Risk of Cardiovascular Disease in Individuals With Nonobese Nonalcoholic Fatty Liver Disease

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Nonalcoholic fatty liver disease (NAFLD) is independently associated with obesity and cardiovascular disease (CVD). CVD is the primary cause of mortality in the predominantly obese population of adults with NAFLD. NAFLD is increasingly seen in individuals who are lean and overweight (i.e., nonobese), but it is unclear whether their risk of CVD is comparable to those with NAFLD and obesity. Using a prospective cohort of patients with NAFLD, we compared the prevalence and incidence of CVD in individuals with and without obesity. NAFLD was diagnosed by biopsy or imaging after excluding other chronic liver disease etiologies. Logistic regression was used to compare the odds of baseline CVD by obesity status. Cox proportional hazards regression was used to evaluate obesity as a predictor of incident CVD and to identify predictors of CVD in subjects with and without obesity. At baseline, adults with obesity had a higher prevalence of CVD compared to those without obesity (12.0% vs. 5.0%, $P = 0.02$). During follow-up, however, obesity did not predict incident CVD (hazard ratio [HR], 1.24; 95% confidence interval [CI], 0.69-2.22) or other metabolic diseases. Findings were consistent when considering body mass index as a continuous variable and after excluding subjects who were overweight. Age (adjusted HR [aHR], 1.05; 95% CI, 1.03-1.08), smoking (aHR, 4.61; 95% CI, 1.89-11.22), and decreased low-density lipoprotein levels (aHR, 0.98; 95% CI, 0.96-1.00) independently predicted incident CVD in the entire cohort, in subjects with obesity, and in those without obesity, respectively. *Conclusion:* Individuals with overweight or lean NAFLD are not protected from incident CVD compared to those with NAFLD and obesity, although CVD predictors appear to vary between these groups. Patients without obesity also should undergo rigorous risk stratification and treatment. (*Hepatology Communications* 2022;6:309-319).

Nonalcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease worldwide, impacting an estimated 25% of the global population and incurring a cost of more than $100 billion per annum in the United States alone.[1,2] NAFLD is projected to continue increasing in prevalence during the next decade.[3] NAFLD is an independent risk factor for cardiovascular disease (CVD) and major adverse CVD events.[4] CVD is a leading cause of mortality in this population,[5]

accounting for 25% of deaths among patients with NAFLD.[6]

While the risk of CVD in NAFLD has been evaluated in several studies,[7-9] the populations studied have primarily been adults with obesity (body mass index [BMI] ≥ 30 kg/m^2) who may have unique cardiometabolic risk factors predisposing them to CVD. However, NAFLD is increasingly identified among individuals who are overweight or lean (defined as BMI 25-29.9 kg/m^2 and <25 kg/m^2, respectively). A recent meta-analysis estimated that approximately 40% of the global NAFLD population is nonobese, with nearly a fifth classified as lean.[10] A second meta-analysis reported the prevalence of NAFLD to be higher in the nonobese Western population than observed in Eastern studies.[11] However, the risk of CVD among individuals with nonobese NAFLD has been less well characterized, and it is unclear whether individuals with nonobese NAFLD carry the same risk of CVD as those with NAFLD and obesity. Several studies reported CVD risk to be comparable among NAFLD populations with and without obesity,[12-14] while further studies demonstrated that metabolic risk factors exert a greater influence than obesity on CVD risk and overall mortality in NAFLD.[15,16] However, Kim et al.[17] identified an association between NAFLD and CVD risk that was significant in individuals without obesity only. Cruz et al.[18] reported increased overall mortality in patients who were lean compared to patients who were overweight or patients with obesity, despite significantly lower incidences of metabolic syndrome and traditional CVD risk factors in the lean population. In contrast, Leung et al.[19] reported significantly more deaths and cardiovascular events among patients with obesity compared to patients without obesity. With a single exception, all the above studies were limited by their use of surrogate endpoints instead of hard clinical outcomes. Furthermore, the majority of prior studies were conducted in Asia; it is unclear to what extent their findings are applicable in the West, given substantial disease heterogeneity between populations.

There is a need to improve our understanding of CVD risk in the growing population of patients with nonobese NAFLD. Therefore, using a prospective cohort of Western subjects with NAFLD, we compared the risks of prevalent and incident CVD and other metabolic diseases between adults with and without obesity.

Participants and Methods

STUDY POPULATION AND DATA COLLECTION

Enrollment took place in the Massachusetts General Hospital Fatty Liver Clinic. All subjects were older than 18 years. NAFLD was diagnosed either by histology or by visualization of increased echogenicity/diffuse fatty infiltration on ultrasound imaging. Individuals with decompensated cirrhosis, concomitant or alternative etiologies of liver disease, prior bariatric surgery, prior liver transplant, or a history

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of excessive alcohol consumption (more than 14 drinks per week for men or more than seven drinks per week for women) were excluded. Eligible patients were invited to participate in the study by their clinic provider. Those who were agreeable were enrolled by a study coordinator. Between October 1, 2002, and October 1, 2019, 394 patients with NAFLD were identified and included in the cohort. Eight patients had no follow-up recorded and were excluded from all longitudinal analyses. Liver biopsies were reviewed in a blinded manner by a single hepatopathologist and evaluated for the presence of nonalcoholic steatohepatitis and fibrosis stage.[20] Fibrosis stage 3 or 4 was considered advanced fibrosis. Transient elastography or ultrasound elastography was performed to stage fibrosis in most individuals diagnosed by imaging. A liver stiffness of >12 on transient elastography or shear wave >1.55 m/second was also considered advanced fibrosis.[21,22] Baseline demographic, clinical, and laboratory data were collected from study visits and the electronic medical record. Non-Asian subjects with enrollment BMI ≥ 30, 25-29.9, and <25 were defined as obese, overweight, and lean, respectively. Asian subjects with enrollment BMI ≥ 27.5, 23-27.5, and <23 were defined as obese, overweight, and lean, respectively. These classifications are in line with World Health Organization recommendations.[23] For our primary analyses, we created a binary categorical exposure variable, i.e., with versus without obesity. The group without obesity included individuals who were lean and those who were overweight. This study was approved by the Massachusetts General Hospital Institutional Review Board and conformed to the Declaration of Helsinki. All patients provided written consent before inclusion in the study cohort.

FOLLOW-UP AND OUTCOMES

Subjects were followed prospectively from time of liver biopsy or imaging to death or end of follow-up (May 1, 2020), whichever came earlier. The primary outcome was incident CVD, which was defined as one or more of the following: a new diagnosis of coronary artery disease (CAD), congestive heart failure (CHF), peripheral vascular disease, cerebrovascular accident/transient ischemic attack (TIA), arrhythmia, or a major adverse cardiac event (MACE), which included myocardial infarction, coronary artery revascularization, or cardiac-related death. The secondary outcomes were a new diagnosis of dyslipidemia (defined as high-density lipoprotein [HDL] < 40 mg/dL in men or <50 mg/dL in women or triglycerides ≥150 mg/dL), hypertension (defined as systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg), and diabetes (defined as hemoglobin A1c >6.4%). Outcomes data were collected by clinician review of the electronic medical record.

STATISTICAL ANALYSIS

Descriptive statistics were calculated for demographic and clinical characteristics. Baseline characteristics of subjects with and without obesity were compared using chi-squared tests or Fisher's exact tests for categorical variables and t tests or Wilcoxon rank-sum tests for continuous variables, depending on the normality of the distribution. Multivariable logistic regression was performed to identify baseline demographic and clinical characteristics independently associated with the presence of obesity and prevalent CVD. Cox proportional hazards regression was performed to identify predictors of incident CVD and metabolic diseases in the overall cohort and again in separate analyses of patients with and without obesity. Obesity and predictors with $P < 0.10$ in univariable analyses were considered in the multivariable analyses and retained at a $P < 0.05$ level of significance, using a backward selection process. Analyses were also performed considering BMI as a continuous variable. Kaplan-Meier curves for survival free of incident CVD and metabolic diseases were additionally computed and compared using log-rank tests. We conducted several sensitivity analyses. First, we excluded individuals who were overweight and repeated the logistic regression analysis using individuals who were obese and lean. Second, we repeated the logistic regression analysis after excluding individuals who were diagnosed with NAFLD by noninvasive means. Third, we included the 19 subjects who were nonobese at the time of enrollment but developed obesity during follow-up and counted these in the obese group intead of the nonobese group. Fourth, we conducted an analysis excluding those 19 subjects. Data were missing in <5% of cases with the exception of lipid values (total cholesterol missing in n = 56/394, HDL n = 65/395, low-density lipoprotein [LDL] n = 79/394, triglycerides n = 66/394). Missing data were imputed from the median value. Analyses were

conducted using SAS Studio software, version 3.71 (SAS Institute, Cary, NC). *P* < 0.05 was the threshold for statistical significance.

Results

BASELINE CHARACTERISTICS

Baseline demographic and clinical characteristics of the full study cohort are presented in Table 1. Of 394 subjects included in the final cohort, 233 (59.1%) had obesity and 161 (40.7%) were nonobese; of these 161 subjects, 35 (21.7%) were lean. Nearly all patients in the group with obesity underwent liver biopsies (n = 220/233; 94.4%), while the subjects without obesity were more likely to be diagnosed by noninvasive means (n = 107/161 with biopsies; 66.5%). Compared with patients without obesity, those with obesity were more likely to be non-Asian and to have dyslipidemia, hypertension, diabetes, obstructive sleep apnea (OSA), and baseline CVD and to use an oral antihyperglycemic medication. They also had lower albumin and HDL cholesterol levels and higher triglyceride levels. The severity of liver disease by fibrosis-4 (FIB-4) score was similar, as were the proportions with advanced fibrosis on biopsy or elastography, which was available in n = 380/394 subjects.

On multivariable analysis, obesity was associated with significantly higher odds of having prevalent OSA, lower HDL levels, and non-Asian race/ethnicity (Table 2). When subjects who were overweight were excluded and analysis was restricted to subjects with obesity and those who were lean, individuals with obesity were more likely to have hypertension (adjusted odds ratio [aOR], 3.65; 95% confidence interval [CI], 1.59-8.38), dyslipidemia (aOR, 2.37; 95% CI, 1.01-5.55), lower HDL levels (aOR, 0.95; 95% CI, 0.93-0.98), to be of non-Asian race/ethnicity (aOR, 0.10; 95% CI, 0.03-0.42), and to have a history of malignancy (aOR, 0.37; 95% CI, 0.14-0.93), compared to lean individuals.

Although individuals with obesity had a higher baseline prevalence of CVD (12.0% vs. 5.0%, *P* = 0.02) and were more likely to have many typical CVD risk factors, obesity was not an independent predictor of incident CVD when accounting for these risk factors (Table 3). The odds of CVD for obesity adjusted for age, sex, smoking, hypertension, diabetes, dyslipidemia, and OSA was 2.14 (95% CI, 0.74-6.22; *P* = 0.16). Further adjustment for FIB-4 score did not alter these results (aOR, 2.37; 95% CI, 0.80-7.03) and neither did inclusion of advanced fibrosis on biopsy or elastography (aOR, 2.12; 95% CI, 0.73-6.17). BMI considered as a continuous variable was also not an independent predictor, with an aOR of 1.01 (95% CI, 0.94-1.09; *P* = 0.81), and this was similarly not affected by degree of fibrosis.

INCIDENT CARDIOVASCULAR AND METABOLIC DISEASE

A total of 386 subjects had follow-up data available, with a median follow-up time of 5.7 years (interquartile range [IQR], 2.9-8.0). Of this cohort, 36 subjects had CVD at baseline and were excluded from longitudinal analysis. Among these 350 subjects without CVD at baseline, incident CVD occurred in 54 (15.4%), 38 of whom were obese (70.4%) and 16 of whom were nonobese (29.6%), after a median of 3.8 years (IQR, 2.3-5.6). In the group with obesity, 17 subjects developed CAD; of these, 3 had MACE, 16 had arrhythmias, 4 developed CHF, 2 developed peripheral artery disease (PAD), and 7 had a stroke/TIA. In the nonobese group, 99 subjects were diagnosed with CAD; of these, 6 had MACE, 1 developed CHF, 2 developed PAD, 3 experienced arrhythmias, and 4 had a stroke/TIA.

Kaplan-Meier curves for time free of CVD by obesity status are shown in Fig. 1A. On univariable analysis, predictors of incident CVD included age, smoking, hypertension, diabetes, OSA, use of antihypertensive medications, use of statins, albumin levels, and platelet counts, with older age and former or current smoking remaining significant predictors on multivariable analysis (Table 4). Obesity was not a significant predictor of CVD on univariable or multivariable analysis (Table 4), and findings were consistent when BMI was considered as a continuous variable (hazard ratio [HR], 1.03; 95% CI, 0.99-1.07; *P* = 0.14). Similarly, when analysis was limited to subjects with obesity and those who were lean, obesity was not associated with incident CVD (HR, 1.11; 95% CI, 0.40-3.13; *P* = 0.84). The HR for obesity (with CVD as the outcome) adjusted for age, sex, smoking, hypertension, diabetes, OSA, and dyslipidemia was 1.14 (95% CI, 0.61-2.11; *P* = 0.69) and for BMI was 1.02 (95% CI, 0.98-1.07; *P* = 0.31). Findings were similar after

TABLE 1. BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF INDIVIDUALS WITH NAFLD WITH AND WITHOUT OBESITY

	Without Obesity (n = 161)	With Obesity (n = 233)	P Value
Age, years	55 (44-62)	53 (42-62)	0.32
Female sex	54.7% (88)	57.1% (133)	0.63
BMI	26.9 (25.1-28.4)	34.8 (32.2-38.7)	0.001
Race/ethnicity			0.002
Hispanic	13.0% (21)	14.2% (33)	
Non-Hispanic white	67.7% (109)	78.5% (183)	
Non-Hispanic black	2.5% (4)	1.3% (3)	
Asian	13.0% (21)	2.6% (6)	
Other/not specified	3.7% (6)	3.4% (8)	
Smoking status			0.25
Current	6.8% (11)	9.0% (21)	
Former	24.8% (40)	30.9% (72)	
Never	68.3% (110)	60.1% (140)	
Comorbidities			
Dyslipidemia	75.2% (121)	84.6% (197)	0.02
Hypertension	58.4% (94)	69.1% (161)	0.03
Diabetes	23.6% (38)	34.8% (81)	0.02
OSA	8.7% (14)	28.8% (67)	0.001
CVD	5.0% (8)	12.0% (28)	0.02
CAD	2.5% (4)	9.9% (23)	0.004
Peripheral artery disease	3.7% (6)	5.2% (12)	0.51
Prior malignancy	21.1% (34)	15.9% (37)	0.18
Medications			
Statin	29.2% (47)	38.2% (89)	0.06
Antihypertensive medication use	43.5% (70)	53.2% (124)	0.06
Oral antihyperglycemic medication use	19.2% (31)	28.3% (66)	0.04
Insulin	5.0% (8)	9.9% (23)	0.08
Laboratory values			
Sodium, mEq/L	140 (138-142)	140 (138-142)	0.69
Creatinine, mg/dL	0.84 (0.74-0.95)	0.84 (0.71-0.99)	0.68
Albumin, g/dL	4.6 (4.3-4.8)	4.4 (4.2-4.7)	0.001
ALT, U/L	46 (29-80)	53 (34-86)	0.06
AST, U/L	38 (26-56)	42 (29-63)	0.07
Total bilirubin, mg/dL	0.5 (0.4-0.7)	0.5 (0.3-0.7)	0.36
Alkaline phosphatase, U/L	78 (64-102)	84 (67-104)	0.12
Total cholesterol, mg/dL*	192.0 ± 45.1	190.0 ± 45.1	0.68
HDL, mg/dL[†]	46 (39-54)	42 (36-50)	0.004
LDL, mg/dL[‡]	111.0 ± 39.2	111.6 ± 38.3	0.89
Triglycerides, mg/dL[§]	128 (102-182)	155 (109-217)	0.007
Platelets, ×10^9/L	232.9 ± 70.9	233.8 ± 68.6	0.91
Liver disease severity			
FIB-4, median	1.23 (0.93-1.96)	1.25 (0.88-1.98)	0.76
<1.3	54.3% (88)	54.9% (128)	0.93
1.3-2.67	32.3% (52)	30.9% (72)	
>2.67	13.0% (21)	14.2% (33)	
Advanced fibrosis[‖]	17.5% (28)	24.6% (54)	0.10

Data expressed as % (n), median (IQR), or mean ± SD.
*Missing in 56/394.
[†]Missing in 65/394.
[‡]Missing in 79/394.
[§]Missing in 66/394.
[‖]Advanced fibrosis on biopsy or, if not available, on transient elastography or ultrasound elastography. Missing in 14/394.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

TABLE 2. FACTORS ASSOCIATED WITH OBESITY IN INDIVIDUALS WITH NAFLD

	Univariable OR (95% CI)	P Value	Multivariable OR (95% CI)	P Value
Race/ethnicity		0.006		0.04
Non-Hispanic white vs. Asian	5.88 (2.30-15.01)		4.29 (1.60-11.51)	
Non-Hispanic black vs. Asian	2.62 (0.46-15.11)		1.55 (0.25-9.81)	
Hispanic vs. Asian	5.50 (1.91-15.87)		4.78 (1.57-14.54)	
Other vs. Asian	5.88 (2.30-15.01)		4.13 (0.94-18.04)	
Hypertension	1.59 (1.05-2.42)	0.03		
Dyslipidemia	1.81 (1.09-2.99)	0.02		
Diabetes	1.72 (1.10-2.71)	0.02		
OSA	4.24 (2.29-7.86)	0.001	3.70 (1.89-7.23)	0.001
Baseline CVD	2.61 (1.16-5.89)	0.02		
Albumin	0.46 (0.26-0.83)	0.01		
HDL	0.98 (0.96-0.99)	0.003	0.97 (0.95-0.99)	0.001
Triglycerides	1.00 (1.00-1.01)	0.01		

Covariates shown are predictors with $P < 0.10$ in univariable analyses and considered in the multivariable logistic regression model.

TABLE 3. PREDICTORS OF PREVALENT CVD IN INDIVIDUALS WITH NAFLD

	Univariable OR (95% CI)	P Value	Multivariable OR (95% CI)	P Value
Age	1.13 (1.08-1.18)	0.001	1.16 (1.10-1.23)	0.001
Male sex	3.73 (1.75-7.80)	0.001	2.92 (1.16-7.32)	0.02
Obesity	2.61 (1.16-5.89)	0.02		
Smoking status		0.01		
Former vs. never	3.23 (1.54-6.75)			
Current vs. never	2.41 (0.74-7.82)			
Diabetes	5.54 (2.66-11.51)	0.001	3.44 (1.46-8.14)	0.005
OSA	5.34 (2.63-10.84)	0.001	4.77 (1.95-11.70)	0.001
Creatinine	10.56 (2.52-44.19)	0.001		
Albumin	0.42 (0.18-0.95)	0.04		
ALT	0.99 (0.98-1.00)	0.049		
Total cholesterol	0.98 (0.97-0.99)	0.001		
HDL	0.95 (0.92-0.99)	0.01	0.96 (0.92-1.00)	0.03
LDL	0.98 (0.97-0.99)	0.001		
Platelets	0.99 (0.98-0.99)	0.001		

Covariates shown are predictors with $P < 0.10$ in univariable analyses and considered in the multivariable logistic regression model. LDL and total cholesterol were collinear; LDL was included.
Abbreviation: ALT, alanine aminotransferase.

further adjustment for parameters of disease severity, including FIB-4 score (HR, 1.14; 95% CI, 0.61-2.11) among the entire cohort or advanced fibrosis by elastography or on biopsy (HR, 1.02; 95% CI, 0.54-1.94). Furthermore, results were not significantly different after including subjects without obesity who developed obesity during follow-up in the obese group (HR, 0.97; 95% CI, 0.52-1.81) or excluding them from the analysis (HR, 1.01; 95% CI, 0.54-1.89).

Of the 386 subjects included in the longitudinal analysis, 258 (66.8%) were evaluated for incident diabetes, 133 for incident hypertension (34.5%), and 70 (18.1%) for incident dyslipidemia. Overall, 34 (13.2%) developed diabetes, 43 (32.3%) were diagnosed with hypertension, and 31 (44.3%) developed dyslipidemia. On univariable analysis, nonobesity (vs. obesity) was associated with an increased risk of incident dyslipidemia (Fig. 1D; Table 5). Obesity was not, however,
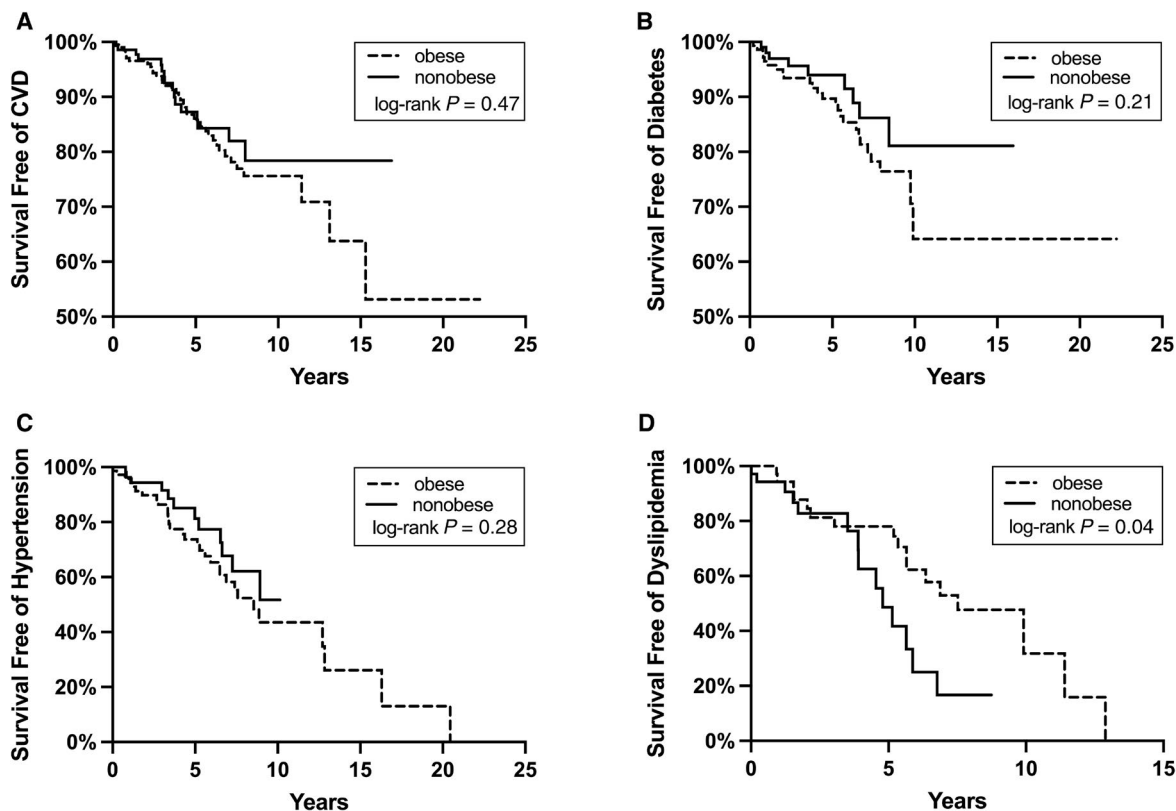
FIG. 1. Kaplan-Meier curves for survival. Kaplan-Meier curves showing survival free of (A) CVD, (B) diabetes, (C) hypertension, and (D) dyslipidemia by obesity status in individuals with NAFLD.

TABLE 4. PREDICTORS OF INCIDENT CVD

	Univariable HR, (95% CI)	P Value	Multivariable HR, (95% CI)	P Value
Obesity	1.24 (0.69-2.22)	0.48		
Age	1.04 (1.02-1.07)	0.001	1.05 (1.03-1.08)	
Smoking status		0.002		
Former vs. never	2.55 (1.43-4.55)		2.06 (1.20-3.56)	
Current vs. never	2.79 (1.25-6.25)		3.65 (1.82-7.30)	
Hypertension	2.54 (1.31-4.93)	0.006		
Diabetes	1.59 (0.92-2.77)	0.098		
OSA	1.92 (1.07-3.45)	0.03		
Use of antihypertensives	1.86 (1.07-3.22)	0.03		
Statin use	1.89 (1.10-3.24)	0.02		
Albumin	0.45 (0.25-0.79)	0.006		
Platelets	1.00 (0.99-1.00)	0.02		

Covariates shown include obesity and predictors with $P < 0.10$ in univariable analyses that were considered in the multivariable Cox proportional hazards regression model. Hypertension and use of antihypertensive medications were collinear, so they were considered separately, although neither was significant.

associated with risk of incident diabetes or hypertension (Fig. 1B,C; Table 5; Supporting Tables S1 and S2). These associations remained nonsignificant when BMI was considered as a continuous variable (diabetes HR, 1.00; 95% CI, 0.95-1.06; $P = 0.98$; hypertension HR, 1.05; 95% CI, 1.00-1.11; $P = 0.07$; dyslipidemia

TABLE 5. OBESITY AS PREDICTOR OF OTHER METABOLIC OUTCOMES IN INDIVIDUALS WITH NAFLD

Outcome	HR (95% CI) for Obesity vs. Nonobesity	P Value	HR (95% CI) for Obesity vs. Leanness	P Value
Diabetes	1.63 (0.76-3.49)	0.21	2.83 (0.38-20.94)	0.31
Hypertension	1.46 (0.74-2.88)	0.28	6.21 (0.84-45.73)	0.07
Dyslipidemia	0.44 (0.21-0.96)	0.04	0.60 (0.22-1.70)	0.34

Shown are univariable HRs for obesity as predictor of incident metabolic disease. Each was performed among a subset without specified outcome at baseline: diabetes n = 258 (total events, 34); hypertension n = 133 (total events, 43), dyslipidemia n = 70 (total events, 31). When overweight individuals were excluded: diabetes n = 168 (total events, 26), hypertension n = 90 (total events, 32), dyslipidemia n = 48 (total events, 22).

TABLE 6. PREDICTORS OF INCIDENT CVD IN INDIVIDUALS WITH NAFLD WITH AND WITHOUT OBESITY

	Without Obesity (n = 140)				With Obesity (n = 210)			
	UV HR (95% CI)	P Value	MV HR (95% CI)	P Value	UV HR (95% CI)	P Value	MV HR (95% CI)	P Value
Age	1.09 (1.02-1.16)	0.008	1.09 (1.03-1.16)	0.004	1.04 (1.01-1.06)	0.007	1.04 (1.01-1.06)	0.02
Smoking		0.02				0.002		0.003
Former vs. never	4.06 (1.44-11.44)				2.04 (1.00-4.15)		1.48 (0.70-3.14)	
Current vs. never	0.94 (0.11-7.86)				4.60 (1.90-11.18)		4.61 (1.89-11.22)	
Hypertension					2.81 (1.23-6.42)	0.01		
Use for antihypertensives					1.95 (1.01-3.77)	0.048		
Statin use					1.82 (0.96-3.48)	0.07		
OSA					2.14 (1.11-4.11)	0.02		
Albumin	0.39 (0.16-0.95)	0.04			0.51 (0.24-1.07)	0.08		
Total bilirubin					1.37 (0.97-1.94)	0.07		
Alkaline phosphatase					1.01 (1.00-1.02)	0.06		
Total cholesterol	0.99 (0.97-1.00)	0.06						
LDL	0.98 (0.97-1.00)	0.03	0.98 (0.96-1.00)	0.02				
Platelets					1.00 (0.99-1.00)	0.08		

Covariates shown include predictors with P < 0.10 in univariable analyses that were considered in multivariable Cox proportional hazards regression models. Hypertension and use of antihypertensive medications were collinear, so they were considered separately, although neither was significant. LDL and total cholesterol were also collinear; LDL was included.
Abbreviations: MV, multivariable; UV, univariable.

HR, 0.96; 95% CI, 0.91-1.02; *P* = 0.16). When the comparator group comprised subjects who were lean only (subjects who were overweight were excluded), obesity was not significantly associated with risk of incident hypertension, diabetes, or dyslipidemia (Table 5). Inclusion of subjects without obesity who developed obesity during follow-up with the obese group did not meaningfully change these results and neither did excluding these individuals (Supporting Table S1). Findings were also similar after adjustment for parameters of disease severity, including FIB-4 score among the entire cohort (diabetes HR, 1.62; 95% CI, 0.75-3.48; hypertension HR, 1.44; 95% CI, 0.73-2.86; dyslipidemia HR, 0.45; 95% CI, 0.20-0.97) or advanced fibrosis by elastography or on biopsy

(diabetes HR, 1.67; 95% CI, 0.78-3.59; hypertension HR, 1.40; 95% CI, 0.71-2.80; dyslipidemia HR, 0.40; 95% CI, 0.18-0.90). Predictors of incident diabetes and hypertension in individuals with NAFLD are presented in Supporting Tables S2-S4.

PREDICTORS OF INCIDENT CVD IN SUBJECTS WITH AND WITHOUT OBESITY

In subjects with obesity, univariable predictors of incident CVD included age, smoking status, hypertension, use of antihypertensive medications, and OSA (Table 6). On multivariable analysis, age and smoking were each significantly associated with increased

risk of developing incident CVD. In subjects without obesity, univariable predictors of incident CVD included age, smoking status, lower albumin levels, and lower LDL levels. On multivariable analysis, age and lower LDL levels were significantly associated with increased risk of incident CVD.

Discussion

Using a prospective cohort of individuals with NAFLD, we demonstrated that while the presence of obesity was associated with prevalent CVD at the time of NAFLD diagnosis, among subjects without a diagnosis of CVD at baseline, individuals without obesity were at a similar risk of developing CVD as those with obesity, i.e., nonobesity did not appear to protect patients with NAFLD from CVD. Findings were consistent when we considered BMI as a continuous variable and after we excluded overweight subjects from the analysis and compared subjects who were lean with those with obesity. We also identified unique predictors of incident CVD in patients with NAFLD with and without obesity. Smoking was an independent predictor of incident CVD in subjects with obesity; lower LDL levels were significantly associated with risk of CVD in subjects without obesity, which may reflect increased statin use among subjects at risk of CVD. Older age was a predictor of CVD that was common to patients with NAFLD with and without obesity.

Compared to patients without obesity, those with obesity were more likely to exhibit blood lipid abnormalities at the time of NAFLD diagnosis. Patients with obesity were also more likely to have hypertension at the time of NAFLD diagnosis compared to patients who were lean. However, during long-term follow-up of patients with NAFLD, obesity was associated with an increased risk of solely incident dyslipidemia, although this association was no longer observed after excluding subjects who were overweight, and their CVD risk was otherwise comparable. Obesity appeared to protect against the development of dyslipidemia in subjects with NAFLD, although this association was not observed after excluding subjects who were overweight or adjusting for disease severity, and may be due to more frequent use of statins in subjects with obesity compared to subjects without obesity. Risk of other incident metabolic disease was comparable between subjects with and without obesity. Overall, these findings suggest that patients with NAFLD without obesity share a cardiometabolic risk profile that is similar to the remainder of the NAFLD population. Furthermore, risks of CVD, hypertension, diabetes, and dyslipidemia in patients with NAFLD with and without obesity in our cohort were higher than risk estimates for the general population[24-27] with and without obesity, suggesting that NAFLD confers increased risk of cardiovascular and metabolic disease, regardless of obesity status.

Consistent with our findings, a recent meta-analysis reported that patients without obesity with NAFLD had a lower incidence of hypertension and higher HDL levels than patients with obesity[11] while other metabolic risk factors were not significantly different. In another meta-analysis, patients with NAFLD both with and without obesity were found to exhibit higher incidences of metabolic risk factors relative to controls, including increased plasma glucose levels, homeostasis model assessment of insulin resistance score, blood lipids, blood pressure, and waist circumference.[28] This suggests that patients with NAFLD exhibit a fundamentally altered cardiometabolic profile, which is common to individuals with and without obesity.

Our findings have important implications for screening and management. Patients without obesity with NAFLD do not appear to be metabolically "healthier" by virtue of having lower BMI values, and their risk of CVD must not be overlooked. Providers should emphasize the importance of appropriate lifestyle measures to reduce CVD risk, screen for metabolic comorbidities on a regular basis, and maintain a low threshold for initiating pharmacologic treatment. Relative to subjects with obesity, we found that subjects who were lean in our cohort were less likely to be prescribed statins or antihypertensive medications (38.2% vs. 20.0%, $P = 0.04$ and 53.2% vs. 28.6%, $P = 0.006$, respectively) and subjects without obesity were less likely to be prescribed oral antihyperglycemic medications (28.3% vs. 19.2%, $P = 0.04$), despite similar incidences of metabolic comorbidities. This may reflect a perception that these patients are at a lower risk for CVD by virtue of being nonobese, which should be challenged.

The main strengths of the present study include its use of a large cohort of Western subjects, its prospective design with long-term follow-up, and the availability of detailed clinical, laboratory, and medication

data. We opted to undertake a comprehensive review of the electronic medical record to identify outcomes because reliance on administrative codes is liable to classification errors. In contrast to previous studies, we examined hard clinical outcomes, including multiple types of CVD and metabolic comorbidities, as opposed to surrogate endpoints. One prior study compared the incidence of hard clinical endpoints among subjects who were lean and those who were not[19]; however, the number of cardiovascular events was low, hence these findings were difficult to interpret.

We also acknowledge several limitations. First, our study is observational in nature, and we cannot exclude the possibility of residual confounding. We attempted to minimize this risk by accounting for all significant univariable predictors in our multivariate analysis and by also adjusting for disease severity. Second, a larger proportion of subjects with obesity than subjects without obesity underwent liver biopsy, which may reflect an overall greater severity of NAFLD among the former group and bias the results. However, when limited to only biopsy-proven NAFLD, the results were not meaningfully different. Furthermore, adjustment for FIB-4 scores or advanced fibrosis on biopsy or elastography did not meaningfully affect our results. Third, the number of patients who were lean in our cohort was small (n = 35), and therefore our study was underpowered to identify predictors of CVD in this group. Fourth, BMI values were recorded at baseline, and we did not account for changes in BMI values during follow-up that may have influenced CVD risk. Finally, we lacked data on waist circumference or other measures of abdominal and visceral adiposity, which are significant predictors of NAFLD, especially in individuals without obesity.[11]

In summary, in this prospective cohort of individuals with NAFLD, the risks of incident CVD were comparable in subjects with and without obesity. Subjects with obesity were more likely to be diagnosed with dyslipidemia and hypertension at baseline compared to subjects without obesity and those who were lean, respectively. During long-term follow-up, patients with obesity were more likely to develop dyslipidemia; however, this association was no longer observed after the exclusion of patients who were overweight, and incidences of other metabolic comorbidities were not increased in the presence of obesity. Older age predicted CVD in the entire cohort. Smoking was identified as a significant predictor of CVD in subjects with obesity, while baseline LDL levels independently predicted CVD in subjects without obesity.

Our results should be validated using an independent cohort of adults with NAFLD that includes a larger number of subjects who are lean. The identification of CVD predictors among individuals with NAFLD who are lean and overweight should ultimately lead to the development of a reliable cardiovascular risk stratification tool for use in this population.

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Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep4.1818/suppinfo.