with the odds of having NAFLD.[10] Given this finding, the authors suggested there are likely "undefined" factors playing a role in the presence and progression of NAFLD, specifically genetic predisposition.[10] Our post hoc analyses support this perspective as the *PNPLA3* G risk allele was found in 76% of MO individuals in our study sample identified with NAFLD. Further, higher levels of steatosis overall were observed for *PNPLA3* risk allele carriers.

More recently, estimates of the prevalence of NAFLD from NHANES 2017-2018 in the US general population by using VCTE were examined.[11] In this study by Zhang et al.,[11] NAFLD was defined by CAP scores ≥ 248 dB/m in the absence of excessive alcohol use and viral hepatitis. Overall, approximately 57% of participants were identified as having NAFLD. However, when stratified by sex and race or ethnicity, Hispanics (63.7%) had a higher prevalence of NAFLD compared to non-Hispanic Whites (56.8%) and non-Hispanic Blacks (46.2%).[11] Hispanic men had the highest prevalence overall (70.7%), regardless of sex and race or ethnicity, and Hispanic women had the highest prevalence among all women (57.0%) in the US. There are a few potential reasons for the differences observed compared to our estimated prevalence rates. We chose to use a CAP score ≥ 288 dB/m to identify NAFLD based on previous work in MO populations.[27] If we had used a CAP score ≥ 248 dB/m, our overall prevalence estimates would have been 77.9%, including 77.3% for women and 78.8% for men. In fact, when authors applied a more stringent cut-off of ≥290 dB/m in NHANES 2017-2018, the prevalence of NAFLD was lower at 40.5% for Hispanics with 47.0% and 34.4% for men and women, respectively.[11] Using the same cut-off, Shaheen et al.[13] estimated the prevalence of NAFLD specifically for Mexican Americans to be 42.8%. As demonstrated

in the studies described above, we would expect higher rates to be observed in this population due to genetic predisposition alone. Further, our sample had an average BMI that was 2 units higher than those in Zhang et al.[11] (34.5 kg/m^2 vs. 32.7 kg/m^2) in those identified with NAFLD.

A potential reason for differences in the prevalence of NAFLD across studies described above could be attributed to the variance in the definitions of NAFLD and assessment techniques used. While liver biopsy is the gold standard for NAFLD diagnosis, the procedure is invasive, has a high degree of variability and sampling error, and carries associated risks and costs.[40] A recent systematic review conducted by Monelli et al.[41] examined existing guidelines for NAFLD assessment and identified the development of noninvasive tests to replace liver biopsy as a research priority. While ultrasound was the most frequently recommended technique to confirm liver steatosis, using other techniques, such as elastography (e.g., VCTE), in combination with liver function tests and fibrosis scores to identify individuals at risk of advanced liver disease has also been recommended.[41] Indeed, a combination of assessment modalities can provide more accurate diagnosis and liver disease severity staging that is critical to continued monitoring and future assessment of treatment options.[42] Further, using a combination of noninvasive assessment techniques, particularly within community-based settings, could provide a more efficient process for referral to a hepatologist for follow-up care beyond the initial assessment and identification of NAFLD. This could have a broader implication for improving health equity among underserved communities, which often have limited time and resources to gain access to health care services for liver disease.

A key strength of our study was adding to the limited number of studies that estimated the prevalence of NAFLD among Hispanics, in this case specifically among MO Hispanics with overweight or obesity residing near the border of United States–Mexico in southern Arizona. This approach is warranted given the disparate rates of this condition among Hispanics based on country of origin.[9] Our study sample was a well-characterized community-based sample of MO adults that were largely Spanish speaking and foreign born. Often times this population is difficult to recruit for research, and our work has demonstrated that we can overcome this barrier, particularly when Hispanic

adults are informed on the emerging concern with NAFLD in the community. Additionally, our comprehensive assessment of risk factors, which included a validated measure of acculturation, allowed us to fit several models to determine if additional insights could be obtained apart from more well-established NAFLD risk factors. In fact, we identified BMI by sex, age, and *PNPLA3* risk allele carrier status as factors associated with steatosis.

This study is not without limitations. We did not have biological samples to measure insulin resistance, and confirm diabetes and hyperlipidemia status, which are other common risk factors of NAFLD. Our sample did not have representation of normal-weight individuals, and as such our prevalence rates likely overestimate prevalence in the overall adult population wherein an estimated 25.3% of Hispanic adults in the region would be expected to be of normal BMI ($\geq$18.5-24.9 kg/m^2).[43]

It has been demonstrated that NAFLD develops in individuals with a normal BMI (lean NAFLD), and risk factors may differ in this group.[44] Lean NAFLD has a greater association with genetic risk factors (e.g., *PNPLA3*), suggesting less metabolic adaptability at lower body weights.[45] Increased visceral adipose tissue (VAT) further contributes to less metabolic adaptability and risk of NAFLD at lower body weights.[45] Future research in this area should include MO participants with lean NAFLD, given the high rates of *PNPLA3*, VAT, and insulin resistance observed for this subpopulation.[46] Further, given that our exclusion criteria were strict, we had a relatively "healthy" group of individuals with overweight or obesity because we excluded many factors that affect liver steatosis. This sample selection bias may have resulted in an underestimation of liver steatosis prevalence in our study sample relative to all Hispanic adults with overweight or obesity and limits the generalizability of our findings. Finally, the cross-sectional design infers no causality because temporal relationships between behavioral and cultural factors cannot be established.

The MO population is among the largest and fastest growing populations in the US. Our data suggest high prevalence rates for NAFLD and steatosis, clinical conditions that could be treated with effective therapeutic interventions for this high-risk group, particularly in southern Arizona. Continued efforts to elucidate the complex interactions between genetics, culture, behaviors, and environmental factors in the prevalence of NAFLD in MO populations are warranted to mitigate the potential long-term impact of this disease on individuals and ultimately the public health system.

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