Cardiovascular Diabetology

https://doi.org/10.1186/s12933-026-03284-z

Article in Press

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Received: 16 May 2026

Accepted: 26 June 2026

Published online: 11 July 2026

Cite this article as: Wang R., Li W., Lazarus J.V. *et al.* Frailty may confound the association between MASLD and cardiovascular mortality in people with cardiometabolic risk factors. *Cardiovasc Diabetol* (2026). https://doi.org/10.1186/s12933-026-03284-z

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Frailty may confound the association between MASLD and cardiovascular mortality in people with cardiometabolic risk factors

Running title: Frailty confounds MASLD-CVD mortality association

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Abstract

Background: While metabolic dysfunction-associated steatotic liver disease (MASLD) has been consistently associated with increased cardiovascular risk in the general population, its association with cardiovascular disease (CVD) mortality in adults with established cardiometabolic risk factor (including obesity, hypertension, diabetes mellitus, or dyslipidemia) remains inconsistent. We aimed to determine whether frailty confounds the MASLD-CVD mortality association.

Methods: We analyzed 10,413 US NHANES III adults with ≥ 1 cardiometabolic risk factor. Frailty was quantified using a 49-item frailty index (FI, ranging from 0 [maximal robustness] to 1 [severe frailty]) and categorized into quartiles. Associations between MASLD and CVD mortality were assessed using multivariable Cox proportional hazards models with and without frailty adjustment. Interaction and mediation analyses were also performed.

Results: Over a mean follow-up of 23.36 years, 1,375 (13.20%) CVD deaths occurred. Frailty was significantly associated with both MASLD and CVD mortality. There was no evidence of interaction between MASLD and frailty, and mediation analysis showed no indirect effect through frailty. Without frailty adjustment, MASLD was not associated with CVD mortality (HR = 0.92, 95% CI: 0.78 - 1.10). After frailty adjustment, MASLD was independently associated with higher CVD mortality (HR = 1.19, 95% CI: 1.07 - 1.32). Stratified by FI quartiles, significant associations were observed only in the higher frailty quartiles (Q3: HR = 1.35, 95% CI: 1.03 - 1.77; Q4: HR = 1.70, 95% CI: 1.07 - 2.69). The population attributable fraction of MASLD for CVD mortality was 10.1-12.5% after frailty adjustment.

Conclusions: Frailty may confound the MASLD-CVD mortality relationship in people with cardiometabolic risk factors. The association between MASLD and CVD mortality is detected only when frailty is adjusted for.

Keywords: Metabolic disorder, hepatic and cardiometabolic interconnections, MASLD, frailty, epidemiology

Research insights

What is currently known about this topic?

- Metabolic dysfunction-associated steatotic liver disease (MASLD) is a well-known systemic condition linked to increased cardiovascular risk.
- The association between MASLD and cardiovascular disease (CVD) mortality in adults with established cardiometabolic risk factors remains inconsistent.
- Unmeasured frailty has been previously shown to confound associations between metabolic conditions and health outcomes.

What is the key research question?

- Does frailty confound the association between MASLD and CVD mortality in adults with established cardiometabolic risk factors?

What is new?

- Frailty may confound the association between MASLD and CVD mortality in people with established cardiometabolic risk factors.
- After accounting for frailty, MASLD was independently and significantly associated with increased CVD mortality.

How might this study influence clinical practice?

- Integrating frailty assessment into MASLD management may improve CVD risk stratification and resource prioritization.

Background

The term of metabolic dysfunction-associated steatotic liver disease (MASLD) was introduced in 2023 by a global consensus to replace nonalcoholic fatty liver disease (NAFLD), emphasizing its foundational link to cardiometabolic health [1]. As the most prevalent chronic liver disease worldwide, MASLD affects approximately 37.8% of adults, posing a public health threat [2,3]. MASLD encompasses a dynamic spectrum of conditions from isolated hepatic steatosis to progressive metabolic dysfunction-associated steatohepatitis, which can advance to liver fibrosis, cirrhosis, and even hepatocellular carcinoma [4,5]. Beyond liver-related outcomes, MASLD is consistently associated with increased risks of cardiovascular-kidney-metabolic (CKM) disorders, extrahepatic cancers and all-cause mortality, underscoring its systemic nature and severe implications for overall health [3,6].

A growing body of evidence has identified MASLD as an independent risk factor for cardiovascular disease (CVD) mortality [6,7]. In a nationwide Korean study (n = 1,298,993), MASLD was significantly associated with elevated risk of CVD mortality (hazard ratio [HR] = 1.30, 95% confidence interval [CI]: 1.23 - 1.36), irrespective of baseline cardiometabolic risk factors (including obesity, hypertension, diabetes mellitus, and dyslipidemia) [8]. However, unlike the outcomes of non-CVD and all-cause mortality, the relationship between MASLD and CVD mortality remains under debate. One large-scale cohort study reported that MASLD was not associated with CVD mortality among adults who had at least one cardiometabolic risk factor (HR = 0.88, 95% CI: 0.75 - 1.04), arguing the presence of MASLD alone was not significantly associated with CVD death [9]. This “MASLD-CVD death paradox” complicates clinical risk stratification and public health strategies.

Frailty, an integrative measure of systemic physiological decline, captures the overall health deficit burden that predisposes individuals to various adverse outcomes [10]. Emerging evidence has indicated that frailty (as measured by a frailty index [FI]) is closely associated with both MASLD and CVD mortality in adults [11,12]. However, the complex interrelationships among frailty, MASLD, and CVD mortality have not been

systematically examined. Unmeasured frailty has previously been shown to confound associations between metabolic conditions and health outcomes. For example, the "obesity paradox" (i.e., higher body mass index unexpectedly related to lower risk of all-cause death in older men) and the "diabetes bone paradox" (i.e., participants with type 2 diabetes mellitus having higher risk of fragility fracture despite their normal or high bone mineral density when compared with participants without diabetes) in population studies were originated from the unmeasured frailty, while taking the FI into consideration could significantly interpret these paradoxes for clarification and help with risk stratification [13,14].

In this study, we aimed to assess the association between MASLD and CVD mortality in participants with established cardiometabolic risk factors, after taking frailty into account. We hypothesized that frailty confounds the MASLD and CVD mortality relationship, and after adjusting for frailty, MASLD may significantly associate with an increased risk of CVD mortality in adults with cardiometabolic risk factors.

Methods

Study participants

We analyzed data from the Third National Health and Nutrition Examination Survey (NHANES III, 1988-1994), a nationally representative survey of non-institutionalized civilian population of the United States using a multistage, stratified probability sampling design (https://wwwn.cdc.gov/nchs/nhanes/). The survey protocol comprised comprehensive household interviews, standardized physical examinations, and laboratory testing [15]. NHANES III was approved by the National Center for Health Statistics of the Centers for Disease Control and Prevention Institutional Review Board. All participants provided written informed consent.

In this study, we restricted our analyses to NHANES III (1988-1994) because (i) our study aimed to explore the relationship between MASLD and risk of long-term CVD mortality, (ii) only the NHANES III collected data on the comprehensive hepatic

ultrasound assessment for participants, and (iii) we tried to compare with previous studies focusing on MASLD, given the majority of prior studies using data from NHANES III exclusively [9,16,17]. Although the NHANES pre-pandemic dataset (from 2017 to March 2020) collected data on vibration controlled transient elastography (VCTE), its utility for our study is limited. The follow-up mortality data are available only through December 2019, resulting in insufficient duration to evaluate long-term CVD mortality outcome. Furthermore, the small sample size with complete VCTE data for participants with established cardiometabolic risk factors, would further constrain the statistical power for a mortality endpoint analysis.

The participant selection process was shown as **SFigure 1**. Briefly, among the 20,050 participants in NHANES III, we excluded 6,204 individuals due to missing hepatic ultrasound data or lack of follow-up mortality data through 2019, leaving 11,917 adults with at least one cardiometabolic risk factor. We further excluded 1,504 participants with missing alcohol consumption data, or presence of viral hepatitis, alcoholic liver disease, or MetALD (metabolic dysfunction and alcohol-associated liver disease) at baseline. Subsequently, a total of 10,413 participants were included for the present analysis.

Outcome measures

The outcome of this study was CVD mortality. Mortality data were ascertained by linkage of NHANES III participants to the National Death Index records through December 2019. CVD-related deaths were identified using the underlying cause of death codes from death certificates, defined as fatalities attributable to heart diseases (ICD-10 codes I00-I09, I11, I13, I20-I51) or cerebrovascular diseases (ICD-10 codes I60-I69).

Definition of MASLD

Hepatic steatosis was identified through ultrasound examinations that were originally recorded using a Toshiba Sonolayer SSA-90A and Toshiba video recorder [18]. Hepatic steatosis was assessed based on liver to kidney contrast, parenchymal brightness, deep

beam attenuation, vessel walls definition, and gallbladder wall definition.

MASLD was defined as the presence of hepatic steatosis combined with at least one of the following cardiometabolic risk factors: (1) body mass index (BMI) ≥ 25 kg/m² or waist circumference > 94 cm (males) / 80 cm (females); (2) fasting glucose ≥ 100 mg/dL, glycated hemoglobin (HbA1c) ≥ 5.7%, a diagnosis of diabetes mellitus, or use of glucose-lowering medication; (3) blood pressure ≥ 130/85 mmHg or use of antihypertensive agents; (4) triglycerides (TG) ≥ 150 mg/dL or lipid-lowering treatment; or (5) high-density lipoprotein (HDL) cholesterol < 40 mg/dL (for males) or < 50 mg/dL (females) [9,19]. Moreover, all eligible participants were required to have an alcohol consumption below 30 g/day for males and 20 g/day for females [9]. Participants were classified as having MASLD or having cardiometabolic risk factors alone (reference group).

Measure of frailty

We quantified frailty by a 49-item FI capturing health deficits across seven key domains: cognition, dependence, depressive conditions, comorbidities, hospital and care, physical anthropometry, and laboratory values (**STable 1**) [10]. MASLD was not included in the comorbidity domain or any other domain of this 49-item FI. Each item was scored from 0 to 1, with higher values indicating more severe health impairments. The FI was calculated as the sum of deficit scores divided by the total number of items assessed, ranging from 0 (maximal robustness) to 1 (severe frailty). Participants were categorized into FI quartiles: Q1 (FI ≤ 0.10), Q2 (0.10 < FI ≤ 0.21), Q3 (0.21 < FI ≤ 0.45), and Q4 (FI > 0.45) [20]. We selected the FI as the primary frailty measure because the deficit-accumulation approach could accurately capture multidimensional vulnerability, which is particularly relevant in the population with heterogeneous cardiometabolic risk [21]. In contrast, the Fried's phenotypic frailty mainly focuses on five physical manifestations (including unintentional weight loss, exhaustion, low physical activity, low grip strength, and slow gait speed), which may be less precise in quantifying and predicting risk of adverse health outcomes [22,23].

Other independent variables

Covariates of consideration included age (years), sex (males or females), BMI (kg/m^2), smoking status (never, previous, or current), alcohol consumption (g/day), race (non-Hispanic white, non-Hispanic black, Mexican-American, or other), marital status (married/living with partner, divorced/separated/widowed, or never married), education (above high school, or high school and below), sedentary lifestyle (yes or no), systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg), waist circumference (cm), total cholesterol (TC, mg/dL), TG (mg/dL), low-density lipoprotein (LDL, mg/dL), HDL (mg/dL), HbA1c (%), aspartate aminotransferase (AST, U/L), alanine aminotransferase (ALT, U/L), gamma glutamyl transferase (GGT, U/L), platelet (10^9/L), hypertension (yes or no), hyperlipidemia (yes or no), pre-diabetes (yes or no) and diabetes mellitus (yes or no). We also included the fibrosis-4 index (FIB-4) that was a widely-used noninvasive marker of liver fibrosis in participants with MASLD in population studies [24]. FIB-4 was calculated as $\text{Age (years)} * \text{AST (U/L)} / [\text{platelets } (10^9/\text{L}) * \sqrt{\text{ALT(U/L)}}]$, with higher index indicating more severe fibrosis in participants.

Statistical analyses

The complex, multistage probability sampling design of NHANES III was accounted for in all analyses by incorporating sampling weights, strata and primary sampling units. We performed descriptive analysis for continuous variables (weighted means and standard error [SE]) and categorical variables (counts and weighted percentages). Baseline characteristics were compared between participants with MASLD and those with cardiometabolic risk factors alone. For continuous variables, comparisons were performed using survey-weighted linear regression models, and *P*-values were derived from design-adjusted Wald F tests. For categorical variables, comparisons were performed using Rao-Scott design-adjusted chi-square tests based on survey-weighted contingency tables. We also illustrated the distribution of the FI for total participants, and for participants with MASLD and cardiometabolic risk factors alone separately.

To explore whether frailty potentially confounded the relationship between MASLD

and CVD mortality, we first investigated the associations between frailty and MASLD (as the exposure for this study) using multivariable logistic regression model. The multivariable logistic model was adjusted for age, sex, BMI, smoking, drinking, race, marital status, education, sedentary lifestyle, hypertension, hyperlipidemia, and diabetes. Furthermore, we modeled frailty as a continuous variable using restricted cubic splines (RCS) with four knots (at the 5^{th}, 35^{th}, 65^{th}, and 95^{th} percentiles) to visualize its dose-response relationship with CVD mortality (as the outcome for this study) from the multivariable Cox model. Subsequently, we constructed two cumulative incidence curves for CVD mortality from the models with and without adjustment of frailty in participants with MASLD and with cardiometabolic risk factors alone. The log-rank test was used to test whether the risk of CVD mortality in participants with MASLD differed from participants with cardiometabolic risk factors alone.

We performed two complementary analyses to further support the potential confounding role of frailty. First, we incorporated the interaction term between MASLD and FI (i.e., MASLD*FI) into the multivariable Cox model adjusting for age, sex, BMI, smoking status, alcohol consumption, race, marital status, education, sedentary lifestyle, hypertension, hyperlipidemia, diabetes, FI and MASLD. A non-significant interaction term would indicate that the association between MASLD and CVD mortality was not significantly different across various FI levels, suggesting that frailty did not serve as an effect modifier. Second, we conducted a mediation analysis to evaluate whether frailty could mediate the MASLD-CVD mortality relationship. A non-significant indirect effect would indicate that frailty was not part of the pathway from MASLD to CVD mortality.

The association between MASLD and CVD mortality was evaluated using multivariable Cox models, with results expressed as HRs and 95% CIs. We constructed two sequential models: Model 1 was adjusted for age, sex, BMI, smoking status, alcohol consumption, race, marital status, education level, sedentary lifestyle, hypertension, hyperlipidemia, and diabetes mellitus; and Model 2 was further adjusted for the frailty. Multicollinearity was assessed using variance inflation factor (VIF) in the Model 2. All

variables had VIF values below 4, indicating no significant multicollinearity (**STable 2**). These analyses were repeated within each FI quartile group.

We calculated the population attributable fraction (PAF) from Model 2 to estimate the proportion of CVD mortality attributable to MASLD at the population level after frailty adjustment. The PAF represents the risk of CVD mortality that would be avoided if the exposure (i.e., MASLD) was reduced to theoretical minimum risk exposure level [25], where participants with cardiometabolic risk factors alone were considered to have the theoretical minimum risk level in this study. Age-specific PAFs were estimated for overall participants and for participants in each FI quartile group across different ages.

We performed subgroup analyses to investigate any potential effect modifications to the relationship between MASLD and CVD mortality after accounting for frailty. Subgroups included age (≤ 60 vs > 60 years), sex (males vs females), smoking (non-smoker vs smoker), alcohol drinking (non-drinker vs drinker), history of hypertension (yes vs no), hyperlipidemia (yes vs no), diabetes mellitus (yes vs no), obesity (yes vs no, using BMI of 30kg/m^2 as cut-off point), and FIB-4 (< 1.3 vs ≥ 1.3, using 1.3 as cut-off point to group participants into low and high risk of advanced liver fibrosis) [26].

Besides, we performed six sensitivity analyses to assess the robustness of our main results by: (i) running multiple imputation for the missing data; (ii) performing competing risk model by taking non-CVD deaths as competing events for CVD deaths; (iii) excluding the participants who died within the first two years of follow-up to minimize reverse causality [27]; (iv) using alternative MASLD definition based on the fatty liver index (FLI) of ≥ 60, where the FLI was calculated as $[Exp(0.953 * ln(TG) + 0.139 * BMI + 0.718 * ln(GGT) + 0.053 * waist\ circumference - 15.745)/[1 + Exp(0.953 * ln(TG) + 0.139 * BMI + 0.718 * ln(GGT) + 0.053 * waist\ circumference - 15.745] * 100$; (v) running a propensity score matching analysis to balance baseline characteristics between participants with MASLD and those with cardiometabolic risk factors alone, where **SFigure 2** demonstrated successful balance of baseline covariates between these two groups after matching; and

(vi) re-defining frailty by the phenotypic frailty based on five criteria (unintentional weight loss, exhaustion, low physical activity, low grip strength, and slow gait speed) [22], with participants categorized as being not frail (meeting none of the five criteria), pre-frail (meeting one or two criteria), or frail (meeting three or more criteria) .

All analyses were accounted for the complex survey design of NHANES III and were performed using R software (version 4.1.1). A two-sided *P*-value < 0.05 was considered statistically significant.

Results

A total of 10,413 participants from NHANES III, including 3,849 (36.96%) with MASLD and 6,564 (63.04%) with cardiometabolic risk factors alone, were included for analysis. As **Table 1** shows**,** compared to the group with cardiometabolic risk factors alone, participants with MASLD were older (mean age 47.94 vs. 44.33 years), had higher BMI (30.46 vs. 27.11 kg/m²), and exhibited a less favorable cardiometabolic profile, including higher SBP and DBP, waist circumference, TG, HbA1c, and liver enzymes (all *P*-values < 0.01). The prevalences of hypertension (38.79% vs. 26.28%), hyperlipidemia (25.59% vs. 21.45%), and diabetes mellitus (19.72% vs. 6.98%) were also significantly higher in the MASLD group. FI was significantly higher in the MASLD group (0.21 vs. 0.19) (**Table 1** & **SFigure 3**).

A significant association between frailty and MASLD (odds ratio [OR] = 1.35, 95% CI: 1.18 - 1.54) was found from the logistic regression model. A linear relationship was identified by RCS, indicating a positive dose-response association between frailty and CVD mortality (**SFigure 4**, *P* for non-linearity = 0.32). The cumulative incidence curves showed no difference in CVD mortality existed between participants with MASLD and with cardiometabolic risk factors alone before frailty adjustment, whereas MASLD was significantly associated with higher risk of CVD mortality after frailty adjustment (**Figure 1**). Moreover, the interaction term between MASLD and FI was not statistically significant (*P* = 0.37), indicating no evidence of effect modification by

frailty. Results from the mediation analysis show no significant indirect effect of MASLD on CVD mortality through frailty (β = 0.004, *P* = 0.62; **SFigure 5**).

Over a mean follow-up of 23.36 years (standard deviation = 7.75), 1,375 (13.20%) CVD deaths occurred (incidence: 5.65 per 1,000 participant-years), among whom 575 (14.94%) in participants with MASLD and 800 (12.19%) in participants with cardiometabolic risk factors alone. MASLD was not associated with CVD mortality from Model 1 without frailty adjustment (HR = 0.92, 95% CI: 0.78 - 1.10). In Model 2 further adjusting for frailty, MASLD was significantly associated with a 19% increased risk of CVD mortality (HR = 1.19, 95% CI: 1.07 - 1.32) (**Figure 2** & **STable 3**). When participants were stratified by FI quartiles, no associations were found in the lower FI quartiles (Q1: HR = 0.84, 95% CI: 0.58 - 1.22; Q2: HR = 0.93, 95% CI: 0.56 - 1.54); however, MASLD were significantly associated with increased risk of CVD mortality in higher FI quartiles (Q3: HR = 1.35, 95% CI: 1.03 - 1.77; Q4: HR = 1.70, 95% CI: 1.07 - 2.69; **Figure 2** & **STable 3**).

As illustrated in **Figure 3**, the PAF after frailty adjustment ranged from 10.1% (at age 85) to 12.5% (at age 29) for the overall participants. Participants in the Q4 group showed highest age-specific PAFs among the four FI quartile groups, peaking at approximately 17% between age 35 and 65 years.

Subgroup analysis results demonstrated no significant effect modifications to the relationship between MASLD and CVD mortality after frailty adjustment (**Figure 4** and **STable 4)**. Results from sensitivity analyses were in line with our main findings (**Table 2**).

Discussion

In this nationally representative cohort, we found that frailty may confound the relationship between MASLD and CVD mortality among adults with cardiometabolic risk factors. After adjusting for frailty, MASLD was significantly associated with a

statistically significant increased risk of CVD mortality. The risk of CVD mortality in MASLD was greater as frailty severity, measured by FI quartile, increased.

These findings may help interpret the inconsistent associations between MASLD and CVD mortality reported in previous studies [8,9]. This could be partially attributed to the unrecognized confounding role of frailty that is now systematically quantified by the FI in our analysis. Of note, the emergence of a significant association after frailty adjustment suggests that frailty does not negate the role of MASLD, but rather reveals its important impact on CVD death among individuals with cardiometabolic risk factors.

The FI is a validated, cumulative deficit-based metric that comprehensively captures physiological, functional, and psychological impairments in individuals [10]. By aggregating deficits across multiple domains, it enables highly precise quantification of an individual's overall health status and vulnerability [28]. In the present study, we comprehensively evaluated the role of frailty based on a typical framework for confounding assessment. First, we found that frailty was significantly associated with both MASLD (exposure) and CVD mortality (outcome). Second, adjustment for frailty significantly changed the direction and magnitude of the MASLD-CVD mortality association; i.e., MASLD was not significantly associated with CVD mortality before FI adjustment, whereas a significant positive association emerged after FI was incorporated into the model. Third, the FI-stratified analyses further supported the confounding role of frailty, displaying no positive association between MASLD and CVD mortality in the lower FI quartiles but progressively stronger positive associations in the higher FI quartiles. These findings indicated that underlying frailty may mask or distort the observed MASLD-CVD mortality relationship when frailty is not accounted for. We further explored whether frailty may alternatively act as a mediator or effect modifier. The non-significant results from mediation analysis indicated that frailty was not involved in the causal pathway between MASLD and CVD mortality. In addition, the test for interaction ruled out a potential moderator effect of frailty on the relationship between MASLD and CVD mortality. Collectively, these results supported that frailty may confound the relationship between MASLD and CVD mortality. The failure to

adjust for frailty in previous analyses could introduce substantial residual confounding, biasing the association estimate toward the null, and thereby obscuring a positive relationship between MASLD and CVD mortality. The lack of clarification on "MASLD-CVD death paradox" could conceal the cardiometabolic and hepatic interconnections, and thus complicate CVD risk stratification and public health strategies.

Frailty and cardiometabolic disorders are closely related in a bidirectional way [29]. Cardiometabolic abnormalities may increase frailty through cumulative systemic stress involving metabolic dysregulation, vascular injury, inflammatory activation, muscle loss and functional decline [30]. Conversely, frailty may worsen outcomes in cardiometabolic disorders by reducing physiological resilience and functional reserve, increasing vulnerability to metabolic and cardiovascular stressors [29]. Recent evidence has also linked frailty in individuals with overlapping cardiometabolic risk factors to a greater burden of subclinical organ impairment and poorer cognitive function [31].

Our analysis demonstrated that MASLD was significantly associated with a 19% increased risk of CVD mortality after adjusting for frailty. MASLD is recognized as both a passive hepatic manifestation of metabolic syndrome, and part of a multisystem disorder that can actively promote systemic pathological cascades central to CVD pathogenesis [32]. Specifically, MASLD contributes to systemic insulin resistance and sustains chronic low-grade inflammation through hepatocyte dysfunction and macrophage activation [33]. In this context, the high prevalence of pre-diabetes among participants with MASLD further reflects the close metabolic link between early glycemic dysregulation, insulin resistance and hepatic steatosis [34]. Pre-diabetes impairs insulin action to increase free fatty acid flux to the liver and promote hepatic fat accumulation. In contrast, hepatic steatosis could further worsen systemic insulin resistance and accelerate deterioration of glucose metabolism [35]. MASLD also disrupts metabolic-immune crosstalk, which is closely linked to CVD death [6,36]. Moreover, the pro-inflammatory and pro-oxidant microenvironment in MASLD directly damages vascular function by impairing endothelial nitric oxide synthase activity, promoting

oxidative stress, and exacerbating atherosclerotic plaque formation and instability [37,38]. Beyond the vasculature, MASLD-induced metabolic disturbances shift myocardial substrate utilization toward inefficient fatty acid oxidation, leading to steatosis and contractile dysfunction, thereby further increasing risks of CVD and CVD death [39]. Given its independent association with CVD mortality, proactive prevention, targeted treatment, and optimal management of MASLD are important to mitigate cardiovascular risk and improve long-term survival outcomes.

Our PAF estimates provided an exploratory assessment of the potential population-level contribution of MASLD to CVD mortality among adults with cardiometabolic risk factors. After frailty adjustment, MASLD accounted for a modest proportion (10.1% to 12.5%) of CVD mortality risk in this population. The observed decline in PAFs after age 75 may reflect the increasing influence of age-related comorbidities and other geriatric syndromes, alongside increased competing risks of non-CVD deaths, which could collectively diminish the relative contribution of MASLD to CVD mortality in older adults [39,40]. These findings suggest that MASLD represents a potentially relevant target for early risk identification and integrated cardiometabolic management, particularly among adults with cardiometabolic risk factors. Nevertheless, these estimates should be interpreted with caution because PAF estimation assumes a causal relationship and theoretical elimination of the exposure, which is difficult to fully verify in an observational study with potential exposure misclassification and residual confounding.

We observed no significant association between MASLD and CVD mortality in physiologically robust individuals with lower FI. In people with low frailty, preserved reserve may attenuate the association between MASLD and CVD mortality [41]. In contrast, the association became progressively stronger and statistically significant in those with higher FI. Among highly frail individuals, MASLD may add to an already elevated burden of systemic deficits and thus be associated with a higher risk of CVD mortality [42,43]. Moreover, the stronger associations observed in higher FI quartiles may reflect greater susceptibility to cardiometabolic stressors, cumulative disease burden,

reduced physiological reserve and competing vulnerability in frailer individuals. Furthermore, although frailty does not lie on the causal pathway between MASLD and CVD mortality, it may capture an underlying systemic vulnerability that influences the observed MASLD-CVD mortality association in the cardiometabolic-risk-enriched population.

Results from the prespecified subgroup analyses suggested no evidence of effect modification across traditional cardiometabolic risk factors to the MASLD-CVD death relationship after accounting for frailty. By focusing on adults with at least one established cardiometabolic risk factor, we inevitably capture a clinically important subgroup of individuals with MASLD who are not obese. “Lean MASLD” is increasingly recognized as a biologically distinct phenotype, and obesity alone could not fully explain heterogeneity in cardiovascular risk among MASLD populations [44,45]. We did not identify a significant subgroup effect by obesity on the MASLD-CVD death relationship, which further reinforced the concept that MASLD biology (not adiposity alone) contributed to risk of CVD death. Likewise, other subgroup analysis results supported that frailty may help explain the “MASLD-CVD death paradox” beyond these traditional cardiometabolic risk factors.

Our findings demonstrated a significant association between MASLD and increased risk of CVD mortality, variably consistent with the results of several previous studies [46,47]. A large Swedish cohort showed that MASLD was independently associated with higher risk of CVD mortality beyond common metabolic confounders [46]. However, another cohort study using NHANES data reported a non-significant association between MASLD and CVD mortality in people with cardiometabolic risk factors [9]. This discrepancy may be likely attributable to the stronger confounding effect of frailty that was not accounted for in the latter analysis. Also, this indicated accounting for traditional cardiometabolic risk factors only, may not be able to precisely capture the true association between MASLD and CVD mortality in participants with cardiometabolic risk factors.

The PAFs of MASLD for CVD mortality highlights the considerable population-level burden of MASLD, reinforcing the value of integrating frailty assessment into MASLD management for risk stratification and resource prioritization [48]. For example, frailty-based assessment in primary care settings may help identify the "MASLD-frailty" phenotype as the high-risk CVD mortality group who may benefit most from interventions to reduce CVD death [49,50].

Strengths and Limitations

This study systematically investigated the role of frailty in the association between MASLD and CVD mortality among individuals with cardiometabolic risk factors. A key strength is that the NHANES III study was a nationally representative, multi-ethnic cohort with long-term follow-up. Furthermore, the consistency of our primary findings across multiple sensitivity analyses, further strengthens the robustness and validity of our conclusions.

Several limitations should be acknowledged. Although the FI was constructed from a comprehensive set of NHANES variables, it may not capture the full spectrum of health deficits, and the possibility of unmeasured confounding cannot be entirely excluded. With the large number of variables in the models, we acknowledge the possibility of overadjustment. Some components of the FI may correlate with cardiometabolic disease severity or partly lie on the causal pathways linking MASLD to CVD mortality. Furthermore, because MASLD is defined by the presence of hepatic steatosis together with at least one cardiometabolic risk factor, and the reference group in this study consisted of participants with cardiometabolic risk factors but without hepatic steatosis, both groups were metabolically enriched. Therefore, the biological differences between these two groups may have been narrower than the differences between MASLD group and the general population. Moreover, given the interrelationship between hepatic steatosis and cardiometabolic risk factors, the independent influence of hepatic steatosis alone on CVD mortality could not be adequately quantified.

In addition, NHANES relies on self-reported or centrally adjudicated data for some

variables, which may be subject to recall bias or misclassification. We were unable to incorporate longitudinal changes in participants' MASLD status, frailty and cardiometabolic risk factors. This is particularly important given the long follow-up period of more than two decades, during which cardiovascular risk may have been substantially modified by lifestyle changes, medication uses and other cardiometabolic interventions. The lack of time-updated data may have introduced residual confounding and exposure misclassification to obscure the observed relationship between MASLD and CVD death. Moreover, NHANES III (1988 - 1994) was conducted before contemporary standards of cardiometabolic care. Thus, the observed associations should be interpreted in this historical context and may not fully reflect risk patterns in contemporary populations receiving more intensive antihypertensive, lipid-lowering, glucose-lowering, weight-loss and liver disease therapies. Besides, MASLD was ascertained using ultrasound examination, which directly visualizes hepatic steatosis and has acceptable diagnostic performance for moderate-to-severe fatty liver. Compared to histology (the gold standard), ultrasound demonstrated an overall sensitivity of 84.8% (95% CI: 79.5 - 88.9) and a specificity of 93.6% (95% CI: 87.2 - 97.0) for detecting moderate-to-severe fatty liver [51]. However, ultrasound has limited sensitivity for mild hepatic steatosis [52]. Therefore, participants with early or low-grade steatosis may have been misclassified into the reference group, leading to potential underestimation of MASLD prevalence and narrowing of the biological contrast between groups. Although we tried to use various statistical analysis techniques, potential biases and residual confounding could not be fully precluded in an observational study. Finally, while NHANES provides valuable nationally representative data, its generalizability to other populations with different healthcare systems and ethnic/racial compositions requires further validation, especially given the reported ethnic/racial differences in clinical epidemiology and cardiovascular conditions [53,54].

Conclusion

Frailty may confound the relationship between MASLD and CVD mortality in people with cardiometabolic risk factors. After accounting for frailty, MASLD was independently associated with a 19% higher risk of CVD mortality in adults with cardiometabolic risk factors, suggesting that failure to account for frailty could obscure the true MASLD-CVD death relationship. Incorporating frailty assessment may therefore be essential for accurate risk stratification and prevention strategies in cardiometabolic populations.

Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CKM	Cardiovascular-kidney-metabolic
CVD	Cardiovascular disease
FI	Frailty index
FIB-4	Fibrosis-4 index
FLI	Fatty liver index
GGT	Gamma glutamyl transferase
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
MASLD	Metabolic dysfunction-associated steatotic liver disease
MetALD	Metabolic dysfunction and alcohol-associated liver disease
NAFLD	Nonalcoholic fatty liver disease
PAF	Population attributable fraction
RCS	Restricted cubic splines
TC	Total cholesterol
TG	Triglycerides
VCTE	Vibration controlled transient elastography

Declarations

Ethics approval and consent to participate

NHANES III was approved by the National Center for Health Statistics of the Centers for Disease Control and Prevention Institutional Review Board. All participants provided written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

All data based on Third National Health and Nutrition Examination Survey (NHANES III) in this study are publicly available (https://wwwn.cdc.gov/nchs/nhanes/).

Competing interests

GYHL serves as a consultant for Novartis, Bayer/Janssen, Biotronik, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Verseon, and Daiichi-Sankyo and as a speaker for Medtronic, Bayer, BMS/Pfizer, Boehringer Ingelheim, and Daiichi-Sankyo. HGCV receives consulting fees from Bayer, BMS, Medtronic, Novo Nordisk, Pfizer; and her research is funded by Canadian Institute of Health Research and PHRI Internal Career Award. GGS reports research grants the German Research Foundation (DFG), German Center for Cardiovascular Research (DZHK), the European Research Council (ERC) and report research agreements and/or speaker honoraria and/or consultancy agreement from Boehringer Ingelheim, Pfizer, Novo Nordisk, e-Therapeutics, and Sanofi. No fees have been received directly or personally. All other authors have declared no conflicts of interest.

Funding

This study was funded by National Natural Science Foundation of China (82473612), Natural Science Foundation of Guangdong Province of China (2025A1515010779), the Science Foundation of Guangdong Second Provincial General Hospital (YY2018-002), and the Young Top Talent Project in Special Support Plan for Training High-level Talents in Guangdong (0720240244).

Authors' contributions

RW, WL, YL and GL: conceived and designed the study. RW, WL, YL, HGCVS, and GL: obtained data, performed analyses and interpretation, and drafted the manuscript. JVL, GGS, GYHL, YC, LQ, HGCVS and GL: provided professional and statistical support, and made critical revisions. All authors read and approved the final manuscript.

Acknowledgements

None.

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Table and figure legends:

Table 1. Description of participants' baseline characteristics and comparisons between participants with MASLD and those with cardiometabolic risk factors alone

Figure 1. Cumulative incidence for CVD mortality before/after adjusting for frailty
(A: results from the model adjusting for age, sex, BMI, smoking status, alcohol consumption, race, marital status, education, sedentary lifestyle, hypertension, hyperlipidemia, and diabetes mellitus; B: results from the model further adjusting for frailty index)

Figure 2. Relationship between MASLD and risk of CVD mortality after accounting for frailty based on frailty index quartiles
(note- models were adjusted for age, sex, BMI, smoking status, alcohol consumption, race, marital status, education, sedentary lifestyle, hypertension, hyperlipidemia, diabetes mellitus, and frailty index. 1 Results shown for per-SD increase in the frailty index)

Figure 3. Age-specific population attributable fraction of MASLD for CVD mortality.
(note- models were adjusted for age, sex, BMI, smoking status, alcohol consumption, race, marital status, education, sedentary lifestyle, hypertension, hyperlipidemia, diabetes mellitus, and frailty index)

Figure 4. Subgroup analyses for the relationship between MASLD and CVD mortality after accounting for frailty
(note- models were adjusted for age, sex, BMI, smoking status, alcohol consumption, race, marital status, education, sedentary lifestyle, hypertension, hyperlipidemia, diabetes mellitus, and frailty index)

Table 2. Sensitivity analysis results for the relationship between MASLD and CVD mortality after accounting for frailty

Table 1. Description of participants' baseline characteristics and comparisons between participants with MASLD and those with cardiometabolic risk factors alone[1]

Characteristics	Total participants (n = 10,413)	Participants with MASLD (n = 3,849)	Participants with cardiometabolic risk factors alone (n = 6,564)	*P*-value[2]
Age, mean (SE), year	45.66 (0.21)	47.94 (0.33)	44.33 (0.28)	< 0.01
Male, n (%)	4,590 (44.36)	1,762 (46.58)	2,828 (43.07)	< 0.01
BMI, mean (SE), kg/m^2	28.35 (0.09)	30.46 (0.15)	27.11 (0.09)	< 0.01
Smoking status, n (%)				
Never smoker	5,217 (49.65)	1,943 (50.56)	3,274 (49.12)	< 0.01
Previous smoker	2,546 (25.06)	1,096 (29.42)	1,450 (22.86)	
Current smoker	2,650 (25.29)	810 (20.01)	1,840 (28.02)	
Alcohol consumption, mean (SE), g/day	3.21 (0.15)	1.56 (0.12)	4.18 (0.21)	< 0.01
Race, n (%)				
Non-Hispanic white	3,781 (36.06)	1,336 (34.76)	2,445 (36.82)	< 0.01
Non-Hispanic black	3,039 (29.67)	921 (23.81)	2,118 (33.09)	
Mexican-American	3,170 (30.02)	1,445 (36.71)	1,725 (25.81)	
Other	423 (4.25)	147 (4.21)	276 (4.28)	
Marital status, n (%)				
Married/living with partner	6,852 (65.39)	2,629 (67.93)	4,223 (63.90)	< 0.01
Divorced/separated/widowed	1,986 (18.98)	769 (19.86)	1,217 (18.47)	
Never married	1,552 (15.62)	441 (12.20)	1,111 (17.63)	
Education, n (%)				
Above high school	2,906 (28.07)	905 (23.82)	2,001 (30.58)	< 0.01
High school and below	7,438 (71.93)	2,923 (76.18)	4,515 (69.42)	
Sedentary lifestyle, n (%)	3,281 (32.27)	1,392 (36.56)	1,889 (29.75)	< 0.01
SBP, mean (SE), mmHg	124.77 (0.29)	127.33 (0.47)	123.28 (0.40)	< 0.01
DBP, mean (SE), mmHg	73.83 (0.16)	75.33 (0.32)	72.95 (0.21)	< 0.01

Waist circumference, mean (SE), cm	95.82 (0.23)	101.37 (0.33)	92.58 (0.24)	< 0.01
TC, mean (SE), mg/dL	208.38 (0.75)	212.42 (1.23)	206.01 (0.89)	< 0.01
TG, mean (SE), mg/dL	155.00 (1.78)	190.41 (3.57)	134.15 (1.73)	< 0.01
LDL, mean (SE), mg/dL	130.03 (0.75)	128.77 (1.15)	130.72 (1.06)	0.24
HDL, mean (SE), mg/dL	48.97 (0.20)	45.59 (0.28)	50.95 (0.24)	< 0.01
HbA1c, mean (SE), %	5.65 (0.01)	5.93 (0.03)	5.48 (0.01)	< 0.01
AST, mean (SE), U/L	21.48 (0.14)	23.68 (0.31)	20.18 (0.16)	< 0.01
ALT, mean (SE), U/L	18.21 (0.19)	21.97 (0.35)	15.98 (0.20)	< 0.01
GGT, mean (SE), U/L	32.63 (0.54)	39.45 (1.16)	28.50 (0.56)	< 0.01
Platelet, mean (SE), 10^9/L	279.11 (1.04)	280.11 (1.49)	278.52 (1.42)	0.45
Hypertension, n (%)	3,218 (31.88)	1,493 (39.24)	1,725 (27.56)	< 0.01
Hyperlipidemia, n (%)	2,393 (23.89)	985 (26.33)	1,408 (22.45)	< 0.01
Pre-diabetes, n (%)	3,726 (35.88)	1,512 (39.90)	2,214 (33.52)	< 0.01
Diabetes mellitus, n (%)	1,217 (12.38)	759 (21.30)	458 (7.13)	< 0.01
FIB-4, mean (SE)	0.96 (0.01)	1.00 (0.02)	0.93 (0.01)	< 0.01
Frailty index, mean (SE)	0.20 (0.16)	0.21 (0.19)	0.19 (0.14)	< 0.01

[1]Data are presented as weighted means (standard errors) for continuous variables or count (weighted percentage) for categorical variables.

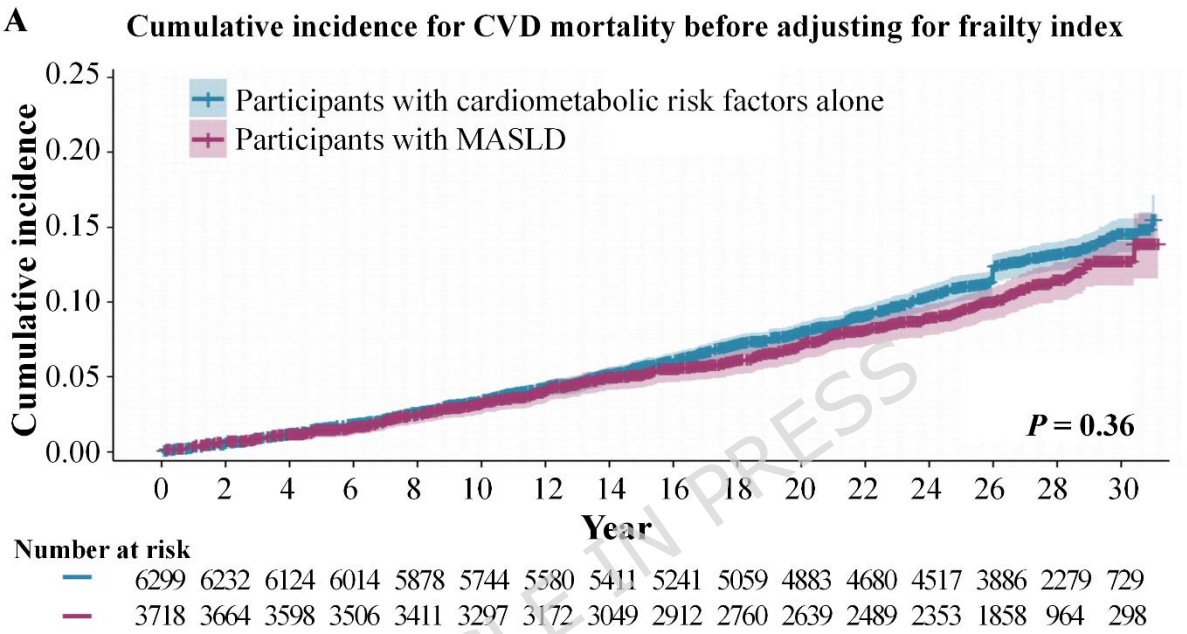
[2]*P*-values were calculated by survey-weighted linear regression models for continuous variables and Rao-Scott design-adjusted chi-square tests for categorical variables.

MASLD, Metabolic dysfunction-associated steatotic liver disease; SE, Standard errors; BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; TC, Total cholesterol; TG, Triglyceride; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; HbA1c, Glycated hemoglobin; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; GGT, Gamma glutamyl transferase; FIB-4, Fibrosis-4 index

Figure 1. Cumulative incidence for CVD mortality before/after adjusting for frailty

(A: results from the model adjusting for age, sex, BMI, smoking status, alcohol consumption, race, marital status, education, sedentary lifestyle, hypertension, hyperlipidemia, and diabetes mellitus; B: results from the model further adjusting for frailty index)

CVD, cardiovascular disease; MASLD, metabolic dysfunction-associated steatotic liver disease



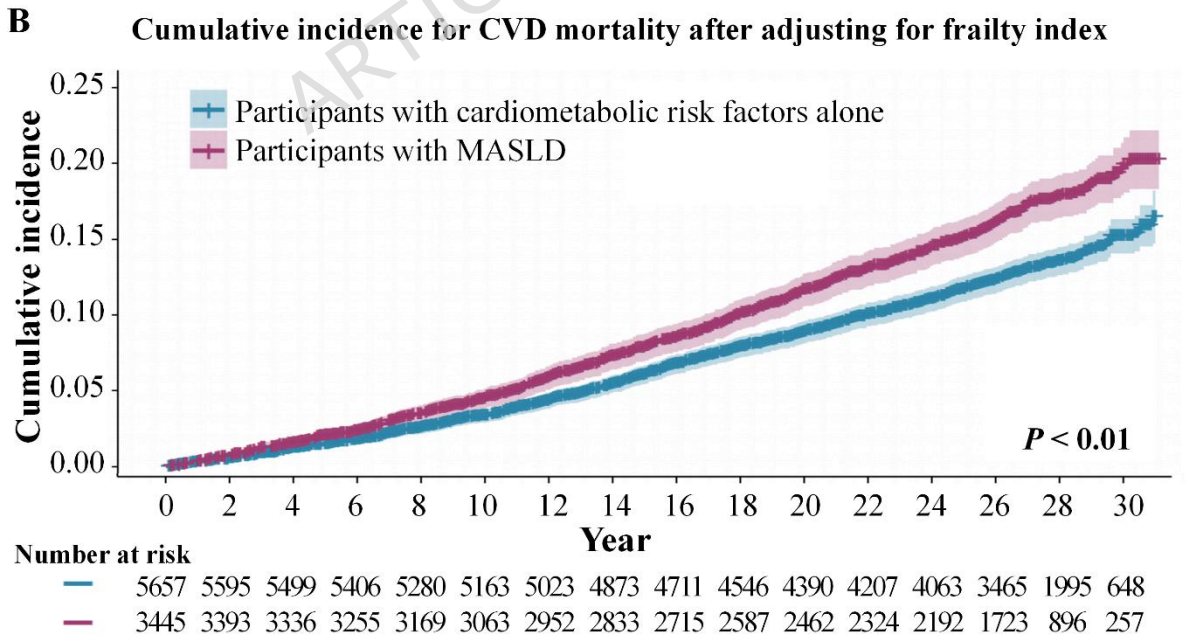


Figure 2. Relationship between MASLD and risk of CVD mortality after accounting for frailty based on frailty quartiles

(note- models were adjusted for age, sex, BMI, smoking status, alcohol consumption, race, marital status, education, sedentary lifestyle, hypertension, hyperlipidemia, diabetes mellitus, and frailty index. [1] Results shown for per-SD increase in the frailty index)

FI, frailty index; HR, hazard ratio; MASLD, metabolic dysfunction-associated steatotic liver disease

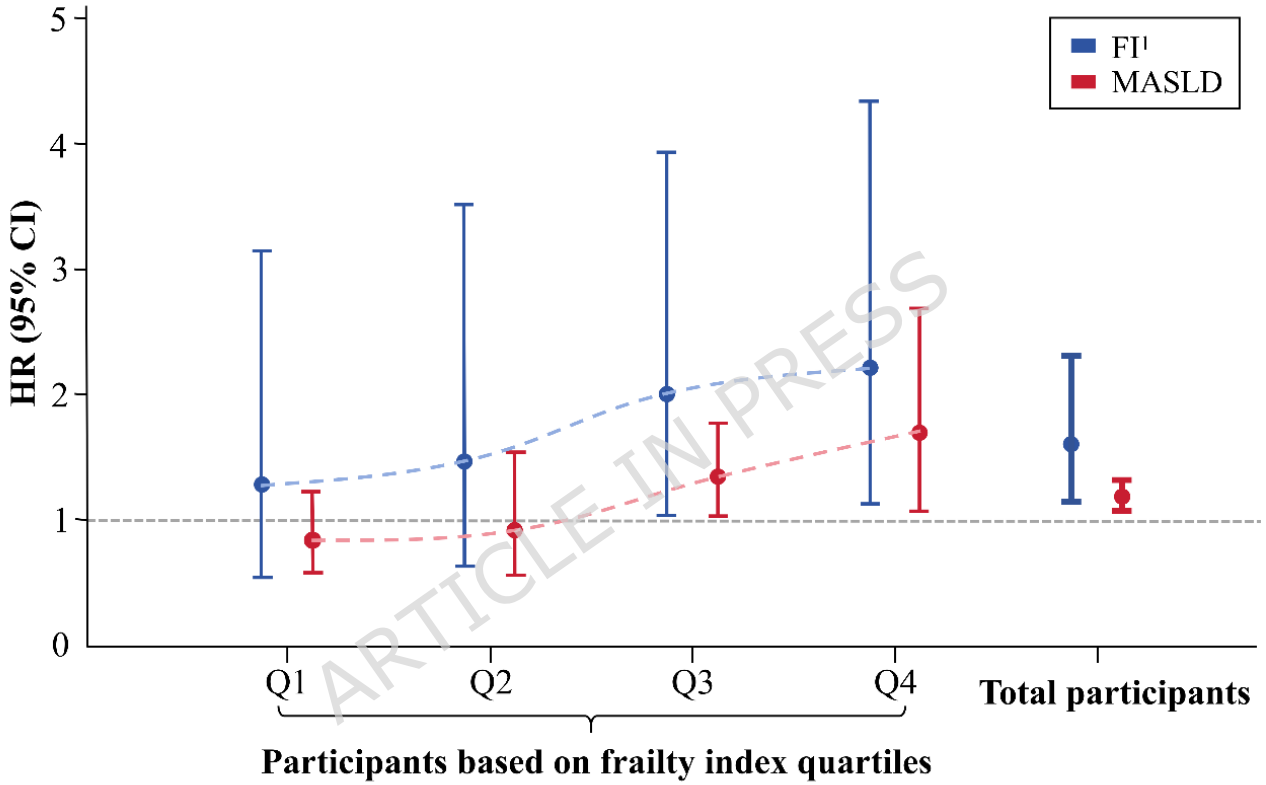


Figure 3. Age-specific population attributable fraction of MASLD for CVD mortality.

(note- models were adjusted for age, sex, BMI, smoking status, alcohol consumption, race, marital status, education, sedentary lifestyle, hypertension, hyperlipidemia, diabetes mellitus, and frailty index)

CVD, cardiovascular disease; FI, frailty index; MASLD, metabolic dysfunction-associated steatotic liver disease; PAF, population attributable fraction

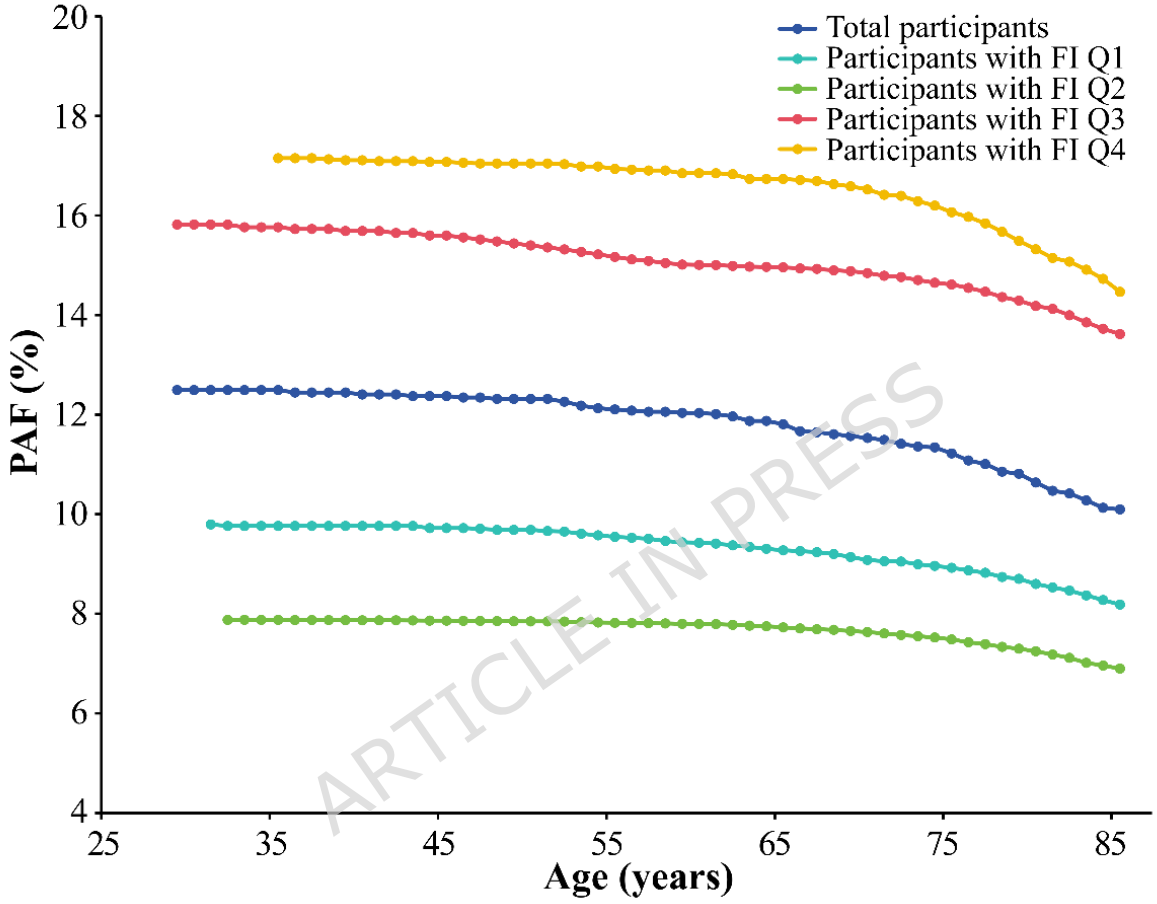


Figure 4. Subgroup analyses for the relationship between MASLD and CVD mortality after accounting for frailty

(note- models were adjusted for age, sex, BMI, smoking status, alcohol consumption, race, marital status, education, sedentary lifestyle, hypertension, hyperlipidemia, diabetes mellitus, and frailty index)

MASLD, metabolic dysfunction-associated steatotic liver disease; CVD, cardiovascular disease; HR, hazard ratio; CI, confidence interval; FIB-4, fibrosis-4 index

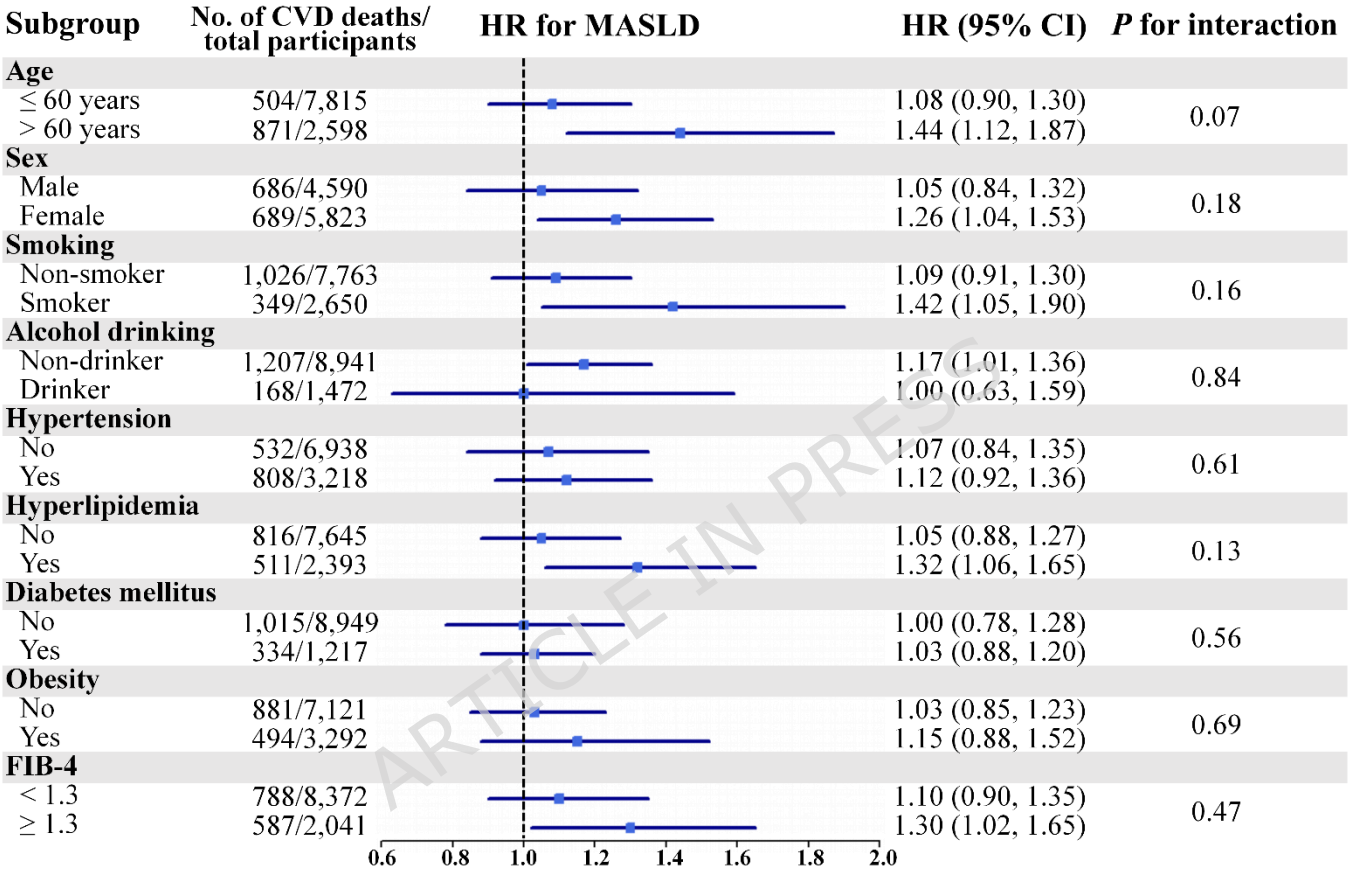


Table 2. Sensitivity analysis results for the relationship between MASLD and CVD mortality after accounting for frailty

Sensitivity analysis	No. of CVD deaths/total participants	HR (95 % CI)[1], *P*-value
Running multiple imputation for missing data		
Participant with cardiometabolic risk factors alone	800/6,564	-
Participant with MASLD	575/3,849	1.19 (1.04, 1.35), 0.03
Performing competing risk model[2]		
Participant with cardiometabolic risk factors alone	800/6,564	-
Participant with MASLD	575/3,849	1.26 (1.11, 1.43), <0.01
Excluding participants who died within the first two years of follow-up[3]		
Participant with cardiometabolic risk factors alone	694/5,923	-
Participant with MASLD	504/3,506	1.15 (1.01, 1.32), 0.04
Using alternative MASLD definition by FLI ≥ 60		
Participant with cardiometabolic risk factors alone	341/2,275	-
Participant with MASLD	916/7,278	1.18 (1.00, 1.39), 0.04
Running propensity score matching analysis		
Participant with cardiometabolic risk factors alone	726/5,994	-
Participant with MASLD	531/3,559	1.15 (1.01, 1.32), 0.04
Defining frailty by using phenotypic frailty[4]		
Participant with cardiometabolic risk factors alone	58/535	-
Participant with MASLD	54/376	1.16 (1.01, 1.32), 0.04

MASLD, Metabolic dysfunction-associated steatotic liver disease; CVD, Cardiovascular disease; FLI, Fatty liver index

[1]Results shown for MASLD; models adjusted for age, sex, BMI, smoking status, alcohol consumption, race, marital status, education, sedentary lifestyle, hypertension, hyperlipidemia, diabetes mellitus, and frailty index

[2] Performing competing risk model by taking non-cardiovascular deaths as competing events for CVD deaths

[3] Excluding the participants who died within the first two years of follow-up to minimize reverse causality

[4] There were 911 participants (383 in non-frail, 392 in prefrail, and 136 in frail group respectively) who had available data to define phenotypic frailty and thus were included for analysis