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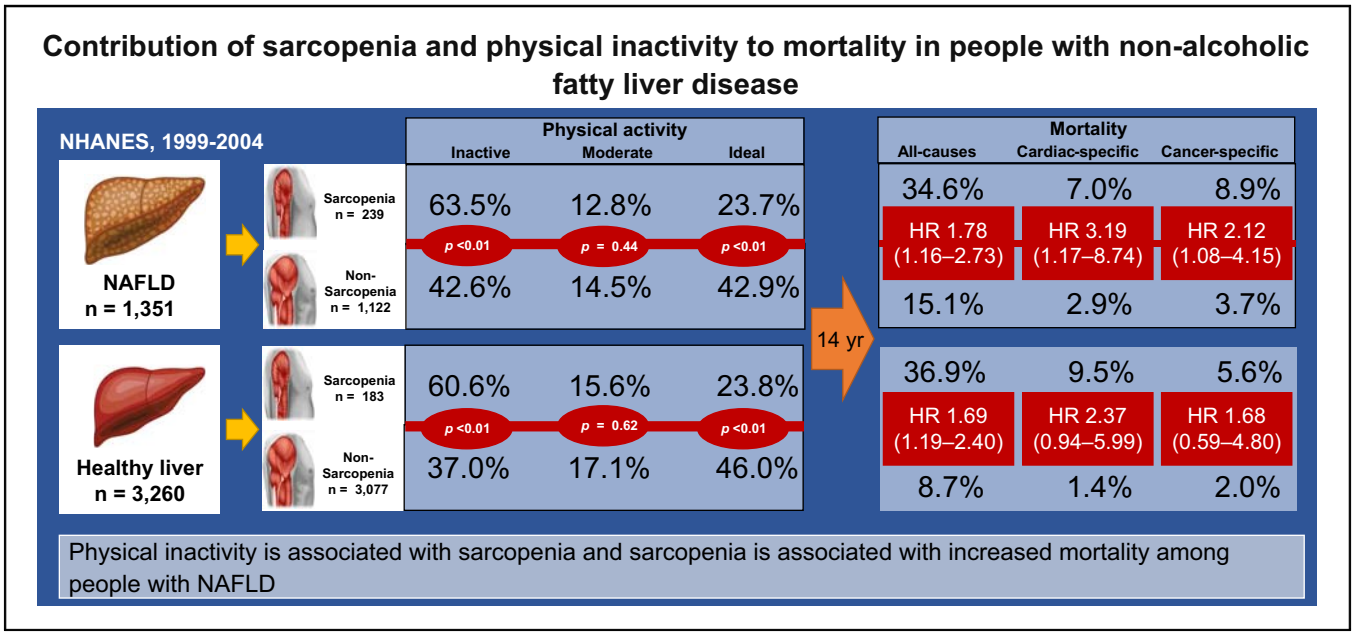
Graphical abstract



Highlights

- Non-alcoholic fatty liver disease (NAFLD) and sarcopenia have similar pathophysiological profiles.
- In our study, amongst NAFLD patients, sarcopenia was inversely related to increased physical activity level.
- The presence of sarcopenia in patients with NAFLD poses increased risk for all-cause and cardiac-specific mortality.

Lay summary

Nonalcoholic fatty liver disease (NAFLD) and sarcopenia have similar pathophysiological profiles. Our data show that sarcopenia is associated with inactivity in subjects with NAFLD. The presence of sarcopenia in patients with NAFLD poses increased risk for all-cause and cardiac-specific mortality.

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Research Article

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Contribution of sarcopenia and physical inactivity to mortality in people with non-alcoholic fatty liver disease

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Background & Aims: Physical inactivity and sedentary lifestyle have contributed to the epidemic of obesity and non-alcoholic fatty liver disease (NAFLD). We assessed the association between physical activity, NAFLD, and sarcopenia, and their contributions to mortality.

Methods: Data from the National Health and Nutrition Examination Survey (NHANES) 1999–2004 with Linked Mortality file (through 2015) was utilised. NAFLD was determined by the US Fatty Liver Index in the absence of secondary causes of liver disease. Sarcopenia was defined using appendicular lean mass divided by body mass index by the Foundation for the National Institutes of Health criteria. Activity level was determined using standard self-reports. Publicly available imputed dual-energy X-ray absorptiometry data sets were used.

Results: Of 4,611 NHANES participants (48.2% males; 72.5% White; mean age 45.9 years), NAFLD was present in 1,351 (29.3%), of whom 17.7% had sarcopenia. Of the NAFLD group, 46.3% was inactive, whilst intermediate and ideal physical activity rates were observed in 14.2% and 39.5%, respectively. Sarcopenia was significantly and inversely related to higher physical activity level, both amongst NAFLD (odds ratio [OR] = 0.45 [95% CI 0.30–0.69]) and non-NAFLD (OR = 0.51 [0.35–0.75]) groups. During a median follow-up of 13.5 years, a total of 586 subjects died, of whom 251 had NAFLD. Amongst those who died with NAFLD, 33.0% had sarcopenia and 54.3% were inactive. Compared with NAFLD without sarcopenia, NAFLD with sarcopenia was associated with a higher risk of all-cause (hazard ratio [HR] = 1.78 [1.16–2.73]), cardiac-specific (HR = 3.19 [1.17–8.74]), and cancer-specific mortality (HR = 2.12 [1.08–4.15]).

Conclusions: Inactivity is associated with presence of sarcopenia, whilst sarcopenia is associated with increased mortality amongst NAFLD patients. Sarcopenia should be a part of clinical assessment of patients with NAFLD. Treatment of NAFLD should include optimal management of sarcopenia.

Introduction

Sarcopenia is a recently described condition that includes loss of muscle mass, muscle strength, and human function (*i.e.* gait speed).[1] The condition implies both organ system change and its functional consequences.[2] The European Working Group on Sarcopenia in Older People defined it as 'a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with the risk of adverse outcomes such as physical disability, poor quality of life and death'.[3]

The prevalence of sarcopenia varies widely, in part, depending on sex, age, method of diagnosis, and its classification (*i.e.* mild or severe). Best estimates for a US cohort is between 5% and 13% for those 60–70 years and between 11% and 50% of those >80 years of age.[4] Worldwide prevalence, based on a systematic review, is 10% in both men and women.[5]

Patients with non-alcoholic fatty liver disease (NAFLD) have been reported to have an increased prevalence of sarcopenia.[6–8] They frequently meet the criteria for metabolic syndrome (MS), with at least 3 of the following abnormalities: obesity, type 2 diabetes, hypertension (HTN), increased waist circumference, elevation of alanine/aspartate aminotransferase, and dyslipidaemia. The role of these abnormalities and sarcopenia has been the subject of great interest recently, with investigators reporting results from large public data sets and retrospective reviews demonstrating that sarcopenia is associated with NAFLD and components of the MS.[8,9] Furthermore, previous studies have shown that sarcopenia was independently associated with increased risk of NAFLD and NAFLD-associated advanced fibrosis independent of well-defined risk factors.[10] Others have noted that the skeletal mass index calculations when based on height, as opposed to weight adjustments, provide different types of relationships.[11]

These publications, as well as the increasing prevalence of NAFLD and the associated risk factors for cardiovascular (CV) mortality, raise an important issue that is yet to be resolved. Is sarcopenia a risk for CV mortality? Is this risk independent of NAFLD? Further, patients with NAFLD or sarcopenia are often

Keywords: Sarcopenia; Non-alcoholic fatty liver disease; Physical activity.
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sedentary. As lack of exercise is believed to be a risk factor for sarcopenia and CV mortality, an important question would be to assess if increasing activity level will mitigate the adverse effects of sarcopenia in patients with NAFLD. All of these issues point to the potential impact of sarcopenia on mortality amongst NAFLD. Therefore, our aim was to assess the associations between sarcopenia, NAFLD, and mortality using population-based data.

Methods

Data source and population

We used the public data files for the 1999–2000, 2001–2002, and 2003–2004 cycles of the National Health and Nutrition Examination Survey (NHANES). NHANES is a population-based programme of studies conducted by the National Center for Health Statistics. To monitor the health and nutritional status of civilian, non-institutionalised individuals in the US population, cross-sectional socio-demographic, dietary, and medical data were collected through interviews, standardised physical examination, and laboratory testing with oversampling of certain subgroups of the US population (people aged more than 60 years, Hispanic, and African American). Full details of each survey have been described elsewhere.[12]

Mortality status of NHANES participants was ascertained through the end of 2015 via linkage of the NHANES data to the National Death Index.[13] Using the 113 categories of underlying causes of death on the public use files, CV deaths were defined as death attributable to major CV disease and cerebrovascular diseases (International Classification of Diseases, Tenth Revision codes: I00–I90, I11, I13, I20–I51, and I60–I69).[14] Participants who were not matched to any death records were presumed alive through the follow-up period. Time to death was counted from baseline (defined as the time when a subject participated in the NHANES survey) to date of death or December 31, 2015, whichever came first.

Definition of NAFLD and advanced fibrosis

NAFLD was defined using the improved Fatty Liver Index for the multi-ethnic US population (US FLI), a surrogate for the clinical diagnosis of NAFLD. The US FLI is a biochemical model that predicts the presence of fatty liver based on age, race/ethnicity, waist circumference, gamma glutamyltransferase (GGT) activity, fasting insulin, and fasting glucose, defined as follows:

$$\text{US FLI} = (e^{-0.8073 * \text{non-Hispanic black} + 0.3458 * \text{Mexican American} + 0.0093 * \text{age} + 0.6151 * \log_e(\text{GGT}) + 0.0249 * \text{waist circumference} + 1.1792 * \log_e(\text{insulin}) + 0.8242 * \log_e(\text{glucose}) - 14.7812})/(1 + e^{-0.8073 * \text{non-Hispanic black} + 0.3458 * \text{Mexican American} + 0.0093 * \text{age} + 0.6151 * \log_e(\text{GGT}) + 0.0249 * \text{waist circumference} + 1.1792 * \log_e(\text{insulin}) + 0.8242 * \log_e(\text{glucose}) - 14.7812}) * 100$$

This model has been previously validated with an area under the receiver operating characteristics curve of 0.80 (95% CI 0.77–0.83) for the detection of NAFLD in subjects with values ≥30.[15] In this study, subjects were presumed to have NAFLD if they have a US FLI score of ≥30 in the absence of any other possible causes of chronic liver disease and excessive alcohol consumption. As a sensitivity analysis, NAFLD was also defined using a fatty liver index of ≥60. NAFLD fibrosis score (NFS) and Fibrosis-4 (FIB-4) score for liver fibrosis were used to categorise NAFLD patients into 2 groups, including low fibrosis risk (NFS ≤0.676; FIB-4 ≤2.67) and high fibrosis risk (NFS >0.676; FIB-4 >2.67).[16]

Dual-energy X-ray absorptiometry measurement and sarcopenia definitions

Dual-energy X-ray absorptiometry (DXA) has been considered the primary method for measuring body composition. In NHANES, the whole DXA scans used a Hologic QDR-4500A fan-beam densitometer (Hologic, Inc., Bedford, MA, USA) to assess the total body, for both arms and both legs, the trunk, and the head. Pregnant females were not scanned. Participants whose weights are over 300 lb (136 kg) or height over 6 ft, 5 in. (198 cm) were excluded because of DXA table limitations. Because of these exclusions for large body sizes, participants with missing data cannot be treated as a random subset of the original sample, leading CDC to perform multiple imputations to resolve the problem of potential biases as a result of missing DXA data. Details of the multiple-imputation protocol are described elsewhere.[17] Our analysis used the DXA data sets released by NHANES from 1990 to 2004 with the publicly available 5 completed (imputed) DXA data files.[18] Appropriate methods for the analysis of imputed data sets were described later in the statistical analysis section. From the DXA measures, appendicular lean mass (ALM) was the sum of lean mass for all 4 extremities (arms and legs). Sarcopenia was defined using the Foundation for the National Institutes of Health (FNIH) sarcopenia definition: ALM divided by body mass index (BMI) (men <0.789; women <0.512).[19]

Other definitions

General demographic characteristics were collected from self-reported information, including age (years), sex, race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, or other race), income level (poverty-to-income ratio [PIR] <1.3 as low, PIR 1.3–3.5 as middle, and PIR >3.5 as high),[20] college degree, and history of medical conditions (cardiovascular disease [CVD], any cancer, and kidney).

The 10-year lifetime risk for developing atherosclerotic CVD was calculated from the atherosclerotic cardiovascular disease (ASCVD) risk score (American College of Cardiology/American Heart Association), which includes each participant's age, race, sex, smoking status, the presence of diabetes, systolic blood pressure, antihypertensive medication, serum cholesterol, and high-density lipoprotein levels. In this study, individuals with a 10-year ASCVD risk score of ≥7.5% were referred to as high risk for CVD.[21] For physical activity, the total physical activity measures (moderate leisure-time physical activity + 2×vigorous leisure-time physical activity + transportation + work) were calculated by using a physical activity questionnaire. Along with the 2008 Adult Physical Activity Guidelines for Americans,[22] total physical activity was categorised into inactive (<150 min/week), moderate (≥150 to <300 min/week), and ideal (≥300 min/week). Obesity pattern was categorised into lean (BMI 18.5–25 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥30 kg/m^2). Type 2 diabetes mellitus (T2DM) was defined by a fasting glucose level ≥126 mg/dl, self-reported medical history of diabetes, oral hypoglycaemic agents, insulin use, or HbA1c of ≥6.5%. HTN was defined by systolic blood pressure measurements ≥130 mmHg or diastolic blood pressure measurements ≥80 mmHg from an average 3 measurements, or history of high blood measurements.[23] Hyperlipidaemia (HL) was defined by either a serum cholesterol level ≥200 mg/dl, LDL level ≥130 mg/dl, HDL cholesterol level ≤40 mg/dl for men and 50 for women, or history of HL. Insulin resistance was defined as a homeostasis model

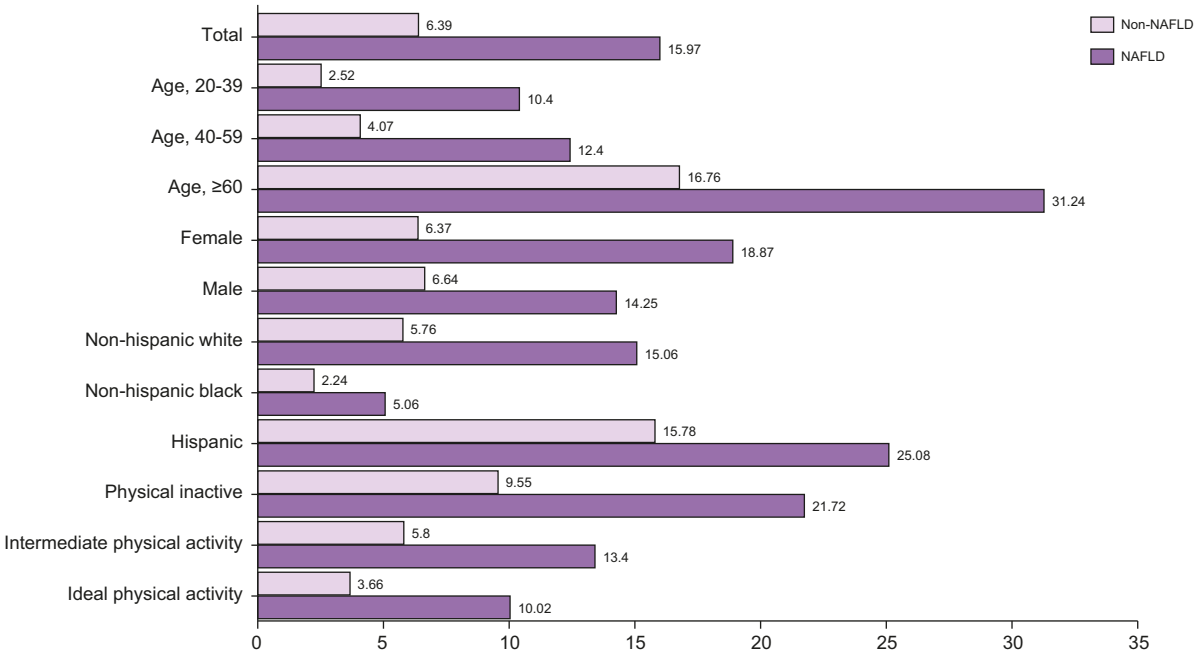

Fig. 1. Age-standardized prevalence of sarcopenia among participants with and without NAFLD, stratified by age, sex, race and physical activity: NHANES 1999-2004. NAFLD, non-alcoholic fatty liver disease; NHANES, National Health and Nutrition Examination Survey.

assessment of insulin resistance of >3.[24] Finally, MS was defined by the National Cholesterol Education Program Adult Treatment Panel III definition.[25]

Statistical analysis

Examination sample weights, accounting for non-response, non-coverage, and unequal selection probabilities for certain categories of the population, were incorporated to produce national estimates for all analyses. Sampling errors were estimated by the Taylor series linearisation method.[26] For combining 3 NHANES study cycles, appropriate selection of sampling weights and adjustment coefficients was implemented in compliance with the NHANES Analytic and Reporting Guidelines.[27]

Age-standardised percentages were calculated by using the direct method to the 2000 projected census population using age groups 20–39, 40–59, and more than 60 years. Differences across groups were tested by the use of orthogonal contrasts. Multivariable logistic regression models were used to identify predictors of sarcopenia. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% CIs for risk of all-cause mortality as well as cause-specific mortality associated with the presence of sarcopenia and NAFLD. Multivariable models were constructed in several stages. Model 1 was adjusted for age, sex, and race. Model 2 was also adjusted for socio-demographic characteristics (income, education, and height). Model 3 was further adjusted for health behaviour (smoking and physical activity). Model 4 was adjusted for all variables in model 3 with metabolic components (HTN, HL, and T2DM). Model 5 was adjusted for all variables in model 3 with a history of cancer, CVD, and kidney disease. Interactions between NAFLD and sarcopenia on mortality were tested, and no evidence interaction was found (p >0.05). The proportional hazards assumption of the Cox models was examined by testing time-dependent covariates,[26,28] which showed no significant departure from proportionality over time.

All our analyses were based on the 5 imputed data sets. We independently analysed each of the 5 versions of the completed data in univariable and multivariable analyses. The 5 sets of results were combined to produce a single mean estimate and adjusted SEs according to Rubin's rules.[29] The number of individuals in each group displayed in this study, except the numbers in the data flow chart, was determined by multiplying the estimated percentage by the total number of individuals in the full sample. All analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC, USA) using 'SURVEY' procedure, which incorporates the sample design. Statistical tests were considered significant at p <0.05 (2 tails).

Results

Of 12,976 non-pregnant adult (≥20 years) participants of 3 cycles of NHANES, 8,365 were excluded based on the study criteria (Fig. S1), and the final cohort included 4,611 participants. Clinico-demographic features of the study population are presented in Table S1.

Sarcopenia prevalence amongst NAFLD population

Individuals with NAFLD had a higher age-standardised prevalence of sarcopenia compared with individuals without NAFLD (16.0% *vs.* 6.4%), as well as across age group, sex, all race/ethnicities, and physical activity group (Fig. 1). Amongst individuals with NAFLD, sarcopenia was more common in women than in men (18.9% *vs.* 14.3%), and the prevalence of sarcopenia was highest amongst Hispanics (25.1%) compared with non-Hispanic Whites (15.1%), and lowest in non-Hispanic Blacks (5.1%).

In the age- and sex-adjusted model, individuals with NAFLD had 2.9 times higher odds of sarcopenia compared with individuals without NAFLD (Table S2). NAFLD was associated with sarcopenia even in the fully adjusted model (Table S3). Independent predictors of having sarcopenia amongst individuals

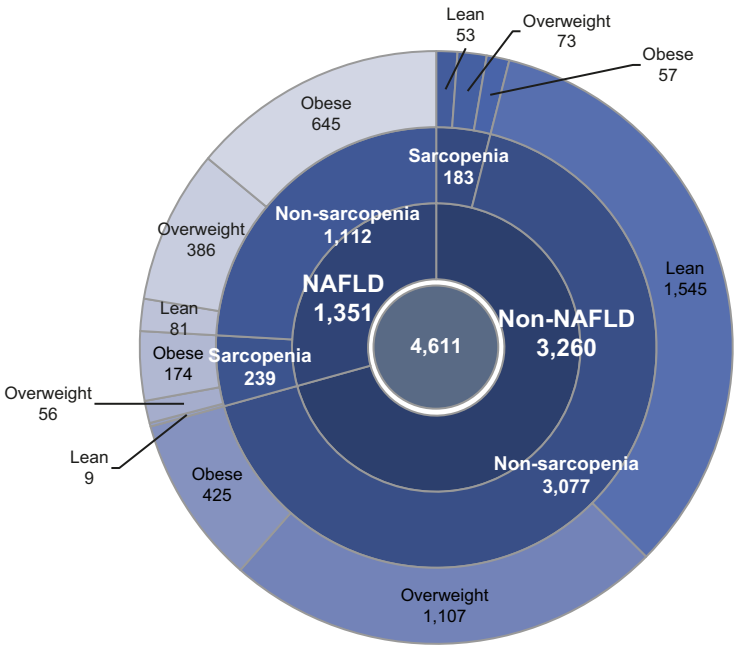

Fig. 2. Distribution of NAFLD, sarcopenia and obesity: NHANES 1999-2004. NAFLD, non-alcoholic fatty liver disease; NHANES, National Health and Nutrition Examination Survey.

with NAFLD included older age, male gender, non-Hispanic White ethnicity, low income, college degree, and physical activity.

Characteristics of individuals according to NAFLD and sarcopenia status

Of the entire cohort, 5.2% had both NAFLD and sarcopenia, 4.0% had sarcopenia without NAFLD, 24.1% had NAFLD without sarcopenia, and 66.7% had neither condition (Fig. 2). The demographic and clinical characteristics of individuals according to the presence of NAFLD and sarcopenia status are presented in Table 1. Compared with NAFLD patients without sarcopenia, individuals with both conditions were older, more likely to be female, and had a worse metabolic picture.

Of the study cohort, 40.6% reported physical inactivity, 16.2% had intermediate physical activity, and 43.2% had ideal physical activity (Table S4). Accounting for socio-demographic and clinical risk factors, sarcopenia was significantly and inversely related to a higher physical activity level amongst individuals with NAFLD (odds ratio 0.45 [95% CI 0.30–0.69]) (Table S5).

All-cause mortality

Of the entire cohort, NAFLD and sarcopenia coexisted in 239 (5.2%) patients. After a median follow-up of 13.5 years, 587 individuals (12.7%) died. Cumulative all-cause mortality was higher for those with either sarcopenia or NAFLD compared with neither sarcopenia nor NAFLD (Table 1).

Changes in the HRs of NAFLD and sarcopenia for all-cause mortality were determined by successive adjustments for age, sex, race, socio-demographic, health behaviours and co-morbidities, and are displayed in Fig. 3 and Table S6. Interestingly, presence of sarcopenia was associated with mortality after all adjustments (models 1–6) (Fig. 3; Table S6). This was true in the fully adjusted model for subjects with or without NAFLD (Table 2). In stratified analyses, association of risk factors with all-cause mortality in the age- and sex-adjusted models was similar across presence of NAFLD and sarcopenia (Table 3).

In contrast, NAFLD was associated with mortality after adjustments when T2DM (type 2 diabetes mellitus) was not included in the model (models 1–4; Fig. 3; Table S6). On the other hand, after adjustment for T2DM, NAFLD was no longer associated with mortality (Fig. 3; Table S6).

Cause-specific mortality

Amongst 587 individuals who died of all causes, 110 deaths (18.7%) were cardiac specific, 133 (22.7%) were cancer specific, and 344 (58.6%) were neither. The age- and sex-adjusted HR for cardiac-specific mortality was 1.71 [1.10–2.67] for NAFLD and 3.95 [2.08–7.49] for sarcopenia (Table S7). After including sarcopenia and NAFLD together (model 1), the HRs of NAFLD for cardiac-specific mortality decreased by 18.7% from those in the age- and sex-adjusted model and moved to non-significance (HR = 1.39 [0.89–2.16]). In the fully adjusted model, sarcopenia was associated with increased risk for cardiac-specific mortality (HR = 2.52 [1.07–5.93]) in the entire study cohort and in subjects with NAFLD (HR = 3.19 [1.17–8.74]) (Table 4). Table S8 demonstrates stratified analysis of different variables by age- and sex-adjusted Cox models.

Patterns for cancer-specific mortality were similar as all-cause mortality. The age- and sex-adjusted HR for cancer-specific mortality was 1.71 [1.24–2.37] for NAFLD and 2.74 [1.75–4.00] for sarcopenia (Table S9). A multivariable model, including metabolic components (model 4), demonstrated that the HR of NAFLD for cancer-specific mortality shifted towards non-significance (HR = 1.40 [0.93–2.11]). Table 5 demonstrates the risk of cancer-specific mortality in the fully adjusted model (Table 5). The association of variables with cancer-specific mortality in stratified analyses is shown in Table S10.

Table 1. Demographic and clinical characteristics of participants according to the presence of NAFLD and sarcopenia (multiple-imputation analysis).

	Individuals with NAFLD			Individuals without NAFLD		
Covariate	**Sarcopenia (n = 239[a])**	**Non-sarcopenia (n = 1,112[a])**	***p* value**	**Sarcopenia (n = 183[a])**	**Non-sarcopenia (n = 3,077[a])**	***p* value**
Age[b]	58.75 (1.32)	49.04 (0.61)	<0.0001	58.75 (1.31)	43.02 (0.50)	<0.0001
Age (years)						
20–39	16.47 (3.25)%	30.46 (1.87)%	<0.0001	20.78 (3.43)%	47.70 (1.44)%	<0.0001
40–59	28.80 (3.63)%	43.69 (1.65)%	0.0009	26.25 (3.75)%	36.69 (1.14)%	0.0076
>60	54.72 (3.73)%	25.86 (1.69)%	<0.0001	52.97 (3.86)%	15.61 (0.94)%	<0.0001
Male	51.44 (3.03)%	61.87 (1.97)%	0.0044	39.24 (3.88)%	43.60 (0.92)%	0.2650
Race						
Non-Hispanic White	71.60 (3.96)%	72.97 (2.70)%	0.7491	68.89 (4.53)%	72.63 (1.92)%	0.3256
Non-Hispanic Black	1.84 (0.68)%	6.60 (0.80)%	<0.0001	3.22 (1.18)%	12.69 (1.37)%	<0.0001
Hispanic	22.19 (3.80)%	16.33 (2.42)%	0.0919	21.70 (3.82)%	10.34 (1.44)%	0.0012
Other race	4.37 (1.86)%	4.11 (0.77)%	0.9078	6.19 (2.54)%	4.34 (0.60)%	0.4308
Income						
Low	27.99 (4.54)%	18.20 (1.74)%	0.0242	28.69 (3.81)%	18.28 (1.29)%	0.0041
Medium	40.13 (4.39)%	34.10 (1.83)%	0.1431	44.71 (3.90)%	35.39 (1.68)%	0.0335
High	31.88 (3.79)%	47.70 (2.51)%	0.0001	26.59 (3.81)%	46.33 (2.01)%	<0.0001
College degree	17.19 (2.46)%	20.74 (1.82)%	0.2953	13.00 (2.33)%	27.01 (1.62)%	<0.0001
Married	71.76 (3.46)%	64.67 (2.22)%	0.0800	61.50 (3.68)%	59.26 (1.41)%	0.5564
Smoking status						
Active	15.27 (2.81)%	17.94 (1.63)%	0.3757	13.09 (2.73)%	24.11 (1.25)%	<0.0001
Former	33.71 (3.20)%	31.77 (1.56)%	0.5516	29.40 (3.82)%	22.36 (1.02)%	0.0573
Non-smoker	51.02 (3.60)%	50.29 (2.31)%	0.8562	57.51 (4.10)%	53.52 (1.38)%	0.3063
Height[b] (cm)	161.94 (0.55)	172.37 (0.35)	<0.0001	157.33 (0.48)	169.38 (0.23)	<0.0001
Waist[b] (cm)	112.16 (1.20)	108.21 (0.60)	0.0010	95.14 (1.05)	89.08 (0.29)	<0.0001
BMI[b] (kg/m^2)	34.62 (0.64)	32.05 (0.22)	<0.0001	28.24 (0.43)	25.63 (0.11)	<0.0001
ALM[b] (g)	21,018.52 (457.34)	25,884.26 (244.72)	<0.0001	16,245.00 (290.62)	21,059.24 (122.64)	<0.0001
ALM/BMI[b]	0.61 (0.01)	0.82 (0.01)	<0.0001	0.58 (0.01)	0.83 (0.00)	<0.0001
Obesity						
Lean	3.57 (0.87)% BMI	7.27 (0.99)% BMI	0.0056	28.72 (3.78)% BMI	50.20 (1.20)% BMI	<0.0001
Overweight	23.60 (3.03)% BMI	34.71 (1.50)% BMI	0.0005	39.91 (3.59)% BMI	35.99 (1.16)% BMI	0.2759
Obese	72.83 (3.24)% BMI	58.02 (1.69)% BMI	<0.0001	31.37 (3.67)% BMI	13.81 (0.84)% BMI	<0.0001
Physical activity						
Inactive	63.47 (3.38)%	42.56 (1.90)%	<0.0001	60.59 (3.86)%	36.96 (1.34)%	<0.0001
Intermediate	12.79 (2.20)%	14.52 (1.33)%	0.4362	15.59 (2.84)%	17.05 (0.70)%	0.6241
Ideal	23.73 (3.34)%	42.92 (1.88)%	<0.0001	23.82 (2.88)%	45.99 (1.43)%	<0.0001
Hypertension	77.06 (3.60)%	66.69 (2.00)%	0.0093	64.97 (4.01)%	39.57 (1.20)%	<0.0001
Hyperlipidaemia	88.14 (2.39)%	87.79 (1.20)%	0.9022	79.92 (3.19)%	63.90 (1.20)%	<0.0001
Insulin resistance	82.90 (2.59)%	82.41 (1.48)%	0.8671	8.80 (2.42)%	8.54 (0.73)%	0.9094
Diabetes	29.87 (3.26)%	18.76 (1.32)%	0.0011	7.19 (1.96)%	3.09 (0.33)%	0.0381
Metabolic syndrome	71.05 (3.44)%	62.21 (1.78)%	0.0244	33.76 (4.79)%	15.20 (0.96)%	<0.0001
History of CVD	17.64 (2.31)%	10.48 (1.03)%	0.0032	19.97 (2.98)%	4.16 (0.37)%	<0.0001
History of cancer	12.52 (2.60)%	8.65 (0.93)%	0.1836	14.19 (3.54)%	6.86 (0.50)%	0.0451
History of kidney disease	2.47 (0.83)%	2.43 (0.78)%	0.9750	4.40 (1.31)%	1.21 (0.19)%	0.0152
High risk for CVD	61.74 (3.46)%	35.75 (1.70)%	<0.0001	53.07 (3.41)%	16.88 (0.92)%	<0.0001
Advanced fibrosis (NFS)	14.34 (2.81)%	6.23 (0.68)%	0.0082	7.09 (1.94)%	1.24 (0.25)%	0.0039
Advanced fibrosis (FIB-4)	3.08 (1.01)%	1.18 (0.37)%	0.0883	2.26 (0.87)%	1.03 (0.18)%	0.1482
Cumulative mortality[c]						
All cause	34.55 (3.71)%	15.12 (1.22)%	<0.0001	36.94 (3.74)%	8.73 (0.47)%	<0.0001
Cardiac specific	7.00 (1.78)%	2.92 (0.53)%	0.0397	9.47 (1.76)%	1.41 (0.21)%	<0.0001
Cancer specific	8.85 (2.22)%	3.74 (0.47)%	0.0312	5.63 (1.53)%	1.96 (0.24)%	0.0164

All values are displayed weighted percentages (SE) except where otherwise noted. ALM, appendicular lean mass; BMI, body mass index; CVD, cardiovascular disease; FIB-4, Fibrosis-4; NAFLD, non-alcoholic fatty liver disease; NFS, NAFLD fibrosis score.
[a] The number of individuals was reported by multiplying the estimated percentage by the total number of individuals in the full sample.
[b] Mean (SE).
[c] Median follow-up of 13.5 years.

Discussion

In the general population, prevalence of NAFLD is estimated to be around 24%,[30] whilst prevalence of sarcopenia is about 10%.[5] Historically, sarcopenia has been more frequently reported in the frail elderly individuals and in people with long-standing chronic illness and disability.[31] Furthermore, sarcopenia is associated with increased mortality.[32] In contrast, sarcopaenic obesity may occur at a younger age, often associated with insulin resistance and in associated with frailty.[33,34] Given the association of NAFLD with body composition and MS, these patients are at risk for sarcopaenic obesity.[35] Given the high prevalence of sarcopenia amongst patients with NAFLD, the impact on long-term outcomes will be important.

Consistent with previous reports, our data show that the prevalence of NAFLD and sarcopenia amongst the general population is 29.3% and 9.2%, respectively.[36,37] Our analysis shows

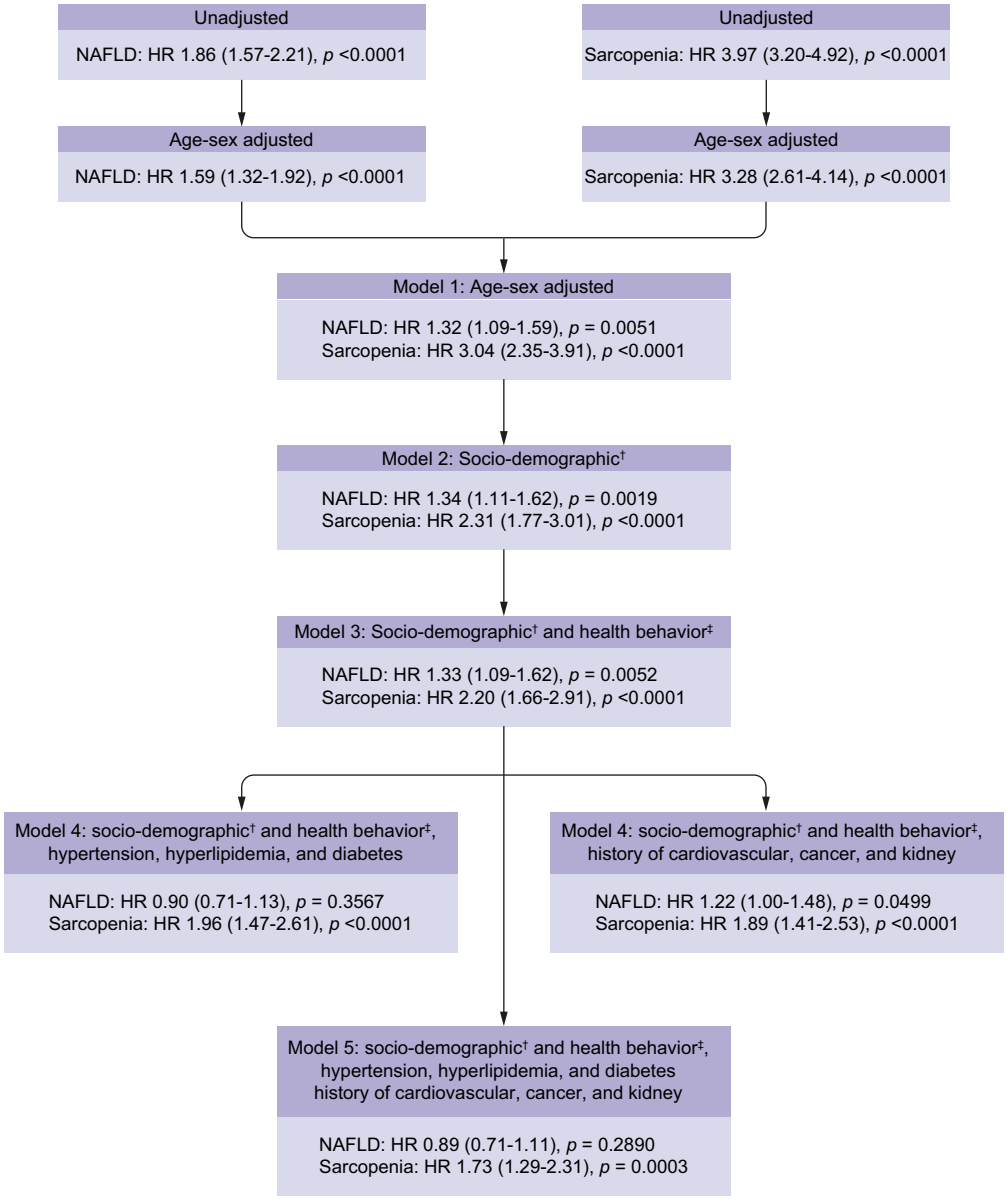

Fig. 3. Change in the hazard ratios (HRs) of NAFLD and sarcopenia for all-cause mortality by successive adjustments for age, sex, race, sociodemographic, health behaviors and comorbidities: NHANES 1999-2004. HR, hazard ratio; NAFLD, non-alcoholic fatty liver disease; NHANES, National Health and Nutrition Examination Survey. †Age, male, race, height, income, education, ‡Physical activity and smoking status.

that patients with NAFLD have significantly higher rates of sarcopenia than patients without NAFLD, and this finding was persistent across all age, sex, race, and physical activity groups. In fact, our age- and sex-adjusted analysis showed that patients with NAFLD were 2.9 times more likely to have sarcopenia than patients without NAFLD. Furthermore, older age, female gender, non-Hispanic White ethnicity, and lower physical activity were the independent predictors of sarcopenia amongst patients with NAFLD. These data are consistent with previous studies, which have documented a close relationship between NAFLD and sarcopenia.[38–43] In a study by Bhanji *et al.*, the main potential pathophysiological mechanisms leading to sarcopenia in patients with non-alcoholic steatohepatitis (NASH) were reported to be insulin resistance and increased inflammation.[44] In this context, these abnormalities could lead to triglyceride accumulation in myocytes and hepatocytes, causing proteolysis and muscle depletion.[44] Although in our study, NAFLD patients with or without sarcopenia had similar rates of insulin resistance, they were significantly more likely to have T2DM.

Another important link between NAFLD and sarcopenia is related to the level of physical activity. In our study, amongst NAFLD, sarcopenia was inversely related to increased physical activity level. Although sarcopenia and physical deconditioning have been reported in patients with end-stage liver disease, the association with NAFLD with relatively early liver disease has been fully reported.[45,46] In this context, our data make an important contribution linking NAFLD, sarcopenia, and level of inactivity.

The association of sarcopenia with adverse outcomes of patients with NAFLD is of great interest. In fact, a recent

Table 2. Fully adjusted HR of risk factors for all-cause mortality according to the presence of NAFLD (multiple-imputation analysis).

	Individuals with NAFLD		Individuals without NAFLD	
Covariate	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Sarcopenia	1.78 (1.16–2.73)	0.0089	1.69 (1.19–2.40)	0.0032
Age (years)				
20–39	Reference		Reference	
40–59	0.40 (0.23–0.72)	0.0021	0.36 (0.22–0.58)	<0.0001
>60	1.50 (1.07–2.09)	0.0174	1.35 (0.93–1.97)	0.1112
Male	2.11 (1.43–3.10)	0.0001	2.04 (1.56–2.67)	<0.0001
Race				
Non-Hispanic White	Reference		Reference	
Non-Hispanic Black	1.14 (0.72–1.81)	0.569	1.02 (0.76–1.37)	0.9115
Hispanic	0.73 (0.48–1.09)	0.1215	0.72 (0.49–1.07)	0.1040
Other race	0.60 (0.18–2.03)	0.4163	0.61 (0.30–1.22)	0.1590
Low income	1.08 (0.74–1.58)	0.689	1.38 (1.15–1.66)	0.0006
College	0.63 (0.41–0.99)	0.0436	0.67 (0.47–0.95)	0.0255
Height (cm)	0.98 (0.96–1.00)	0.1044	0.97 (0.95–0.98)	0.0005
Physical inactivity	1.19 (0.83–1.71)	0.3459	1.13 (0.88–1.45)	0.3272
Active smoker	1.48 (0.93–2.34)	0.0983	1.07 (0.81–1.42)	0.6344
Hypertension	2.10 (1.37–3.23)	0.0007	2.59 (1.84–3.67)	<0.0001
Hyperlipidaemia	0.75 (0.51–1.10)	0.1379	1.26 (0.96–1.65)	0.1019
Diabetes	2.23 (1.57–3.15)	<0.0001	1.68 (1.14–2.46)	0.0082
History of cancer	2.91 (2.25–3.76)	<0.0001	3.02 (2.29–3.98)	<0.0001
History of CVD	2.31 (1.49–3.60)	0.0002	2.80 (1.93–4.05)	<0.0001
History of kidney disease	1.59 (0.82–3.08)	0.1692	2.31 (1.54–3.48)	<0.0001

CVD, cardiovascular disease; HR, hazard ratio; NAFLD, non-alcoholic fatty liver disease.

meta-analysis amongst more than 3,000 NAFLD patients demonstrated a significant direct association between sarcopenia, NASH, and advanced fibrosis.[47] Additionally, other studies have confirmed these associations.[7,48–50] Given the lack of liver biopsy, we were unable to provide additional data supporting the association of sarcopenia with histological severity as documented by NASH activity or stage of advanced hepatic fibrosis.

Nevertheless, it is important to know that stage of fibrosis and histological NASH are surrogates of long-term mortality. In this context, establishing the association of sarcopenia with long-term outcomes amongst patients with NAFLD will be of utmost importance. In fact, our analysis shows that amongst patients with NAFLD, the presence of sarcopenia was associated with a 78% increase in all-cause mortality. More strikingly, in the NAFLD population, sarcopenia was associated with a 320% increase in cardiac-specific mortality. In this context, sarcopenia should be regarded as a key factor playing a significant role in worsening of both overall and cardiac-specific mortality amongst patients with NAFLD. Our data suggest that the presence of sarcopenia is independently associated with all-cause mortality, CV mortality, and cancer-related mortality in patients with NAFLD.

There are a few limitations to this study. First, we have utilised US FLI as a non-invasive diagnostic method for NAFLD in the absence of secondary causes of liver disease. Although a radiological- or histological-based diagnosis of NAFLD may be more accurate, ultrasound data are only available at the outdated NHANES III database (1988–1994) amongst NHANES survey cycles. However, the US FLI was established as a reliable method for non-invasive diagnosis of NAFLD in the US population and is associated with a higher risk of liver-specific mortality and all-cause mortality. Second, with respect to sarcopenia, there is evidence that its definition requires strength measures, a functional measure (usually of ambulation), and a measure of percent body fat/lean appendicular muscle mass. NHANES does not provide data on grip strength, the most commonly used measure of strength in many studies. Third, we used the FNIH guideline for sarcopenia instead of the Revised European Working Group on Sarcopenia in Older People (EWGSOP2) guideline, based on height adjustment. In these data, the crude prevalence of sarcopenia, defined by the EWGSOP2 guideline, was lower amongst individuals with NAFLD than amongst individuals without NAFLD (4.3% *vs.* 16.8%). We believed that the definition of FNIH would be a better choice for this study. Although the FNIH definition would lead to misclassification and overestimate the true prevalence of sarcopenia, we hope that the likelihood of misclassification may be alleviated by adjusting the height on multivariable analyses. Fourth, whilst we have reported mortality data, they come from a separate national database and have to be matched with the NHANES data. The association of sarcopenia and NAFLD with liver-specific mortality was not evaluated because of the unavailability of a specific cause of death in the public-use mortality files. Finally, the study we report here is cross sectional and does not provide data on the progression or regression of liver status. Another limitation is the lack of data on liver-specific mortality. Given that publicly available causes of mortality are only available for top 10 causes of death, liver-specific mortality was not available. Despite these study limitations, NHANES provides a nationally representative sample of the US population and the evaluation of various features of NAFLD with sarcopenia using multivariate analyses. To our knowledge, this approach has not been previously reported and we believe reduces bias. Finally, we believe this is the first study to link the prevalence data of NAFLD and sarcopenia and demographic and clinical findings to all-cause and CVD mortality.

In summary, our data show that sarcopenia is associated with inactivity in subjects with NAFLD. Furthermore, the presence of sarcopenia in patients with NAFLD poses increased risk for all-cause and cardiac-specific mortality. Given that exercise is an effective treatment for NAFLD and sarcopenia, these data make it imperative that clinicians should aim to diagnose and optimally mange sarcopenia in patients with NAFLD.

Table 3. Age- and sex-adjusted HR of risk factors for all-cause mortality by NAFLD and sarcopenia status (multiple-imputation analysis).

	Individuals with NAFLD		Individuals without NAFLD		Individuals with both NAFLD and sarcopenia		Individuals with NAFLD but non-sarcopenia		Individuals with sarcopenia but non-NAFLD		Individuals with neither sarcopenia nor NAFLD	
Covariate	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Sarcopenia (unadjusted)	2.58 (1.84–3.63)	<0.0001	5.12 (3.90–6.72)	<0.0001								
Sarcopenia	1.54 (1.07–2.21)	0.0192	1.95 (1.38–2.75)	0.0001								
Age	1.08 (1.06–1.10)	0.001	1.10 (1.09–1.11)	<0.0001	1.06 (1.03–1.09)	0.001	1.08 (1.06–1.11)	<0.0001	1.07 (1.05–1.09)	<0.0001	1.10 (1.09–1.11)	<0.0001
Male	1.67 (1.24–2.23)	<0.0001	1.65 (1.36–2.00)	<0.0001	2.04 (1.34–3.11)	0.001	1.55 (1.11–2.18)	0.0109	1.59 (1.03–2.45)	0.0371	1.67 (1.37–2.03)	<0.0001
Non-Hispanic White	0.78 (0.55–1.10)	0.1498	0.75 (0.55–1.01)	0.0589	0.92 (0.54–1.56)	0.7501	0.74 (0.52–1.06)	0.103	1.11 (0.67–1.84)	0.6647	0.71 (0.52–0.97)	0.0318
Non-Hispanic Black	1.52 (1.05–2.22)	0.0289	1.37 (1.00–1.86)	0.0467	2.00 (0.99–4.06)	0.0543	1.64 (1.13–2.37)	0.0104	0.74 (0.44–1.25)	0.248	1.58 (1.16–2.16)	0.0052
Hispanic	1.14 (0.76–1.73)	0.5139	1.28 (0.82–2.00)	0.2702	1.12 (0.69–1.82)	0.6252	1.02 (0.63–1.67)	0.9282	0.79 (0.48–1.32)	0.362	1.30 (0.73–2.33)	0.367
Other race	1.12 (0.38–3.28)	0.8298	1.00 (0.39–2.53)	0.9926	0.68 (0.14–3.25)	0.6227	1.40 (0.42–4.65)	0.5757	1.37 (0.38–4.97)	0.6219	0.81 (0.27–2.36)	0.6869
Low income	1.51 (1.08–2.11)	0.0172	2.29 (1.86–2.82)	<0.0001	1.27 (0.83–1.93)	0.2624	1.50 (0.99–2.27)	0.054	1.34 (0.79–2.29)	0.2713	2.47 (1.91–3.19)	<0.0001
College degree	0.44 (0.28–0.68)	0.0004	0.58 (0.41–0.83)	0.0033	0.50 (0.22–1.14)	0.0967	0.43 (0.28–0.65)	0.0002	0.86 (0.51–1.46)	0.5684	0.56 (0.38–0.83)	0.0046
Married	0.64 (0.46–0.89)	0.0085	0.52 (0.40–0.68)	<0.0001	0.62 (0.38–1.01)	0.0545	0.61 (0.42–0.89)	0.0111	0.45 (0.32–0.64)	<0.0001	0.54 (0.38–0.76)	0.0007
Active smoker	2.10 (1.35–3.26)	0.0014	1.62 (1.23–2.14)	0.001	1.24 (0.57–2.71)	0.5766	2.55 (1.54–4.25)	0.0006	0.83 (0.45–1.54)	0.5426	1.88 (1.43–2.47)	<0.0001
Lean	1.66 (1.31–2.10)	<0.0001	1.35 (1.09–1.67)	0.0074	1.52 (0.77–2.99)	0.2235	1.82 (1.37–2.43)	0.0001	1.22 (0.77–1.94)	0.3822	1.49 (1.18–1.88)	0.0012
Physical inactivity	1.45 (1.09–1.93)	0.0128	1.60 (1.25–2.05)	0.0004	1.20 (0.77–1.87)	0.4217	1.45 (1.01–2.08)	0.0425	1.25 (0.80–1.95)	0.3258	1.55 (1.19–2.01)	0.0014
Hypertension	1.30 (0.92–1.84)	0.1393	1.40 (0.97–2.02)	0.0703	1.02 (0.45–2.31)	0.9668	1.37 (0.86–2.20)	0.1835	1.08 (0.66–1.75)	0.7583	1.42 (0.96–2.10)	0.0755
Hyperlipidaemia	0.73 (0.52–1.02)	0.062	0.94 (0.65–1.34)	0.7104	0.73 (0.44–1.22)	0.2247	0.74 (0.48–1.13)	0.1553	0.61 (0.38–1.00)	0.0483	0.98 (0.63–1.53)	0.9284
Insulin resistance	0.92 (0.70–1.20)	0.5142	0.83 (0.52–1.33)	0.4229	0.88 (0.49–1.57)	0.6582	0.88 (0.65–1.19)	0.4119	0.59 (0.22–1.60)	0.2901	0.86 (0.53–1.38)	0.5159
Diabetes	2.05 (1.53–2.74)	<0.0001	2.51 (1.91–3.28)	<0.0001	2.42 (1.55–3.79)	0.0003	1.79 (1.25–2.56)	0.0022	0.90 (0.40–2.06)	0.8035	3.21 (2.35–4.39)	<0.0001
Metabolic syndrome	1.23 (0.94–1.61)	0.1236	1.13 (0.78–1.63)	0.5122	0.94 (0.60–1.48)	0.789	1.31 (0.99–1.73)	0.0595	0.77 (0.50–1.18)	0.2189	1.18 (0.78–1.79)	0.4265
History of CVD	2.08 (1.54–2.80)	<0.0001	23.16 (13.85–38.73)	<0.0001	2.07 (1.33–3.23)	0.0018	2.13 (1.51–3.01)	<0.0001	1.58 (1.02–2.45)	0.0411	19.60 (12.44–30.87)	<0.0001
History of cancer	1.56 (1.07–2.28)	0.0211	3.42 (2.71–4.31)	<0.0001	1.73 (1.00–2.98)	0.0495	1.55 (0.98–2.45)	0.0613	1.35 (0.81–2.25)	0.2445	4.16 (3.15–5.50)	<0.0001
History of kidney disease	2.47 (1.05–5.83)	0.0394	16.82 (10.99–25.72)	<0.0001	1.60 (0.68–3.78)	0.2715	3.03 (0.99–9.25)	0.0519	1.80 (0.84–3.85)	0.1236	17.17 (9.05–32.57)	<0.0001
High risk for CVD	3.83 (2.20–6.69)	<0.0001	9.40 (3.40–25.94)	<0.0001	4.91 (2.28–10.56)	0.0002	3.22 (1.55–6.68)	0.0023	1.96 (0.94–4.08)	0.0725	11.30 (3.19–40.02)	0.0004
Advanced fibrosis (NFS)	1.67 (1.28–2.18)	0.0003	2.44 (1.73–3.44)	<0.0001	1.99 (1.18–3.34)	0.0108	1.44 (1.03–2.00)	0.0339	1.92 (1.11–3.32)	0.0205	25.13 (15.79–39.99)	<0.0001
Advanced fibrosis (FIB-4)	2.89 (1.73–4.84)	0.0001	33.96 (21.91–52.62)	<0.0001	2.48 (1.00–6.18)	0.051	3.20 (1.70–6.02)	0.0006	2.34 (1.22–4.48)	0.0116	35.43 (22.24–56.44)	<0.0001

CVD, cardiovascular disease; FIB-4, Fibrosis-4; HR, hazard ratio; NAFLD, non-alcoholic fatty liver disease; NFS, NAFLD fibrosis score.

Table 4. Fully adjusted HR of risk factors for cardiac-specific mortality according to the presence of NAFLD (multiple-imputation analysis).

	Individuals with NAFLD		Individuals without NAFLD	
Covariate	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Sarcopenia	3.19 (1.17–8.74)	0.0239	2.37 (0.94–5.99)	0.068
Age (years)				
20–39	Reference		Reference	
40–59	0.62 (0.14–2.78)	0.5289	0.39 (0.06–2.52)	0.325
>60	2.86 (1.22–6.70)	0.0153	2.49 (1.20–5.17)	0.0142
Male	3.32 (1.11–9.91)	0.0312	3.30 (1.61–6.76)	0.0011
Race				
Non-Hispanic White	Reference		Reference	
Non-Hispanic Black	2.04 (0.86–4.86)	0.1060	0.53 (0.23–1.18)	0.1205
Hispanic	1.57 (0.53–4.63)	0.4125	0.44 (0.13–1.52)	0.1955
Other race	N/A		0.17 (0.02–1.54)	0.1156
Low income	0.69 (0.26–1.81)	0.45	2.31 (1.33–4.01)	0.0031
College	0.88 (0.36–2.14)	0.7833	0.39 (0.14–1.12)	0.0812
Height (cm)	1.00 (0.96–1.05)	0.8556	0.98 (0.94–1.02)	0.3903
Physical inactivity	1.15 (0.50–2.69)	0.7401	1.29 (0.64–2.58)	0.4784
Active smoker	2.04 (0.94–4.45)	0.0726	0.62 (0.25–1.52)	0.2931
Hypertension	1.44 (0.52–3.96)	0.4821	2.99 (1.29–6.93)	0.0107
Hyperlipidaemia	2.00 (0.59–6.82)	0.2691	1.15 (0.47–2.84)	0.7562
Diabetes	3.06 (1.26–7.42)	0.0133	3.93 (1.83–8.47)	0.0005
History of cancer	4.42 (2.20–8.89)	<0.0001	3.18 (1.48–6.84)	0.0031
History of CVD	1.81 (0.77–4.27)	0.1765	1.30 (0.59–2.85)	0.5115
History of kidney disease	3.21 (0.78–13.24)	0.1058	3.65 (1.18–11.34)	0.0249

CVD, cardiovascular disease; HR, hazard ratio; NAFLD, non-alcoholic fatty liver disease.

Table 5. Fully adjusted HR of risk factors for cancer-specific mortality according to the presence of NAFLD (multiple-imputation analysis).

	Individuals with NAFLD		Individuals without NAFLD	
Covariate	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Sarcopenia	2.12 (1.08–4.15)	0.0293	1.68 (0.59–4.80)	0.3299
Age (years)				
20–39	Reference		Reference	
40–59	0.36 (0.08–1.68)	0.1948	0.57 (0.27–1.23)	0.1534
>60	3.43 (1.78–6.60)	0.0002	1.70 (0.82–3.53)	0.153
Male	2.20 (0.92–5.24)	0.0747	1.96 (0.94–4.06)	0.071
Race				
Non-Hispanic White	Reference		Reference	
Non-Hispanic Black	1.17 (0.34–4.06)	0.8008	3.08 (1.70–5.56)	0.0002
Hispanic	0.45 (0.24–0.87)	0.0164	1.51 (0.60–3.80)	0.3864
Other race	0.18 (0.02–1.61)	0.1254	1.76 (0.49–6.33)	0.3882
Low income	1.35 (0.64–2.86)	0.4376	1.14 (0.61–2.13)	0.6716
College	0.55 (0.20–1.52)	0.2508	0.80 (0.37–1.74)	0.5751
Height (cm)	0.99 (0.96–1.02)	0.4819	1.00 (0.96–1.03)	0.8443
Physical inactivity	0.93 (0.49–1.78)	0.8301	0.75 (0.42–1.34)	0.3397
Active smoker	1.87 (0.94–3.73)	0.0738	1.83 (1.18–2.84)	0.0067
Hypertension	1.49 (0.77–2.87)	0.2367	1.89 (1.11–3.20)	0.0181
Hyperlipidaemia	2.04 (0.82–5.06)	0.1261	1.17 (0.68–1.99)	0.5724
Diabetes	1.00 (0.56–1.81)	0.9913	0.83 (0.32–2.18)	0.7044
History of cancer	1.91 (1.05–3.46)	0.0341	2.49 (1.18–5.26)	0.0171
History of CVD	2.13 (0.99–4.59)	0.0532	6.12 (3.72–10.06)	<0.0001
History of kidney disease	0.91 (0.18–4.49)	0.9073	1.52 (0.52–4.45)	0.4475

CVD, cardiovascular disease; HR, hazard ratio; NAFLD, non-alcoholic fatty liver disease.

Abbreviations

ALM, appendicular lean mass; BMI, body mass index; CV, cardiovascular; CVD, cardiovascular disease; DXA, dual-energy X-ray absorptiometry; EWGSOP2, Revised European Working Group on Sarcopenia in Older People; FNIH, Foundation for the National Institutes of Health; GGT, gamma glutamyltransferase; HL, hyperlipidaemia; HR, hazard ratio; HTN, hypertension; MS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; NFS, NAFLD fibrosis score; NHANES, National Health and Nutrition Examination Survey; T2DM, type 2 diabetes mellitus; US FLI, Fatty Liver Index for the multi-ethnic US population.

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Conflicts of interest

Z.M.Y. is a consultant to Bristol Myers Squibb, Gilead, Intercept, Novo Nordisk, Novartis, Terns, Merck, Viking, and Shinogi. All other authors have no conflicts of interest to disclose.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conceptualisation, investigation, and article writing: P.G. Conceptualisation, supervision, visualisation, writing, review, and editing: L.G. Data curation, formal analysis, and methodology: J.M.P. Article writing: R.D., L.deA. Resources, supervision, visualisation, writing, review, and editing: Z.M.Y. Z.M.Y. is the guarantor of this work, had full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final version of the article. The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2020.100171.

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