Mortality of NAFLD According to the Body Composition and Presence of Metabolic Abnormalities

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Although nonalcoholic fatty liver disease (NAFLD) is associated with obesity, it can also occur in lean and metabolically normal individuals. Our aim was to determine the effect of different combinations of abdominal adiposity and overall adiposity on the mortality of NAFLD. The Third National Health and Nutrition Examination Survey with mortality data from the National Death Index were used. NAFLD was defined as steatosis without other liver diseases. Body composition was categorized according to waist circumference (WC) and body mass index (BMI). Obesity pattern was defined according to BMI (lean, overweight, and obese) and WC (normal and obese) using accepted definitions. The "metabolically abnormal" group had visceral obesity, insulin resistance, type 2 diabetes, hypertension, or hyperlipidemia. Of the 9,341 study individuals (47.9% male; 76.8% white), NAFLD was present in 3,140 (33.6%), of whom 0.6% had lean BMI and normal WC, and 1.7% had lean BMI and obese WC. The prevalence of metabolically normal NAFLD was 3.26% (95% confidence interval [CI]: 2.62%-3.90%), with most of these subjects having lean BMI (79.2%). During an average follow-up of 22.4 years, 24.1% of the subjects died from all causes. Among these deceased individuals, 41.7% had NAFLD at baseline. Causes of death were cardiovascular disease (24.8%), cancer-related (24.3%), type 2 diabetes–related (4.4%), and liver-related (1.7%). Individuals with NAFLD who were lean by BMI but obese by WC had higher risk of all-cause mortality. Individuals with NAFLD with normal BMI but obese WC had a higher risk of cardiovascular mortality (hazard ratio 2.63 [95% CI: 1.15-6.01]) as compared with overweight (by BMI) NAFLD with normal WC. *Conclusion:* The risk of mortality in NAFLD can be affected by the presence of visceral obesity, especially in the lean BMI group. These data have important management implications for patients with NAFLD. (*Hepatology Communications* 2020;4:1136-1148).

Nonalcoholic fatty liver disease (NAFLD) has emerged as one of the most common causes of chronic liver disease worldwide and is expected to become the leading indication for liver transplantation in the United States.[1] About one quarter of the world population have NAFLD, and these rates are significantly higher in individuals with diabetes and who are obese.[2,3] In addition to obesity, older age, Hispanic race, metabolic disorders such as dyslipidemia, insulin resistance and hypertension (HTN), as well as genetic factors have been associated with increased risk for NAFLD.[4-6]

As noted, components of metabolic syndrome (visceral obesity, insulin resistance, type 2 diabetes [T2DM], dyslipidemia, and HTN) not only increase the risk of NAFLD but also lead to increased risk

Abbreviations: APRI, AST-to-platelet ratio index; ASCVD, atherosclerotic cardiovascular disease; AST, aspartate aminotransferase; BMI, body mass index; CVD, cardiovascular disease; CI, confidence interval; CKD, chronic kidney disease; FIB-4, Fibrosis-4 index; HL, hyperlipidemia; HR, hazard ratio; HTN, hypertension; NAFLD, nonalcoholic fatty liver disease; NCHS, National Center for Health Statistics; NFS, NAFLD fibrosis score; NHANES III, Third National Health and Nutrition Examination Survey; NASH, nonalcoholic steatohepatitis; NDI, National Death Index; T2DM, type 2 diabetes; WC, waist circumference.

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for developing nonalcoholic steatohepatitis (NASH), advanced hepatic fibrosis, and experiencing liver-related mortality.[7,8] Although NAFLD is strongly associated with obesity and metabolic syndrome, a portion of patients with NAFLD are not obese. The prevalence of lean NAFLD can range from 7% to 10% in the United States and up to 19% in some Asian countries.[9-12] The definition of lean NAFLD can vary based on the use of body mass index (BMI) or waist circumference (WC) thresholds.[9,13] It has also been suggested that BMI reflects the total body fat and may not accurately reflect the presence of visceral obesity, which is more relevant for patients with NAFLD.[14] Despite the importance of visceral obesity according to waist circumference in NAFLD, most long-term studies could not provide consistent WC data. Nevertheless, the importance of visceral obesity as a predictor of long-term outcomes has been established.[15] In this context, it is highly plausible that assessment of visceral adiposity can be an important predictor of long-term outcome among those with NAFLD, even those who are considered lean by BMI classification. Therefore, the aim of the current study was to determine the effect of different combinations of abdominal adiposity (WC) and overall adiposity (BMI) on the prevalence and mortality of NAFLD in the United States.

Methods

DATA SOURCE AND POPULATION

The study population was selected from longitudinal data of the general population. The criteria were to have sufficient clinical and laboratory data, in which the diagnosis of NAFLD can be made with ultrasound and laboratory tests (excluding other causes of liver disease). Additionally, the study design required that long-term mortality data and causes of death must be available. Therefore, our primary analysis cohort included individuals from the Third National Health and Nutrition Examination Survey (NHANES III), conducted by the National Center for Health Statistics (NCHS) with mortality data from the National Death Index (NDI).

From 1988 through 1994, a nationally representative cross-sectional sample of approximately 34,000 individuals in the United States were selected by a complex, multistage probability design and examined to monitor the health and nutritional status of civilian, noninstitutionalized individuals through standardized physical examination, laboratory tests, and questionnaires that covered various health-related topics. Each survey participant completed a household interview and underwent physical and laboratory examinations at the mobile examination center. Full details of each survey have been described elsewhere.[16] Data collection for NHANES III was approved by the NCHS Research Ethics Review Board (ERB). Analysis of de-identified data from the survey is exempt from the federal regulations for the protection of human research participants. Analysis of restricted data through the NCHS Research Data Center is also approved by the NCHS ERB.

DEFINITIONS OF NAFLD AND ADVANCED FIBROSIS

Abdominal ultrasonography was performed using a Toshiba Sonolayer SSA-90A and Toshiba video recorders (Tokyo, Japan) in NHANES III individuals aged 20 to 74 years. Between 2009 and 2010, the archived gallbladder ultrasound examination

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videotapes were reviewed to grade the presence of fat within the hepatic parenchyma. More detailed information on methodology and quality control were described elsewhere.[17] Briefly, hepatic steatosis was graded as normal, mild, moderate and severe, based on five main criteria: parenchymal brightness, liver to kidney contrast, deep beam attenuation, bright vessel walls, and gallbladder wall definition. Excellent interrater and interrater reliability of these assessments has been reported (percentage of agreements of 88.7% and 91.3%, respectively). For the current analysis, NAFLD was diagnosed by having the presence of mild, moderate, or severe hepatic steatosis by ultrasound in the absence of other causes of chronic liver disease (alcohol consumption <20 g/day for males and 10 g/day for females, hepatitis B surface antigen–negative, anti–hepatitis C virus antibody negative, transferrin saturation <50%).[11]

NAFLD-associated advanced fibrosis was defined using three noninvasive markers: aspartate aminotransferase (AST) to platelet ratio index (APRI) >1.5, Fibrosis-4 index (FIB-4) >2.67, and NAFLD fibrosis score (NFS) >0.676, respectively. APRI was calculated with the following formula: ([AST/upper-limit of normal AST] × 100)/Platelets [10^9/L]). The upper limit of normal of AST used for APRI was 33 IU/L, based on the published NHANES reference ranges. FIB-4 is based on the four factors and calculated by the following formula: age × AST (IU/mL)/(Platelets [10^9/L] × alanine aminotransferase [ALT; IU/mL]$^{1/2}$). NFS was calculated with the following formula: NFS = −1.675 + 0.037 × age + 0.094 × BMI (kg/m^2) + 1.13 × impaired fasting glycaemia or T2DM + 0.99 × AST/ALT − 0.013 × platelet count − 0.66 × albumin, where "impaired fasting glycemia" has a value of 1 if the subject has a fasting plasma glucose value of 100 to 125 mg/dL and 0 if otherwise.

DEFINITIONS OF OVERALL ADIPOSITY AND ABDOMINAL ADIPOSITY

BMI was used as a measure of overall adiposity, whereas WC was used as a measure of abdominal adiposity. According to guidelines,[18] overall adiposity was classified as follows: lean as a BMI 18.5 to <25; overweight as a BMI 25.0 to <30; obese as a BMI ≥30. Abdominal adiposity was categorized into two groups: normal as WC <102 cm for men and <88 cm for women, and obese as WC ≥102 cm for men and ≥88 cm for women.[19] Furthermore, obesity patterns were categorized into six exclusive groups by the combinations of overall adiposity (BMI) and abdominal adiposity (WC): (1) lean BMI–normal WC, (2) lean BMI–obese WC, (3) overweight BMI–normal WC, (4) overweight BMI–obese WC, (5) obese BMI–normal WC, and (6) obese BMI–obese WC.

ASCERTAINMENT OF DEATH

Mortality status for NHANES III individuals was ascertained using probabilistic record matching with the NDI.[20] International Statistical Classification of Disease and Related Health Problems, Tenth Revision codes as the underlying cause of death were used to specify the cause of death: cardiovascular diseases (codes I00-I78), extrahepatic cancer (C00-C21 and C23-C97), liver diseases (viral hepatitis [B15-B19], liver cancer [C22], chronic liver disease and cirrhosis [K70 and K73-K74]), and diabetes (E10-E14). Individuals who did not have any death records were presumed alive through the follow-up period. Time to death was calculated from baseline to date of death or December 31, 2015, whichever came first.

OTHER DEFINITIONS

Information on demographic characteristics (i.e., age, sex, and race/ethnicity), lifestyle (i.e., smoking status, physical activity, and alcohol consumption), and previous medical conditions (cardiovascular disease [CVD] and any cancer) was collected at baseline through self-reports.

T2DM was defined by a fasting glucose level greater than or equal to 126 mg/dL, self-reported medical history of diabetes, and use of oral hypoglycemic agents, insulin use, or hemoglobin A1c greater than or equal to 6.5%.

Insulin resistance was defined as a homeostasis model assessment of insulin resistance of over 3.

HTN was defined as having a systolic blood pressure of over 130 mm Hg or diastolic blood pressure of over 80 mm Hg from an average of three measurements or history of high blood pressure or history of oral antihypertensive medications.[21]

Hyperlipidemia (HL) was defined as a serum cholesterol level of 200 mg/dL or higher, LDL of 130 or higher, or HDL of 40 mg/dL or lower in men (50 mg/dL or lower in women), or history of HL.

We used the National Cholesterol Education Program Adult Treatment Panel III definition.[22] For the purpose of this study, "metabolically abnormal" was defined as having at least one of the following components of metabolic syndrome: visceral obesity, insulin resistance, T2DM, HTN, and HL. Again, for the purpose of this study only, individuals who did not have the clinical diagnosis of these "components of metabolic syndrome" were regarded as metabolically normal.

The 10-year lifetime risk for developing atherosclerotic cardiovascular disease (ASCVD) was calculated from the ASCVD risk score (American College of Cardiology/American Heart Association) with each participant's age, race, sex, smoking status, presence of T2DM, systolic blood pressure, antihypertensive medication, serum cholesterol, and high-density lipoprotein levels. Individuals with a 10-year ASCVD risk score of 7.5% or higher were referred to as high cardiac risk.[22]

Chronic kidney disease (CKD) was defined as a glomerular filtration rate, estimated by the Chronic Kidney Disease Epidemiology Collaboration equation of ≤60 mL/min/1.73 m^2 or urinary albumin-to-creatinine ratio ≥30 mg/g.[23]

STATISTICAL ANALYSIS

Comparisons of covariates among individuals with different combinations of BMI/WC, presence of NAFLD, and metabolic abnormality were evaluated using a t-statistic for continuous variables and the Rao-Scott chi-square test for categorical variables. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and their corresponding 95% confidence interval (CI) for risk of all-cause mortality associated with obesity pattern compared with the reference lean BMI–normal WC category and the Fine and Gray competing risks regression model for risk of cause-specific mortality. Multivariable models were constructed in several stages, including unadjusted, age–sex adjusted, socio-demographic adjusted, and important confounders adjusted models. The full model was adjusted for age, sex, race/ethnicity, income, education, active smoking, sedentary physical activity, advanced fibrosis (based on FIB-4), CKD, previous cancer, previous CVD, HTN, HL, and T2DM. The proportional hazards assumption of the Cox models was examined by testing time-dependent covariates,[24] which showed no significant departure from proportionality over time ($P > 0.05$). Stratified analyses by age (<65 vs. ≥65 years), sex, race/ethnicity (white vs. black, Mexican American), and the presence of metabolic abnormality (yes vs. no) were also performed.

Among individuals with NAFLD, we also identified predictors for all-cause mortality and cause-specific mortality according to BMI (lean BMI vs. non-lean BMI [both overweight and obese BMI combined]) and WC (normal WC vs. obese WC) categories, separately through Cox proportional hazards regression models and the Fine and Gray competing risks regression model. The choice of predictors was carried out using an automatic procedure: bidirectional stepwise selection (significance level for entry into the model was 0.2, and staying in the model was 0.05). The predictors considered were as follows: age, sex, race/ethnicity, either BMI for WC category or WC for BMI category, income, education, sedentary physical activity, HTN, HL, T2DM, advanced hepatic fibrosis (based on FIB-4), CKD, previous history of CVD, and previous history of cancer. All differences reported here are statistically significant unless otherwise mentioned. Due to a small number of T2DM deaths and liver-related deaths, a multivariable model to identify predictors was not performed for them.

All analyses were performed using survey procedures (SAS version 9.4; SAS Institute, Cary, NC), which estimate standard error using Taylor series linearization to account for the NHANES complex sample design. Examination sample weights, accounting for nonresponse, noncoverage, and unequal selection probabilities for certain categories of the population, were incorporated to produce national estimates for all analyses, except the analyses of identifying predictors of mortality. The number of individuals in each group displayed in this study was reported by multiplying the estimated percentage by the total number of individuals in the full sample. All differences reported here are statistically significant otherwise mentioned at the 0.05 level.

Results

Of the 19,172 nonpregnant participants of NHANES III, 17,367 (90.6%) attended an examination at a mobile examination center. We excluded 3,014 who were not eligible for an ultrasound examination due to age being older than 75 years or less than 20 years; 769 who had an ultrasound that was ungradable or missing; 405 who were positive for serum hepatitis B surface antigen or hepatitis C antibody; 180 who had alcoholic liver disease; 386 who had a transferrin saturation over 50%; and 827 with significant alcohol consumption (≥20 g per day in men and ≥10 g per day in women). We also excluded 387 with missing data on BMI or WC; 214 with extremely low BMI, 1,835 with missing data on at least one metabolic syndrome component; and 9 with missing data on mortality status. The final study cohort had 9,341 NHANES participants. Compared with the study cohort, excluded subjects were more likely to be black and had lower socio-demographic factors, including income, education, smoking status, and physical activity. There was no difference in other demographic characteristics.

ASSOCIATIONS AMONG NAFLD, BODY COMPOSITION, AND METABOLIC ABNORMALITY

The baseline demographic and clinical characteristics of individuals based on the presence of NAFLD and metabolic syndrome components, as well as combinations of abdominal adiposity (WC) and overall adiposity (BMI) categories, are found in Tables 1 and 2 and Supporting Table S1. Distributions of NAFLD, adiposity patterns, and metabolic syndrome components are displayed in Fig. 1.

Of the 9,341 individuals (47.9% male; 76.8% non-Hispanic white; 9.9% non-Hispanic black; 5.4% Hispanic; mean [SEM] age, 43.6 [0.4] years), NAFLD was present in 3,140 (33.6%), of whom 25.4% were lean, 33.2% were overweight, and 41.4% were obese as per their BMI, whereas of the 6,201 (66.4%) individuals without NAFLD, 50.7% were lean, 33.6% were overweight, and 15.7% were obese.

Older age, male gender, Mexican-American race, lower income, less education, low physical activity (being sedentary), having more metabolic syndrome components, previous CVD, family history of CVD, CKD, and advanced fibrosis as determined by NFS and APRI are associated with NAFLD (Table 1).

Individuals with lean BMI–obese WC accounted for 2.1% of the study cohort (1.7% of individuals with NAFLD vs. 2.2% of individuals without NAFLD, $P = 0.168$) and 4.9% of individuals with lean BMI (6.9% of NAFLD individuals with lean BMI vs. 4.4% of individuals without NAFLD with lean BMI, $P = 0.028$). Across BMI categories, individuals with obese WC were more likely to be older, female, have low income, less education, higher proportion of sedentary physical activity, more components of metabolic syndrome, higher CVD risk, and higher CKD rates (Supporting Table S1). These associations in the full sample were preserved among both individuals with NAFLD and individuals without NAFLD, but the differences by WC in each BMI category were more pronounced among individuals with NAFLD (Supporting Tables S2 and S3).

Across BMI categories, individuals with obese WC were more likely to have NAFLD than individuals with normal WC (Supporting Table S1). Logistic regression analyses were performed to assess the association between NAFLD and BMI/WC combinations (Supporting Table S4). Even after multivariable adjustments, compared to patients with lean BMI and normal WC, individuals with obese WC in each BMI category were at increased risk of NAFLD. The higher risk of NAFLD was significant only among individuals with obese BMI–obese WC (odds ratio 4.08, 95% CI: 2.17-7.67). In the whole study cohort, the prevalence of NAFLD with no metabolic syndrome component was 3.26% (95% CI: 2.62 to 3.90%), with most of these subjects having lean BMI (79.2%) (Fig. 1).

ASSOCIATION OF DIFFERENT COMBINATIONS OF BMI AND WC BODY COMPOSITION WITH ALL-CAUSE AND CAUSE-SPECIFIC MORTALITY AMONG INDIVIDUALS WITH NAFLD AND WITHOUT NAFLD

During an average follow-up of 22.4 years (interquartile range: 18.7-22.4 years), 2,253 (24.1%) individuals died. Among deceased individuals, 41.7% had NAFLD at baseline.

TABLE 1. CHARACTERISTICS OF INDIVIDUALS AGED 20-74 YEARS ACCORDING TO PRESENCE OF NAFLD (NHANES III, U.S. 1988-1994)

Covariate	Full Sample (n = 9,341)	Individuals Without NAFLD (n = 6,201)	Individuals With NAFLD (n = 3,140)	*P* Value
Age, mean (SEM)	43.64 (0.37)	42.28 (0.39)	46.32 (0.49)	<0.0001
Male (%)	47.88 (0.69)	46.47 (1.06)	50.67 (1.36)	0.0351
Race (%)				
non-Hispanic white	76.78 (1.36)	77.12 (1.41)	76.11 (1.71)	0.4772
non-Hispanic black	9.88 (0.64)	10.65 (0.73)	8.38 (0.68)	0.0008
Mexican American	5.38 (0.48)	4.73 (0.45)	6.67 (0.69)	0.0002
Other race	7.95 (0.99)	7.51 (1.04)	8.83 (1.14)	0.1184
Income (%)				
Low	16.72 (1.14)	16.30 (1.18)	17.53 (1.61)	0.4042
Medium	45.15 (1.23)	44.00 (1.27)	47.38 (1.96)	0.0858
High	38.14 (1.44)	39.69 (1.39)	35.09 (2.31)	0.0341
College (%)	43.20 (1.37)	46.31 (1.47)	37.07 (1.92)	<0.0001
Married (%)	70.63 (0.99)	69.54 (0.99)	72.78 (1.57)	0.0349
Body composition (%)				
Lean BMI–normal WC	40.13 (1.04)	48.49 (1.13)	23.63 (1.41)	<0.0001
Lean BMI–obese WC	2.07 (0.19)	2.23 (0.24)	1.74 (0.26)	0.1682
Overweight BMI–normal WC	19.75 (0.52)	21.45 (0.60)	16.40 (0.99)	<0.0001
Overweight BMI–obese WC	13.70 (0.53)	12.14 (0.65)	16.79 (0.96)	<0.0001
Obese BMI–normal WC	1.60 (0.21)	1.68 (0.27)	1.45 (0.31)	0.5868
Obese BMI–obese WC	22.75 (0.94)	14.01 (0.87)	39.99 (1.85)	<0.0001
Active smoking (%)	27.34 (0.93)	28.97 (1.09)	24.14 (1.20)	0.0004
Sedentary physical activity (%)	12.53 (0.82)	11.17 (0.84)	15.21 (1.25)	0.0004
HTN (%)	40.51 (1.00)	34.73 (1.05)	51.91 (1.38)	<0.0001
HL (%)	70.57 (1.04)	66.19 (1.29)	79.23 (1.29)	<0.0001
Diabetes (%)	6.80 (0.47)	3.40 (0.33)	13.50 (1.02)	<0.0001
Insulin resistance (%)	23.38 (1.03)	13.44 (0.85)	43.01 (1.82)	<0.0001
Metabolic abnormal (%)	81.02 (0.96)	76.32 (1.32)	90.31 (0.77)	<0.0001
Metabolic syndrome* (%)	26.97 (1.16)	16.93 (0.92)	46.78 (1.75)	<0.0001
History of (%)				
Any cancer	6.53 (0.41)	6.61 (0.53)	6.36 (0.57)	0.7446
CVD	4.46 (0.32)	3.52 (0.38)	6.33 (0.48)	<0.0001
Family CVD	17.01 (0.63)	16.23 (0.80)	18.55 (0.89)	0.0424
High cardiac risk (%)	24.18 (0.80)	20.24 (0.85)	31.99 (1.10)	<0.0001
Advanced fibrosis (%, NFS)	2.29 (0.21)	1.73 (0.23)	3.38 (0.40)	<0.0001
Advanced fibrosis (%, FIB-4)	1.03 (0.14)	0.97 (0.19)	1.14 (0.17)	0.4801
Advanced fibrosis (%, APRI)	0.46 (0.09)	0.19 (0.07)	0.98 (0.26)	0.0003
CKD (%)	8.71 (0.38)	7.56 (0.45)	10.97 (0.65)	<0.0001
Cumulative mortality (%)				
All-cause	24.13 (0.81)	21.18 (0.86)	29.94 (1.26)	<0.0001
CVD	6.23 (0.31)	5.63 (0.36)	7.41 (0.62)	0.009
Cancer	6.25 (0.39)	5.73 (0.39)	7.28 (0.76)	0.042
T2DM	0.59 (0.10)	0.22 (0.07)	1.31 (0.28)	<0.0001

Note: All values are displayed as weighted percentages (SEM) except where otherwise noted.
*National Cholesterol Education Program Adult Treatment Panel III (2005 revision).

To assess the association of different combinations of body composition according to BMI and WC on all-cause and cause-specific mortality among individuals with NAFLD, Cox proportional hazards regression and cause-specific hazard models were performed (Table 3). In the multivariable model, compared to

TABLE 2. CHARACTERISTICS OF INDIVIDUALS AGED 20-74 YEARS ACCORDING TO PRESENCE OF METABOLIC ABNORMALITY (NHANES III, U.S. 1988-1994)

Covariate	Individuals With Metabolic Abnormality (n = 7,872)	Individuals Without Metabolic Abnormality (n = 1,461)	*P* Value
NAFLD (%)	37.49 (1.26)	17.18 (1.77)	<0.0001
Body composition (%)			
Lean BMI–normal WC	31.08 (0.96)	78.95 (1.62)	<0.0001
Lean BMI–obese WC	2.55 (0.23)	0 (0.00)	
Overweight BMI–normal WC	19.82 (0.56)	19.40 (1.51)	0.8015
Overweight BMI–obese WC	16.91 (0.61)	0 (0.00)	
Obese BMI–normal WC	1.59 (0.23)	1.65 (0.70)	0.9372
Obese BMI–obese WC	28.05 (1.05)	0 (0.00)	

Note: All values were displayed weighted percentages (SEM) except where otherwise noted.

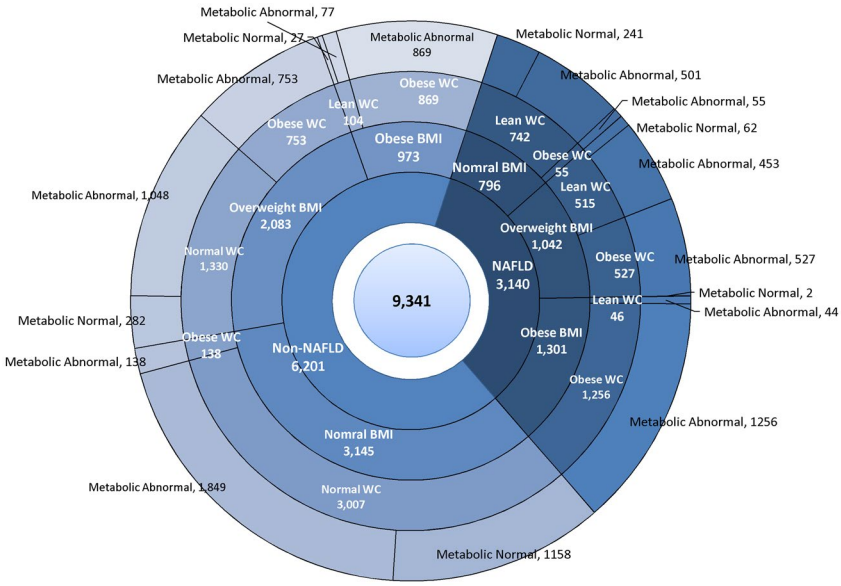

FIG. 1. Distributions of NAFLD, obesity patterns, and metabolic abnormality: NHANES III, U.S. 1988-1994.

NAFLD patients with lean BMI–normal WC, patients with NAFLD who were categorized as obese by WC in each BMI category were shown to be at increased risk for all-cause mortality; however, this comparison reached statistical significance only in the lean BMI–obese WC category (HR 1.51, 95% CI: 1.10-1.96). The fully adjusted model (with addition of HTN, Hyperlipidemia, and T2DM) also demonstrated a similar finding with statistical significance for patients with NAFLD with lean BMI–obese WC only (HR 1.42, 95% CI: 1.03-1.96) (Table 3). On the other hand, among individuals without NAFLD, there were no significant differences in the risk of all-cause mortality across BMI/WC combinations (Supporting Table S5).

For CVD-related and cancer-related mortality, we excluded individuals with obese BMI–normal WC because of the small number of events, and analyses of stratification were not conducted. In the unadjusted competing risk model, compared to patients with NAFLD with lean BMI–normal WC, obese WC in each BMI category had a higher risk for CVD mortality (HR 2.44, 95% CI: 1.21-4.92 for lean BMI–obese WC; HR 2.26, 95% CI: 1.55-3.30 for overweight BMI–obese WC; and HR 1.72, 95% CI: 1.22-2.44

TABLE 3. ASSOCIATION OF BMI/WC COMBINATIONS WITH ALL-CAUSE AND CAUSE-SPECIFIC MORTALITY AMONG INDIVIDUALS WITH NAFLD

	Individuals With NAFLD					
	Lean		Overweight		Obese	
	Normal WC	Obese WC	Normal WC	Obese WC	Normal WC	Obese WC
N	742	55	515	527	46	1,256
All-cause mortality	148	30	106	227	5	423
Unadjusted HR	Reference	3.40 (2.00-5.76)	1.04 (0.74-1.46)	2.54 (1.89-3.40)	0.57 (0.17-1.93)	1.84 (1.36-2.48)
Age–sex adjusted HR	Reference	1.37 (0.97-1.92)	0.77 (0.51-1.16)	1.04 (0.77-1.40)	0.85 (0.26-2.77)	1.14 (0.91-1.44)
HR 1	Reference	1.35 (1.01-1.81)	0.74 (0.50-1.09)	1.06 (0.78-1.44)	0.84 (0.24-3.04)	1.16 (0.93-1.45)
HR 2	Reference	1.51 (1.10-2.07)	0.77 (0.54-1.09)	1.07 (0.77-1.49)	0.89 (0.25-3.10)	1.13 (0.87-1.40)
Fully adjusted HR	Reference	1.42 (1.03-1.96)	0.74 (0.51-1.09)	1.00 (0.72-1.38)	0.87 (0.25-2.99)	1.02 (0.77-1.33)
Age stratification*						
<65	Reference	2.32 (1.12-4.79)	0.68 (0.38-1.24)	1.45 (0.91-2.33)	0.21 (0.07-0.65)	1.21 (0.78-1.87)
≥65	Reference	1.47 (0.82-2.61)	0.99 (0.54-1.82)	0.93 (0.63-1.38)	NA	0.87 (0.61-1.25)
Sex stratification*						
Female	Reference	1.54 (0.88-2.67)	1.08 (0.47-2.49)	1.38 (0.78-2.44)	3.54 (0.49-25.91)	1.19 (0.77-1.83)
Male	Reference	2.34 (1.27-4.33)	0.61 (0.39-0.93)	0.74 (0.49-1.12)	0.64 (0.17-2.5)	0.90 (0.63-1.30)
Race stratification*						
non-Hispanic white	Reference	1.58 (1.12-2.24)	0.79 (0.51-1.23)	1.20 (0.84-1.71)	0.89 (0.16-4.89)	1.18 (0.85-1.00)
non-Hispanic black	Reference	1.87 (0.36-9.58)	0.38 (0.22-0.67)	0.64 (0.33-1.22)	0.85 (0.23-3.09)	0.58 (0.37-0.93)
Mexican American	Reference	0.59 (0.32-1.09)	0.44 (0.26-0.74)	0.59 (0.32-1.10)	0.53 (0.13-2.19)	0.56 (0.38-0.82)
Metabolic abnormality stratification*						
No	Reference	1.11 (0.25-4.97)	0.52 (0.13-2.06)	0.42 (0.03-6.27)	NA	NA
Yes	Reference	1.47 (1.09-2.00)	0.75 (0.53-1.07)	1.04 (0.77-1.41)	0.87 (0.26-2.96)	1.11 (0.86-1.44)
CVD mortality	37	6	17	55	—	115
Unadjusted HR	Reference	2.44 (1.21-4.92)	1.03 (0.65-1.63)	2.26 (1.55-3.30)		1.72 (1.22-2.44)
Age–sex adjusted HR	Reference	1.34 (0.64-2.80)	0.74 (0.46-1.19)	1.11 (0.75-1.62)		1.23 (0.86-1.75)
HR 1	Reference	1.34 (0.63-2.85)	0.57 (0.34-0.94)	0.97 (0.65-1.45)		1.14 (0.79-1.64)
HR 2	Reference	1.49 (0.68-3.26)	0.57 (0.34-0.96)	1.01 (0.66-1.54)		1.14 (0.78-1.67)
Fully adjusted HR	Reference	1.35 (0.61-3.00)	0.52 (0.30-0.88)	0.89 (0.58-1.35)		0.97 (0.66-1.44)
Cancer mortality	38	9	325	53	—	95
Unadjusted HR	Reference	1.56 (0.73-3.31)	1.02 (0.67-1.54)	1.52 (1.05-2.21)		1.11 (0.79-1.54)
Age–sex adjusted HR	Reference	0.91 (0.43-1.93)	0.83 (0.54-1.27)	0.85 (0.58-1.24)		0.80 (0.57-1.13)
HR 1	Reference	0.94 (0.44-2.03)	0.92 (0.60-1.43)	0.85 (0.57-1.27)		0.82 (0.57-1.16)
HR 2	Reference	0.97 (0.45-2.10)	0.92 (0.59-1.45)	0.85 (0.56-1.28)		0.81 (0.56-1.17)
Fully adjusted HR	Reference	0.96 (0.44-2.10)	0.91 (0.58-1.45)	0.83 (0.54-1.27)		0.79 (0.54-1.17)

Note: Model 1 is adjusted for age, male, race, income, education, active smoking, and physical activity. Model 2 is adjusted for variables in model 1 and advanced fibrosis based on FIB-4, CKD, previous cancer, and previous CVD. The full model is adjusted for variables in model 2 and HTN, HL, and T2DM.
*HRs in stratified analyses were adjusted for factors in the full model except the stratified factor.
Abbreviation: NA, not applicable. "—" indicates fewer than five cases.

for obese BMI–obese WC). However, when compared to individuals with NAFLD with overweight BMI–normal WC, individuals with NAFLD with lean BMI–obese WC had a higher risk of CVD (HR 2.63, 95% CI: 1.15-6.01) in the fully adjusted competing risk model. For individuals without NAFLD, risk of CVD mortality was higher in the obese BMI–obese WC category than any other BMI/WC categories. In contrast, we identified no association of different combinations of BMI/WC with cancer mortality among both individuals with NAFLD and without NAFLD (Table 3).

INDEPENDENT PREDICTORS OF ALL-CAUSE AND CAUSE-SPECIFIC MORTALITY AMONG INDIVIDUALS WITH NAFLD ACCORDING TO THE BODY COMPOSITION CLASSIFICATIONS

Among individuals with NAFLD with lean BMI, previous CVD (HR 3.02, 95% CI: 1.93-4.72) was the strongest predictor of all-cause mortality, followed by presence of CKD and T2DM. Among individuals with NAFLD with normal WC, previous CVD (HR 2.79, 95% CI: 1.63-4.78), was the strongest independent predictor of all-cause mortality, followed by male gender and low income (Table 4). Among individuals with NAFLD with non-lean BMI, active smoking (HR 1.68, 95% CI: 1.43-1.99) and previous CVD (HR 1.66, 95% CI: 1.38-1.99) were the strongest predictors of all-cause mortality, followed by the presence of CKD and T2DM. For individuals with NAFLD with obese WC, the predictors of all-cause mortality were the same as those among individuals with NAFLD with non-lean BMI (Table 4).

In terms of CVD mortality, WC was a predictor of CVD mortality in each BMI category, whereas BMI was not in each WC category. The strongest predictor of CVD mortality was T2DM among both individuals with lean BMI (HR 2.15, 95% CI: 1.08-4.29) and with normal WC (HR 2.40, 95% CI: 1.04-5.55), followed by age. Active smoking, HTN, HL, and previous CVD were predictors of CVD mortality among both individuals with NAFLD with non-lean BMI and with obese WC, whereas CKD was a predictor only among individuals with NAFLD with obese WC (Table 4).

Assessing cancer-related mortality showed that age and active smoking were among the leading predictors of cancer mortality across all NAFLD categories. However, for patients with NAFLD with lean BMI (HR 3.64, 95% CI: 1.49-8.94) and normal WC (HR 3.18, 95% CI: 1.05-9.58), advanced fibrosis was the strongest predictor of cancer-related mortality. Previous history of CVD was the strongest predictor of cancer mortality for individuals with NAFLD with non-lean BMI (HR 1.72, 95% CI: 1.11-2.65) and with obese WC (HR 1.65, 95% CI: 1.10-2.48) (Table 4).

Discussion

In this study, using a representative sample of the U.S. adult population, we have demonstrated the importance of anthropometric assessment on the long-term outcomes of patients with NAFLD. In this context, our results show associations of different combinations of BMI and WC to all-cause, CVD-related, and cancer-related mortality. Our analyses show that individuals with NAFLD with lean BMI and obese WC had an elevated risk of all-cause mortality, which is higher than individuals with NAFLD with other combinations of BMI and WC. Furthermore, the risk of CVD mortality among individuals with NAFLD with lean BMI with obese WC was almost 3 times higher than among individuals with NAFLD with overweight BMI and normal WC. However, the associations of obesity patterns with cancer-related mortality among patients with NAFLD could not be clearly discerned.

The close association of NAFLD with obesity and other components of metabolic syndrome has been established. In this context, obesity can be estimated by overall adiposity, as measured by BMI, or visceral obesity, which is estimated by WC. Although these two anthropometric measures of obesity correlate with each other, they may have different effects on the long-term outcomes of patients with NAFLD.[25-27] Even though most of the epidemiologic studies of NAFLD have primarily used BMI as a measure of body composition, it is possible that replacing BMI with WC may provide additional perspective about the long-term outcomes of these patients. Our data show that the age-adjusted prevalence of NAFLD is 33.9% in our cohort, and patients with NAFLD are older, more commonly male, Mexican American, less physically active, with significantly higher metabolic syndrome components than patients without NAFLD. According to BMI, the prevalence of lean NAFLD was 8.4% in this cohort, which is in agreement with previous reports.[28-31] The addition of WC to this comparison provides some interesting findings, as the proportion of lean BMI with normal WC was 48.5% among the non-NAFLD group, while it was only 23.6% in patients with NAFLD. Similarly, the proportion of obese BMI with obese WC was 14% among the non-NAFLD group but it was as high as 40% in patients with NAFLD. Furthermore, within each BMI category, central adiposity as measured by

TABLE 4. INDEPENDENT PREDICTORS OF ALL-CAUSE MORTALITY AND CAUSE-SPECIFIC MORTALITY AMONG INDIVIDUALS WITH NAFLD ACCORDING TO THE BODY COMPOSITION CLASSIFICATIONS (NHANES III, U.S. 1988-1994)

	All-Cause Mortality				CVD Mortality				Cancer Mortality			
Predictors	NAFLD Lean BMI	NAFLD Nonlean BMI	NAFLD Normal WC	NAFLD Obese WC	NAFLD Lean BMI	NAFLD Nonlean BMI	NAFLD Normal WC	NAFLD Obese WC	NAFLD Lean BMI	NAFLD non-Lean BMI	NAFLD Normal WC	NAFLD Obese WC
Age	1.07 (1.06-1.08)	1.08 (1.07-1.09)	1.07 (1.06-1.08)	1.08 (1.07-1.09)	1.06 (1.04-1.09)	1.08 (1.06-1.09)	1.07 (1.05-1.1)	1.07 (1.06-1.09)	1.04 (1.03-1.06)	1.06 (1.04-1.07)	1.06 (1.04-1.08)	1.05 (1.04-1.06)
Male	1.67 (1.25-2.23)	1.32 (1.15-1.52)	2.09 (1.33-3.28)	1.38 (1.21-1.58)				1.39 (108-1.79)				
Low income	1.50 (1.10-2.04)	1.17 (1.00-1.36)	1.90 (1.33-2.71)	1.16 (1.00-1.35)								
College		0.80 (0.67-0.97)										
WC		1.01 (1.00-1.02)			1.05 (1.00-1.09)	1.01 (1.00-1.02)						
BMI			0.89 (0.83-0.96)								0.86 (0.76-0.96)	
Actively smoking	1.73 (1.28-2.33)	1.68 (1.43-1.99)		1.77 (1.51-2.07)		1.81 (1.34-2.45)		1.64 (1.22-2.20)	2.11 (1.21-3.69)	1.53 (1.17-2.11)	2.06 (1.02-4.15)	1.64 (1.22-2.21)
Sedentary physical activity	1.66 (1.19-2.32)			1.20 (1.03-1.41)								
T2DM	1.73 (1.19-2.52)	1.52 (1.30-1.76)		1.63 (1.41-1.88)	2.15 (1.08-4.29)		2.40 (1.04-5.5)					
HTN		1.24 (1.05-1.62)	1.59 (1.10-2.31)	1.22 (1.03-1.44)		1.46 (1.04-2.03)		1.40 (1.02-2.49)				
HL		1.30 (1.05-1.62)				1.86 (1.14-3.03)		1.60 (1.02-2.49)				
CKD	1.80 (1.23-2.64)	1.55 (1.32-1.82)		1.54 (1.32-1.81)				1.37 (1.01-1.85)				
Advanced fibrosis									3.64 (1.49-8.94)		3.18 (1.05-9.58)	
Previous CVD	3.02 (1.93-4.72)	1.66 (1.38-1.99)	2.79 (1.63-4.78)	1.74 (1.46-2.08)		2.00 (1.47-2.74)		1.92 (1.41-2.62)		1.72 (1.11-2.65)		1.65 (1.10-2.48)
Previous cancer		1.39 (1.10-1.76)		1.41 (1.13-1.75)					2.14 (1.08-4.23)			

WC created significant changes in the proportions of metabolic syndrome components. In all BMI categories, compared to NAFLD patients with normal WC, individuals with obese WC had significantly higher rates of HTN, HL, T2DM, and insulin resistance. Again, these findings are in agreement with previous studies reporting worse metabolic pictures in obese patients with NAFLD compared to their lean counterparts.[32-34]

Another crucially important finding of the current study is the long-term outcomes of subjects with NAFLD according to different body composition. Compared to patients with NAFLD with lean BMI–normal WC, patients with NAFLD with obese WC in lean, overweight, and obese BMI categories had higher all-cause mortality; however, this association was statistically significant only in the lean BMI group (lean BMI–normal WC vs. lean BMI–obese WC). On the other hand, compared with the lean BMI–normal WC group, we did not see a statistically significant difference in CVD-related and cancer-related mortality in other groups. The effect of obese WC in mortality suggests that the presence of central obesity in patients with NAFLD may be the driving force for increased mortality. Our multivariate analysis also demonstrated that for patients with NAFLD with obese WC, and for subjects with NAFLD who had nonlean BMI, the independent predictors of all-cause mortality were active smoking, previous CVD, T2DM, and CKD. As one would expect, those factors are also associated with the presence of hepatic fibrosis, advanced liver disease, and adverse outcomes in patients with NAFLD. For example, T2DM is not only a risk factor for NAFLD and NASH, but also an independent predictor of advanced fibrosis and increased mortality risk in NAFLD.[33-40] Furthermore, advanced fibrosis is an important driver of all-cause mortality in patients with NAFLD.[41-44] In a similar fashion, our multivariate analysis demonstrated that history of CVD increased the risk of all-cause mortality by almost 3 times in patients with normal WC and in patients with normal BMI, reflecting the importance of CVD in NAFLD as the leading cause of mortality.[45-47]

The strengths of our study include its large, nationally representative sample of U.S. adults with mortality status after up to 27 years of follow-up. However, this study has several limitations that need to be considered. First, because no liver histology data were provided in the NHANES data, NAFLD was diagnosed by ultrasonography data, which have good sensitivity (85%) and specificity (94%) for fatty liver[48]; NHANES III is the only national sample of adults in the United States with ultrasonography data available to determine the presence of hepatic steatosis. However, ultrasonography cannot identify smaller amounts of hepatic steatosis. Similarly, as we did not have any histological data, we used clinical prediction models for the assessment of advanced fibrosis in this cohort, which has poor positive predictive value. Second, NHANES III data included only the baseline metabolic components and comorbidities collected. We were unable to quantify the effects of changes in cardio-metabolic risk factors over the time on all-cause and cause-specific mortality among individuals with NAFLD due to the cross-sectional nature of this study. Third, the NHANES III–linked mortality file determined causes of death through the NDI abstracted from the death certification, which may not be accurate.[49] Fourth, participants excluded in this present analysis were more likely to be black and had lower lifestyle factors, which might have influenced the results.

To summarize, both anthropometric measurements, WC and BMI, are clinically important tools to risk-stratify patients with NAFLD. Increasing adiposity even in patients with normal BMI appears to be associated with higher risk of all-cause mortality in patients with NAFLD. Different management programs for patients with NAFLD according to their body composition can potentially provide a more personalized approach for patients with NAFLD, and using WC more frequently in daily practice may help the risk stratification of patients with NAFLD for worse outcomes.

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