Prevalence of Nonalcoholic Fatty Liver Disease in the Female Population

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There is a paucity of recent data about the epidemiology and long-term outcomes of nonalcoholic fatty liver disease (NAFLD) in the female population. Our aim was to assess the prevalence, risk factors, and mortality of NAFLD in female adults of the United States. Data from the National Health and Nutrition Examination Survey (NHANES) III and NHANES 1999-2014 were used. NAFLD status was determined by the U.S. Fatty Liver Index (US-FLI) in the absence of other liver diseases and excessive alcohol consumption. The prevalence rates, risk factors, and 5-year all-cause and cardiovascular mortality were determined in women with NAFLD. The most recent prevalence of NAFLD among female adults (2007-2014) in the United States was 24.4% (95% confidence interval [CI], 22.48-26.33). Prevalence was higher among women >44 years of age and those with body mass index ≥30 kg/m^2. In addition, the average age of the female population with NAFLD has decreased over time. The fully adjusted odds ratios in women with NAFLD compared to those without NAFLD were 1.48 (95% CI, 1.20-1.82) for cardiovascular disease (CVD), 1.89 (95% CI, 1.42-2.52) for atherosclerotic cardiovascular disease (ASCVD) score ≥7.5%, and 1.76 (95% CI, 1.37-2.25) for either CVD or ASCVD ≥7.5%. The 5-year mortality for female adults with NAFLD was significantly higher than for those without NAFLD (adjusted hazard ratio, 1.48; 95% CI, 1.07-2.05). Among women with NAFLD, those with ASCVD ≥7.5% had significantly higher 5-year all-cause mortality and CVD mortality. *Conclusion:* The prevalence of NAFLD in female NHANES participants from the United States has continued over recent years. In the female population with NAFLD, ASCVD ≥7.5% is an independent predictor of overall and cardiac-specific mortality. (*Hepatology Communications* 2019;3:74-83).

Nonalcoholic fatty liver disease (NAFLD) is a growing global health problem, affecting almost a quarter of the world's population.[1] NAFLD represents a spectrum of chronic liver diseases that range from simple steatosis to nonalcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma.[2,3]

It has been shown that the global prevalence of NAFLD has been on the rise.[1-4] The prevalence of NAFLD has increased from 15% in 2005 to 25% in 2010 in the United States.[4] A number of risk factors predispose individuals to develop NAFLD, including obesity, type 2 diabetes mellitus (T2DM), hypertension (HTN), and hyperlipidemia (HL).[5,6] In this context, NAFLD is considered the hepatic manifestation of the metabolic syndrome (MS), which is a multisystem disruption of energy homeostasis primarily driven by insulin resistance (IR).[7,8] In addition, some studies have demonstrated that the prevalence of NAFLD is higher among the male population, increases with age, and varies among different ethnicities.[9-11] Moreover, it has been clearly demonstrated

that NAFLD is associated with an increased risk of cardiovascular disease (CVD), independent of other risk factors of CVD, such as obesity and diabetes, and CVD is the most frequent cause of death among patients with NAFLD.[12,13]

Although the spectrum of NAFLD is reported to be more common in men, NASH was initially described as a liver disease of elderly women.[14] It is known that after menopause, the prevalence of NAFLD increases compared to the premenopausal state, with rates similar to the prevalence of NAFLD in men as well as a comparable risk of progression of liver disease.[11] Given that most of these data come from tertiary care centers or review articles, there is a paucity of data using a population-based data set about the burden and outcomes of NAFLD in the adult female population. Therefore, our aim was to assess the prevalence and mortality in female patients with NAFLD, using data from the National Health and Nutrition Examination Survey (NHANES)-III, NHANES (1999-2006), and NHANES (2007-2014). We also assessed the association of CVD and cardiovascular (CV) mortality in patients with NAFLD.

Participants and Methods

STUDY POPULATION

This study was based on the NHANES series conducted by the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention.[15] The data were compiled through household interviews, physical examinations, and laboratory assays on collected blood and urine specimens to assess the prevalence of disease, disease risk factors, and nutritional status of the civilian noninstitutionalized U.S. population. NHANES III was carried out from 1988 to 1994, and starting in 1999, data were collected continuously and were released in 2-year blocks. Therefore, we used data that included NHANES III (1988-1994); combined NHANES 1999-2000, 2001-2002, 2003-2004, and 2005-2006 (NHANES 1999-2006); and combined NHANES 2007-2008, 2009-2010, 2011-2012, and 2013-2014 (NHANES 2007-2014), following NCHS recommendations. Participants were included if they were women, aged ≥20 years with available demographics (age and ethnicity), and seen in a mobile medical examination center where laboratory measurements were taken. Participants with insufficient data for the diagnosis of NAFLD were excluded from the study.

NAFLD

Because abdominal ultrasounds were only performed in NHANES III, we used the U.S. Fatty Liver Index (US-FLI), which has been validated to establish NAFLD in the U.S. population.[16] The US-FLI includes age, race, waist circumference, gamma-glutamyltransferase, fasting insulin, and fasting glucose. Using ultrasound as standard, hepatic steatosis can be predicted by the US-FLI with an area under the curve value of 0.80 (95% CI, 0.77-0.83).[16] For our study, participants were presumed to have NAFLD if they had a US-FLI score of ≥30 in the absence of other causes of liver disease, such as extensive alcohol intake (>10 g/day), chronic hepatitis B (CHB) (hepatitis B surface antigen-positive), chronic hepatitis C (hepatitis C virus RNA-positive), or a history of autoimmune liver diseases or other chronic liver diseases.[17]

DEMOGRAPHICS AND COMORBIDITIES

Sociodemographic characteristic of participants, including age (20-44, 45-64, and >65 years), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, or "other," which included other Hispanics,

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Aleut, Eskimo, Asians, Native Americans, or Pacific Islander), sex, smoking status, and poverty-income ratio (PIR) (PIR <1.3 as low, PIR 1.3-3.5 as middle, and PIR >3.5 as high),[18] were obtained as self-reported data during the interview.

Obesity was defined as a body mass index (BMI) of ≥30 kg/m^2. T2DM was defined as self-reported use of oral hypoglycemic medications or insulin or a fasting glucose measure of ≥126 mg/dL.[19] HTN was defined as a systolic blood pressure of ≥140 mm Hg, diastolic blood pressure of ≥90 mm Hg, or self-reported use of oral antihypertensive medications.[20] HL was defined as a serum cholesterol level of >200 mg/dL, low-density lipoprotein level of ≥130 mg/dL, or high-density lipoprotein level of <40 mg/dL for men and <50 mg/dL for women. MS was defined as having at least three of the following: obesity, T2DM, HTN, or HL. IR was defined as having a homeostasis model assessment score of >3.[21] Excessive alcohol consumption was defined as ≥20 g/day for men and ≥10 g/day for women. Elevated liver enzyme was defined as increased alanine aminotransferase of ≥40 U/L in men and ≥31 U/L in women or aspartate aminotransferase level of ≥37 U/L in men and ≥31 U/L in women. Alcoholic liver disease was defined by excessive alcohol use and elevated liver enzymes. Chronic hepatitis C was defined as positive hepatitis C virus RNA, and CHB was defined as positive hepatitis B surface antigen. CVD was defined by a self-reported medical history of congestive heart failure, coronary artery disease, heart attack, or stroke. Chronic obstructive pulmonary disease (COPD) was defined by a self-reported medical history of chronic bronchitis or emphysema. Cancer was defined as a self-reported history of any cancer. The atherosclerotic cardiovascular disease (ASCVD) risk score was calculated from each participant's age, race, sex, smoking status, presence of diabetes, systolic blood pressure, antihypertensive medication, serum cholesterol levels, and high-density lipoprotein levels.[22] ASCVD score ≥7.5% corresponded to a high-risk group for a first ASCVD event.

STATISTICAL METHODS

Examination sample weights, accounting for nonresponse, noncoverage, and unequal selection probabilities for certain categories of the population, were incorporated in order to produce national estimates. The standard errors of estimates were estimated using Taylor series linearization, a design-based method.[23] For combining NHANES study cycles, appropriate selection of sampling weights and adjustment coefficients was implemented in compliance with the NHANES Analytic and Reporting Guidelines.[18] Various sociodemographic and clinical parameters among U.S. female adults with NAFLD were compared among the three study cycles, i.e., NHANES III, NHANES (1999-2006), and NHANES (2007-2014), by using Rao-Scott chi-square for categorical variables or Wald test for continuous variables.[24,25] Female adults with NAFLD and no NAFLD were compared using the combined NHANES (1984-2014). Logistic regressions were used to assess the association of CVD and ASCVD ≥7.5% with NAFLD.

To assess the effects of NAFLD on the 5-year all-cause mortality and CVD mortality using the Cox proportional hazards models, we restricted our analysis to the combined NHANES cohort (1984-2006) to have at least 5 years of follow-up. Mortality data were obtained by using the public-use linked mortality file.[26] For our study, CVD mortality was defined as death due to CV and cerebrovascular diseases (International Classification of Diseases, Tenth Revision, codes I00-I90, I11, I13, I20-I51, and I60-I69).[27] The proportional hazards assumption of the Cox models was examined by testing time-dependent covariates,[28] which showed no significant departure from proportionality over time. We used two models with a hierarchical fashion: model 1 adjusted for age and ethnicity and model 2 further adjusted for smoking status, MS, and important comorbidities. Due to collinearity between MS and metabolic components (obesity, T2DM, HTN, and HL), the latter components were not included in the fully adjusted model. All analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC), using the "SURVEY" procedure, which incorporates the sample design. Statistical tests were considered significant at $P < 0.05$ (2-tailed). "SURVEY" functions were used to account for the complex survey design.

Results

The study cohort included 13,559 female subjects. Of these, 3,811 (28.1%) had NAFLD and 9,748 did not. Female patients with NAFLD were older, more

TABLE 1. CHARACTERISTICS OF U.S. FEMALE ADULTS BY NAFLD STATUS, NHANES (1988-2014)

Characteristics	No NAFLD (n = 9,748)		NAFLD (n = 3,811)		ALL (n = 13,559)	
	n	Weighted % ± SEM	n	Weighted % ± SEM*	n	Weighted % ± SEM
Age, years*		44.35 ± 0.32		53.16 ± 0.40		46.38 ± 0.29
Age, %						
20-44	5,482	57.62 ± 0.86	1,223	32.59 ± 1.18	6,705	51.86 ± 0.71
45-64	2,466	27.98 ± 0.68	1,406	40.55 ± 1.25	3,872	30.87 ± 0.55
≥65	1,800	14.40 ± 0.63	1,182	26.86 ± 1.09	2,982	17.27 ± 0.63
RACE, %						
non-Hispanic white	4,550	72.77 ± 1.24	1,508	68.87 ± 1.52	6,058	71.87 ± 1.20
non-Hispanic black	2,562	12.24 ± 0.70	618	9.02 ± 0.67	3,180	11.50 ± 0.65
Hispanic	1,967	7.29 ± 0.50	1,503	16.28 ± 1.16	3,470	9.36 ± 0.60
Other	669	7.70 ± 0.59	182	5.83 ± 0.77	851	7.27 ± 0.52
Income (PIR), %						
Low (PIR <1.3)	2,722	19.76 ± 0.92	1,346	26.96 ± 1.09	4,068	21.41 ± 0.82
Middle (1.3<PIR<3.5)	3,558	38.79 ± 0.84	1,381	42.02 ± 1.38	4,939	39.53 ± 0.76
High (PIR >3.5)	2,677	41.45 ± 1.07	723	31.01 ± 1.59	3,400	39.07 ± 1.04
Current smoker, %	1,787	23.00 ± 0.68	543	18.88 ± 1.02	2,330	22.08 ± 0.64
Metabolic components, %						
Obesity	2,083	18.13 ± 0.55	2,583	70.54 ± 1.08	4,666	30.15 ± 0.68
Type 2 diabetes mellitus	475	3.16 ± 0.19	1,135	26.24 ± 0.85	1,610	8.45 ± 0.31
Hypertension	2,598	21.85 ± 0.63	2,081	53.79 ± 1.06	4,679	29.20 ± 0.61
Hyperlipidemia	6,548	64.85 ± 0.78	3,320	88.49 ± 0.67	9,868	70.29 ± 0.64
Metabolic syndrome	848	6.32 ± 0.31	1,752	45.20 ± 1.03	2,600	15.27 ± 0.44
Comorbidities, %						
Cancer	721	8.31 ± 0.36	380	12.26 ± 0.72	1,101	9.22 ± 0.33
COPD	654	7.44 ± 0.44	367	11.90 ± 0.86	1,021	8.46 ± 0.39
CVD	490	4.04 ± 0.25	457	10.30 ± 0.61	947	5.48 ± 0.27
ASCVD ≥7.5%	2,076	16.89 ± 0.58	1,565	37.16 ± 1.21	3,641	21.51 ± 0.60
CVD or ASCVD ≥7.5%	2,237	17.99 ± 0.60	1,687	38.66 ± 1.22	3,924	22.75 ± 0.61

*Significantly different from no NAFLD.
[†]Expressed as weighted mean ± SEM.

commonly Hispanic, and had higher comorbidity, including metabolic conditions and CV disease and associated risks (Table 1).

CHARACTERISTICS OF U.S. FEMALE ADULTS WITH NAFLD

The unadjusted prevalence of NAFLD among female adults in the United States has increased: 18.54% (95% confidence interval [CI], 16.41-20.66) in 1988-1994; 21.36% (95% CI, 19.63-23.09) in 1999-2006; and 24.86% (95% CI, 22.9-26.82) in 2007-2014 (Fig. 1). The prevalence of NAFLD was lower in those aged 20 to 44 years than in those aged ≥45 years across NHANES cycles. Nevertheless, the prevalence rates

for female adults aged 20 to 44 years also increased from 10.8% in 1988-1994 to 17.3% in 2007-2014. Finally, the prevalence of NAFLD in female adults with BMI ≥30 kg/m^2 was significantly higher than in those with BMI <30 kg/m^2 (Supporting Table S1).

Among U.S. female adults with NAFLD, the prevalence of metabolic components, including obesity, T2DM, and HTN, increased from 1988-1994 to 2007-2014 (Table 2). Consistent with these changes, the prevalence of MS also increased from 40.1% in 1988-1994 to 49.1% in 2007-2014 (Table 2).

In female adults, the age-standardized prevalence of NAFLD increased from 20.96% (95% CI, 18.77-23.15) in 1988-1994 to 26.19% (95% CI, 24.32-28.06) in 2007-2014. In each survey cycle, the
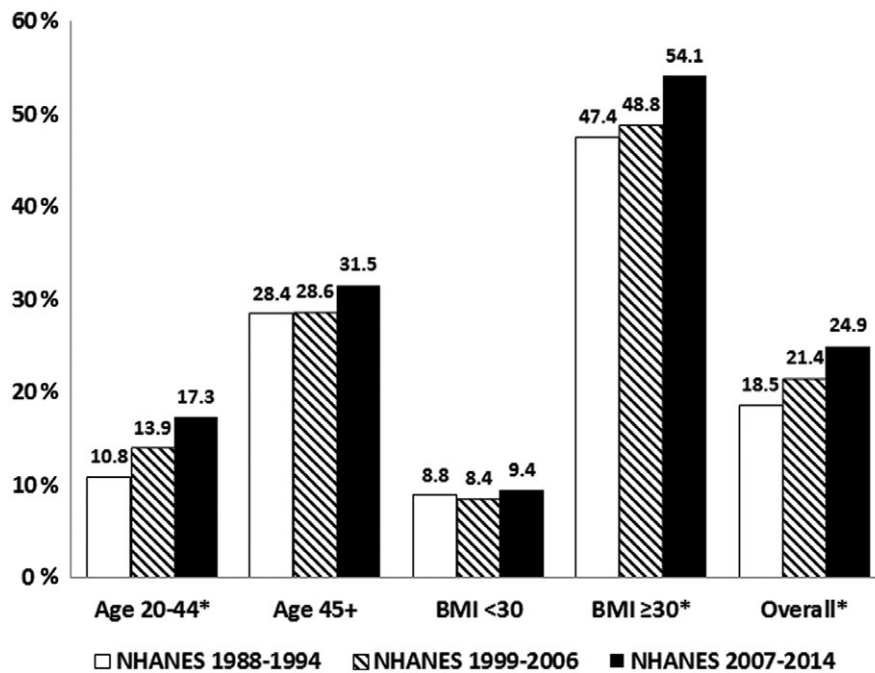
FIG. 1. Prevalence (%) of NAFLD among U.S. female adults, NHANES (1988-2014). *Indicates the linear trend over time with *P* < 0.05.

age-standardized prevalence of NAFLD was substantially higher among Mexican American women, followed by non-Hispanic whites and non-Hispanic blacks. However, non-Hispanic whites was the only group in which the prevalence of NAFLD increased from 19.28% (95% CI, 17.59-20.98) in 1988-1994 to 25.47% (95% CI, 23.24-27.71) in 2007-2014. In contrast, the prevalence of NAFLD among Mexican American women remained high but did not show a significant change over time.

Except for non-Hispanic blacks, the age-standardized prevalence of NAFLD was lower in female adults than male adults across the study cycles (Supporting Table S2).

CVD AND HIGH RISK FOR CVD IN FEMALE SUBJECTS ACCORDING TO NAFLD

Age-adjusted prevalence of CVD was 7.70% (95% CI, 6.83-8.57) among women with NAFLD compared to 4.65% (95% CI, 4.16-5.14) among those without NAFLD (*P* < 0.0001). Age-adjusted prevalence of ASCVD ≥7.5% was 28.05% (95% CI, 26-30.11) among women with NAFLD compared

with 19.94% (95% CI, 19.42-20.46) among those without NAFLD (*P* < 0.0001) (Table 3). The fully adjusted odds ratios (ORs) in female participants with NAFLD compared to those without NAFLD were 1.5 (95% CI, 1.21-1.84) for CVD, 1.96 (95% CI, 1.47-2.6) for ASCVD ≥7.5%, and 1.81 (95% CI, 1.41-2.32) for either CVD or ASCVD ≥7.5% (Table 3).

THE 5-YEAR MORTALITY FROM ALL CAUSES AND CVDS ACCORDING TO NAFLD

The 5-year all-cause mortality, adjusted for age, was 3.49% (95% CI, 2.77-4.2) among the female population with NAFLD compared to 2.51% (95% CI, 2.05-2.98) among those without NAFLD. Age-adjusted 5-year CV mortality was 1.13% (95% CI, 0.68-1.58) among female adults with NAFLD compared to 0.77% (95% CI, 0.53-1.01) among those without NAFLD. The fully adjusted hazard ratios (HRs) in female adults with NAFLD compared to those without NAFLD were 1.5 (95% CI, 1.09-2.07) for all-cause mortality and 1.45 (95% CI, 0.78-2.68) for CV mortality (Table 4).

TABLE 2. CHARACTERISTICS OF U.S. FEMALE ADULTS WITH NAFLD, NHANES 1988-2014

Characteristics	1988-1994 (n = 1,563)		1999-2006 (n = 993)		2007-2014 (n = 1,256)	
	n	Weighted % ± SEM	n	Weighted % ± SEM	n	Weighted % ± SEM
Age, years[†]		54.64 ± 0.69		52.73 ± 0.64		51.85 ± 0.46*
Age, %						
20-44	525	32.89 ± 2.49	315	32.05 ± 1.72	383	32.68 ± 1.66
45-64	504	36.94 ± 2.11	358	40.48 ± 2.04	544	44.67 ± 2.14*
≥65	534	30.17 ± 2.13	320	27.46 ± 1.90	328	22.65 ± 1.40*
RACE, %						
non-Hispanic white	598	72.13 ± 2.72	418	67.54 ± 2.83	492	66.29 ± 2.62
non-Hispanic black	309	9.76 ± 1.14	135	8.65 ± 1.17	174	8.49 ± 0.98
Hispanic	575	8.88 ± 1.25	415	20.73 ± 2.97*	513	20.98 ± 2.08*
Other	81	9.23 ± 1.94	25	3.08 ± 0.74*	76	4.24 ± 0.75*
Income, %						
Low	596	27.22 ± 2.19	307	26.15 ± 2.05	443	27.34 ± 1.43
Middle	595	49.03 ± 2.28	365	37.18 ± 2.31*	421	38.17 ± 1.83*
High	210	23.74 ± 2.86	246	36.67 ± 2.30*	267	34.49 ± 2.44*
Current smoker, %	217	17.45 ± 1.47	142	22.80 ± 1.95*	184	17.86 ± 1.65
BMI		33.22 ± 0.41		34.79 ± 0.36*		35.56 ± 0.22*
HOMA		7.91 ± 0.24		6.46 ± 0.25*		6.52 ± 0.16*
Metabolic components,%						
Obesity	981	64.51 ± 2.01	684	72.99 ± 1.97*	918	75.38 ± 1.16*
Type 2 diabetes mellitus	472	26.76 ± 1.71	275	22.80 ± 1.37	388	28.48 ± 1.41*
Hypertension	761	48.16 ± 2.08	588	58.95 ± 1.99*	732	55.94 ± 2.05*
Hyperlipidemia	1,382	89.54 ± 1.25	860	87.98 ± 1.33	1,078	87.73 ± 0.96
Metabolic syndrome	646	40.05 ± 1.84	476	47.52 ± 2.53*	630	49.12 ± 1.64*
Comorbidities, %						
Cancer	132	11.45 ± 1.14	105	12.07 ± 1.04	143	13.31 ± 1.54
COPD	146	12.30 ± 1.22	93	12.80 ± 1.43	128	10.72 ± 1.46
CVD	208	11.44 ± 1.21	112	10.53 ± 1.17	137	8.82 ± 0.99
ASCVD ≥7.5%	703	42.69 ± 2.27	409	36.21 ± 1.74*	453	31.61 ± 1.89*
CVD or ASCVD ≥7.5%	746	43.97 ± 2.45	447	38.11 ± 1.86	494	33.12 ± 1.79*

Abbreviation: HOMA, homeostasis model assessment.
*Significantly different from NHANES III (1988-1994).
[†]Expressed as weighted mean ± SEM.

Among female participants with NAFLD, those with higher ASCVD score (≥7.5%) had an increased risk of all-cause mortality (HR, 514; 95% CI, 1.79-14.72) and CV mortality (HR, 142.62; 95% CI, 17.36-1171.5) (Table 5).

Discussion

This study presents the most in-depth analysis of the prevalence, risks, and outcomes of female patients with NAFLD in the United States. Based on these data, there is clear evidence that the prevalence of NAFLD among the female population is rising and is fueled by the epidemic of metabolic diseases, such as T2DM and obesity.[1] Furthermore, the relationship between older age and increased prevalence of NAFLD is confirmed in female subjects from the NHANES.[29,30] However, among the female population, various other factors, including alterations in body composition, fat distribution, hormonal and metabolic changes after menopause, as well as polycystic ovary disease, have been associated with NAFLD.[31-34] In fact, data suggest that estrogen appears to have a

TABLE 3. ODDS RATIOS FOR CVD AND ASCVD (≥7.5%) BY NAFLD STATUS AMONG U.S. FEMALE ADULTS, NHANES (1988-2014)

		Adjusted Odds Ratio (95% CI)	
	Age-Adjusted Prevalence % (95% CI)*	Model 1[†]	Model 2[‡]
CVD			
No NAFLD	4.65 (4.16-5.14)	Reference	Reference
NAFLD	7.70 (6.83-8.57)[§]	1.82 (1.54-2.15)	1.5 (1.21-1.84)
ASCVD ≥7.5%			
No NAFLD	19.94 (19.42-20.46)	Reference	Reference
NAFLD	28.05 (26-30.11)[§]	3.08 (2.46-3.86)	1.96 (1.47-2.6)
CVD or ASCVD ≥7.5%			
No NAFLD	21.04 (20.41-21.67)	Reference	Reference
NAFLD	29.66 (27.55-31.77)[§]	2.73 (2.23-3.34)	1.81 (1.41-2.32)

*Age adjustment is based on the direct method to the census 2000 population, using the age groups 20-44, 45-64, and ≥65 years.
[†]Model 1, adjusted for age and race.
[‡]Model 2, adjusted for Model 1 plus current smoker, MS, cancer, and COPD; due to multicollinearity between MS and metabolic components, the letters were excluded.
[§]Significantly different from no NAFLD.

TABLE 4. HAZARD RATIOS OF 5-YEAR MORTALITY BY NAFLD STATUS AMONG U.S. FEMALE ADULTS, NHANES (1988-2014)

		Hazard Ratio (95% CI)		
	Age-Adjusted Mortality, % (95% CI)*	Unadjusted	Model 1[†]	Model 2[‡]
All-cause mortality				
No NAFLD	2.51 (2.05-2.98)	Reference	Reference	Reference
NAFLD	3.49 (2.77-4.2)[§]	2.57 (2.01-3.29)	1.43 (1.12-1.81)	1.5 (1.09-2.07)
Cardiovascular mortality				
No NAFLD	0.77 (0.53-1.01)	Reference	Reference	Reference
NAFLD	1.13 (0.68-1.58)	2.83 (1.72-4.65)	1.54 (0.96-2.46)	1.45 (0.78-2.68)

*Age adjustment is based on the direct method to the census 2000 population, using the age groups 20-44, 45-64, and ≥65 years.
[†]Model 1, adjusted for age and race.
[‡]Model 2, adjusted for Model 2 plus active smoker, income, metabolic syndrome, cancer, COPD, and ASCVD ≥7.5%; due to multicollinearity between MS and metabolic components, the letters were excluded.
[§]Significantly different from no NAFLD.

protective role. In this context, females with NAFLD seem to have lower levels of estradiol,[34,35] and receiving hormone replacement therapy may result in lower rates of NAFLD.[36] However, given significantly higher rates of metabolic derangement and the increasing prevalence of obesity, it can be suggested that a change in the metabolic trends is a more important factor contributing to higher rates of NAFLD than other sex-specific mechanisms. Moreover, the mean age of women with NAFLD has decreased over time from 54.6 years to 52 years, and the prevalence of NAFLD among younger patients (20-44 years) has increased from 11% to 17%. This can be explained by the rising prevalence of obesity

among young women in the United States.[37] Again, our findings are in agreement with previous studies demonstrating higher rates of components of MS in patients with NAFLD.[6,38-40]

Racial differences in the prevalence of NAFLD led to some interesting observations. Our data suggest that Mexican American female adults have a higher prevalence of NAFLD than non-Hispanic black and non-Hispanic white female adults. The cause for this has not been well established but may be related to genetic predisposition and a higher prevalence of components of MS. Recent data from the Centers for Disease Control and Prevention showed that in Hispanic women, the rate of obesity

TABLE 5. HAZARD RATIOS OF 5-YEAR MORTALITY BY ASCVD (≥7.5%) AMONG U.S. FEMALE ADULTS WITH NAFLD, NHANES (1988-2014)

	Age-Adjusted Mortality, % (95% CI)*	Hazard Ratios (95% CI)		
		Unadjusted	Model 1†	Model 2‡
All-cause mortality				
NAFLD with ASCVD <7.5%	1.18 (−0.08-2.44)	Reference	Reference	Reference
NAFLD with ASCVD ≥7.5%	4.95 (3.44-6.47)§	15.92 (7.33-34.59)	5.68 (2.21-14.58)	5.14 (1.79-14.72)
Cardiovascular mortality				
NAFLD with ASCVD <7.5%	0.02 (0-0.04)	Reference	Reference	Reference
NAFLD with ASCVD ≥7.5%	1.83 (0.81-2.85)	151.56 (40.48-567.45)	55.42 (12.07-254.5)	142.62 (17.36-1171.5)

*Age adjustment is based on the direct method to the census 2000 population, using the age groups 20-44, 45-64, and ≥65 years.
†Model 1, adjusted for age and race.
‡Model 2, adjusted for Model 2 plus active smoker, income, metabolic syndrome, cancer, and COPD; due to multicollinearity between MS and metabolic components, the letters were excluded.
§Significantly different from no NAFLD.

is 50.6%, hyperlipidemia is 41.2%, and diabetes is 11.7%, which places Hispanic women at significant risk for NAFLD.[41-43] Additionally, there may be genetic predisposition for development and progression of NAFLD. In fact, Chincilla-Lopez et al.[44] have recently suggested that polymorphism of the patatin-like phospholipase domain containing 3 (*PNPLA3*) gene may be more common in native Mexicans, and this association places these individuals at higher risk for NAFLD (OR, 1.711; 95% CI, 1.014-2.886; *P* = 0.044). Despite these data, additional investigation is needed to elucidate the driving factors for this increased prevalence of NAFLD in the Mexican American female population.

Another important finding of our study is the assessment of long-term mortality outcomes. Our data show that women with NAFLD have a significantly higher rate of 5-year all-cause mortality. Similarly, patients with NAFLD and an ASCVD score of >7.5% had an even higher risk for all-cause and CV mortality. It is well known that, due to the shared pathophysiologic pathways and comorbidities, NAFLD has been strongly associated with CVD,[45-47] and CVD is the leading cause of mortality among patients with NAFLD.[13,48,49] Furthermore, it has been recently demonstrated that having an ASCVD score of >7.5 is an independent predictor of both overall and cardiac-specific mortality in patients with NAFLD.[50] Moreover, among patients with NAFLD, the presence of diabetes and existing heart disease was proven to increase CVD mortality.[5] These data that have been shown for all patients with NAFLD or using data from tertiary care centers were confirmed for the female population using a population database.

A key limitation of our study is that we used a noninvasive test (US-FLI) to identify NAFLD because hepatic ultrasound data were not always available in population-based studies. Although US-FLI correlates well with NAFLD, the gold standard remains liver biopsy or other sensitive radiologic tests. The recent public-use mortality file provides follow-up data on vital status by December 31, 2011; therefore, only six cycles from NHANES III (1988-1994) to NHANES (2005-2006) have at least 5 years of follow-up. A longer follow-up period is needed to establish an independent association of CVD mortality with NAFLD. Despite these limitations, this study includes a large cohort of female adults with NAFLD where in-depth clinical and laboratory data are available and generalizes the results to the U.S. general population.

In conclusion, our data show that NAFLD is growing in the female population in the United States. In this context, NAFLD is associated with metabolic risk factors and increases the risk of CVD and mortality. This issue is important because CV diseases and mortality in female adults have been underemphasized. Our data suggest that detection of NAFLD in women is considered a serious risk threat that needs to be addressed to potentially improve their long-term outcomes.

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