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ORIGINAL RESEARCH

Associations Between Frailty and Risk of All-Cause and Cardiovascular Mortality in Patients with Prediabetes: A Population-Based Study

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Objective: Diabetes is a well-known risk factor for frailty that has been associated with adverse prognosis. However, the association of frailty with all-cause and cardiovascular disease (CVD) mortality in patients with prediabetes has not been thoroughly explored.

Methods: Participants with prediabetes were derived from the 1999–2018 National Health and Nutrition Examination Survey and followed up for all-cause and CVD mortality until December 31, 2019. A frailty index calculated using a 49-item deficit accumulation model > 0.21 was used to indicate the presence of frailty. Kaplan-Meier curves and weighted Cox proportional hazards regression were used to assess the association between frailty and mortality.

Results: The weighted prevalence of frailty was 28.21% in this cohort of 7845 prediabetic participants with a mean age of 62.89 years. During a median follow-up time of 90 months, a total of 1983 all-cause (636 CVD-related) deaths occurred. Each 0.01 score increase in the frailty index was associated with a 5% and 6% increased risk of all-cause and CVD-related mortality, respectively. The hazard ratio and 95% confidence interval for all-cause and CVD mortality in the frailty group were 2.28 (1.89–2.76) and 2.84 (2.01–4.02), respectively, compared with those without frailty. Restricted cubic spline analysis showed a linear association between frailty index and all-cause or CVD mortality. Similar results were observed in the sensitivity analyses.

Conclusion: The frailty index was positively associated with all-cause and CVD mortality in participants with prediabetes, highlighting that appropriate screening and management of frailty may help reduce mortality in patients with prediabetes.

Keywords: all-cause mortality, cardiovascular disease, frailty, prediabetes

Introduction

Prediabetes, a transitional state between normal glucose regulation and diabetes, is increasingly recognized as a chronic disease affecting more than 500 million adults worldwide.[1] Accumulating evidence suggests that prediabetes may progress to diabetes and increase the risk of premature mortality by inducing complications such as chronic kidney disease, cardiovascular disease, and dementia.[2] Therefore, accurate identification of risk factors for adverse outcomes in patients with prediabetes may serve to inform management.

Frailty has been increasingly recognized as an age-dependent clinical syndrome characterized by excessive vulnerability of the individual to endogenous or exogenous stressors as a consequence of functional decline in multiple physiological systems. The deficit accumulation approach operationalizes frailty as a stochastic, dynamic process in a system with an accumulation of deficits that ultimately impair the system.[3] Earlier studies have indicated that frailty is intimately associated with diabetes in older adults, in the sense that diabetes promotes the development of frailty, and frailty may simultaneously expose older diabetic adults to increased adverse outcomes, such as falls, fractures, hospitalizations and mortality.[4,5] Moreover, frailty has also been implicated in the progression of prediabetes to overt diabetes in the Chinese and British populations.[6] Therefore, several society guidelines have recommended the assessment

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of frailty as a routine component of a comprehensive diabetes evaluation.[7] However, the impact of frailty on long-term outcomes in individuals with prediabetes remains largely unknown.

To bridge this gap, this study aimed to evaluate the associations between frailty and all-cause or cardiovascular disease (CVD) mortality in individuals with prediabetes using nationally representative data from the US National Health and Nutrition Examination Survey (NHANES).

Methods

Data Source and Participant Population

The NHANES is an ongoing, cross-sectional survey conducted by the National Center for Health Statistics to assess the health and nutritional status of the non-institutionalized US civilian population. The NHANES employed a complex, multi-stage, probability sampling design to select participants representative of the civilian, non-institutionalized US population. The detailed survey design and data collection methods are provided and freely available on the NHANES website at http://www.cdc.gov/nchs/nhanes. The study was approved by the Ethics Review Board of the National Center for Health Statistics, and all adult participants provided informed consent. According to item 1 and 2 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects of the People's Republic of China, the data used in this study will not cause any form of harm to human beings, nor will it touch sensitive personal privacy or trade secrets, so the ethical review can be exempted.

The current study extracts data from non-pregnant individuals with prediabetes, defined as those with a clear physician diagnosis, or 5.6 mmol/L ≤ fasting blood glucose level < 7.0 mmol/L or 5.7% ≤ glycated hemoglobin A1C < 6.5%, or an oral glucose tolerance test 2-hour blood glucose of 7.8–11.0 mg/dL. Participants aged < 20 years (n=1908), with missing follow-up data (n=34), or with > 20% missing variables in the 49-item frailty index (n=7413) were excluded. As shown in Figure 1, the final analytic sample consisted of data from 7845 prediabetic participants.

Frailty Assessment

In the current study, we applied the deficit accumulation approach to operationalize the definition of frailty by referring to the 49-item frailty index reported in previous studies (Supplementary Table 1).[8,9] The 49-item frailty index comprehensively assesses various organ systems, including cognition, dependency, depression, comorbidities, hospital utilization and general health, anthropometry, and laboratory data, with each variable assigned a score from 0 (absent) to 1 (most severe). Finally, the frailty index was calculated by dividing the cumulative score of each variable by the number of variables assessed. Consistent with previous reports,[8,9] a frailty index > 0.21 was chosen to represent the presence of frailty.

Outcomes Measurement

We focused on all-cause mortality and CVD-related mortality in this cohort by linking NHANES data to the National Death Index death certificate records through December 31, 2019. CVD-specific mortality was defined as causes of death with the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision codes I00–I09, I11, I13, I20–I51, and I60–I69.

Covariates

Data on covariates were collected, including participants' age, sex, race/ethnicity, marital status, educational level, poverty-income ratio, smoking, drinking, physical activity, and laboratory results of total cholesterol, triglycerides, and high-density lipoprotein cholesterol. Race/ethnicity was self-report and categorized as non-Hispanic white, non-Hispanic black, Mexican American, other Hispanic and other. Smoking status was classified into never, former and current. Participants were categorized as former, never, mild, moderate and severe based on self-reported average number of alcoholic beverages consumed per day.[10]

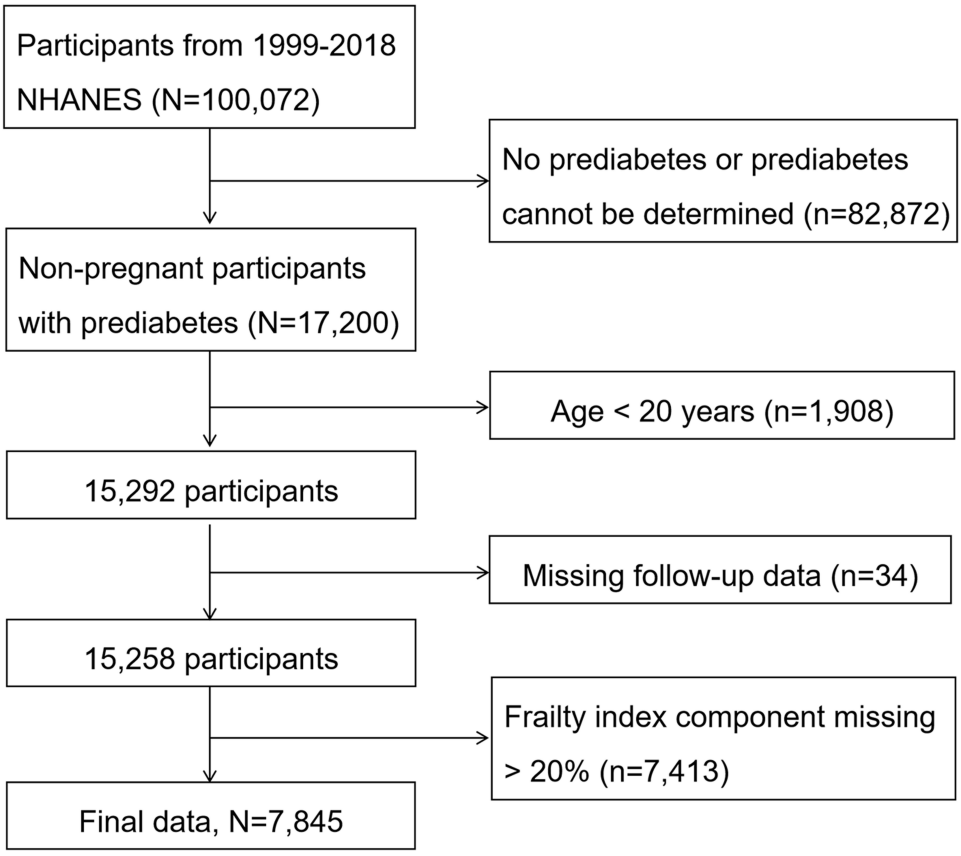

Figure 1 Flowchart showing the inclusion and exclusion of study participants.

Statistical Analysis

Weighted Student's *t*-test and Rao-Scott chi-squared test were applied for the comparisons between continuous variables and categorical variables, respectively. The Kaplan-Meier curves for both all-cause and CVD-related mortality were plotted separately for follow-up time, and survival between the frailty and non-frailty groups was compared using the Log rank test. Survey-weighted multivariable Cox proportional hazards regression analysis was used to calculate the corresponding hazard ratios (HRs) and 95% confidence intervals (CIs). Overall, 3 statistical models were established: the crude non-adjusted model; model 1, adjusted for participants' age, sex, marital status, race/ethnicity, educational level, and poverty-income ratio; model 2, further adjusted for smoking, drinking, physical activity, total cholesterol, triglycerides and high-density lipoprotein, in addition to factors listed in model 1. To assess the linearity of the frailty index with all-cause and CVD-related mortality, we performed restricted cubic spline analysis. To test the robustness of the results, we performed a sensitivity analysis by excluding participants who died within 24 months of follow-up. All statistical analyses were performed using R software. A two-tailed P value < 0.05 indicated statistical significance.

Results

Comparison of Baseline Characteristics

Data from 7845 participants, representing 27,919,992 non-institutionalized US citizens, were analyzed. The weighted mean age was 62.89 years, with a male and frailty proportion of 46.77% and 28.21%, respectively. As shown in Table 1, compared with the non-frailty group, participants in the frailty group were more likely to be females, single, less educated, economically disadvantaged, have a higher body mass index, and more likely to be current smokers. In terms of medical comorbidities, prediabetic participants in the frailty group had an increased prevalence of hypertension, stroke, coronary heart disease,

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Table 1 Weighted Comparisons Between the Frailty and Non-Frailty Group in Participants with Prediabetes

	Total (n=7845)	Non-frailty Group (n=5512)	Frailty Group (n=2333)	P
N	**27,919,992**	**20,042,882**	**7,877,110**	
Age, years	62.89±0.21	63.08±0.22	62.41±0.38	0.09
Sex (n, %)				< 0.001
Male	3883 (46.77)	2887 (50.11)	996 (38.28)	
Female	3962 (53.23)	2625 (49.89)	1337 (61.72)	
Race (n, %)				< 0.001
Non-Hispanic White	4003 (75.69)	2766 (77.07)	1237 (72.17)	
Non-Hispanic Black	1604 (9.61)	1096 (8.66)	508 (12.04)	
Mexican American	1007 (4.40)	760 (4.45)	247 (4.29)	
Other Hispanic	639 (4.09)	439 (3.69)	200 (5.11)	
Other	592 (6.21)	451 (6.14)	141 (6.40)	
Marital status (n, %)				< 0.001
Non-single	4509 (62.07)	3398 (65.88)	1111 (53.26)	
Single	3303 (37.53)	2090 (34.12)	1213 (46.74)	
Education (n, %)				< 0.001
< High school	1174 (7.70)	781 (6.65)	393 (10.39)	
High school	3144 (39.24)	2121 (37.38)	1023 (44.10)	
> High school	3514 (52.97)	2603 (55.97)	911 (45.51)	
Poverty-income ratio	2.88±0.04	3.13±0.05	2.24±0.05	< 0.001
BMI, kg/m^2	29.76±0.13	29.16±0.14	31.30±0.24	< 0.001
SBP, mmHg	129.90±0.35	130.00±0.40	129.62±0.59	0.56
DBP, mmHg	70.29±0.25	70.58±0.29	69.54±0.36	0.01
Physical activity, Met/min-week	3214.24±97.99	3303.67±110.64	2903.32±201.94	0.08
Drinking (n, %)				< 0.001
Never	1163 (12.02)	833 (13.38)	330 (12.40)	
Former	1706 (19.17)	1079 (18.29)	627 (27.69)	
Mild	2708 (38.23)	2038 (44.30)	670 (34.83)	
Moderate	779 (11.45)	574 (12.93)	205 (11.30)	
Heavy	827 (10.87)	550 (11.10)	277 (13.78)	
Smoking (n, %)				< 0.001
Never	3629 (46.00)	2690 (49.16)	939 (38.14)	
Former	2666 (33.77)	1881 (33.97)	785 (33.37)	
Current	1541 (20.13)	933 (16.87)	608 (28.49)	

(*Continued*)

Table 1 (Continued).

	Total (n=7845)	Non-frailty Group (n=5512)	Frailty Group (n=2333)	P
Hypertension (n, %)	5036 (61.33)	3275 (55.55)	1761 (76.02)	< 0.001
Stroke (n, %)	503 (5.80)	173 (3.08)	330 (12.77)	< 0.001
Coronary heart disease (n, %)	580 (7.42)	236 (4.70)	344 (14.49)	< 0.001
Angina (n, %)	357 (4.41)	119 (2.07)	238 (10.42)	< 0.001
Congestive heart failure (n, %)	380 (4.43)	96 (1.78)	284 (11.27)	< 0.001
Heart attack (n, %)	623 (7.37)	241 (4.32)	382 (15.18)	< 0.001
HbA1C, %	5.70±0.01	5.68±0.01	5.76±0.01	< 0.001
Triglyceride, mg/dL	156.95±2.02	153.06±2.23	166.92±3.43	< 0.001
Total cholesterol, mg/dL	201.31±0.72	203.00±0.85	196.97±1.26	< 0.001
HDL, mg/dL	53.66±0.34	54.21±0.39	52.23±0.48	< 0.001
Hemoglobin, g/dL	14.25±0.03	14.41±0.03	13.84±0.06	< 0.001

Notes: N signified the number of represented individuals after weighting.
Abbreviations: BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure.

angina, congestive heart failure and heart attack. With regard to laboratory measures, the frailty group was associated with higher HbA1C, higher triglycerides, lower high-density lipoprotein cholesterol and lower hemoglobin.

Associations Between Frailty Index, Frailty and Outcomes

During a median follow-up time of 90 (interquartile range 46–138) months, a total of 1983 all-cause (636 CVD-related) deaths were recorded. Kaplan-Meier survival curve analysis demonstrated significantly higher survival probabilities for

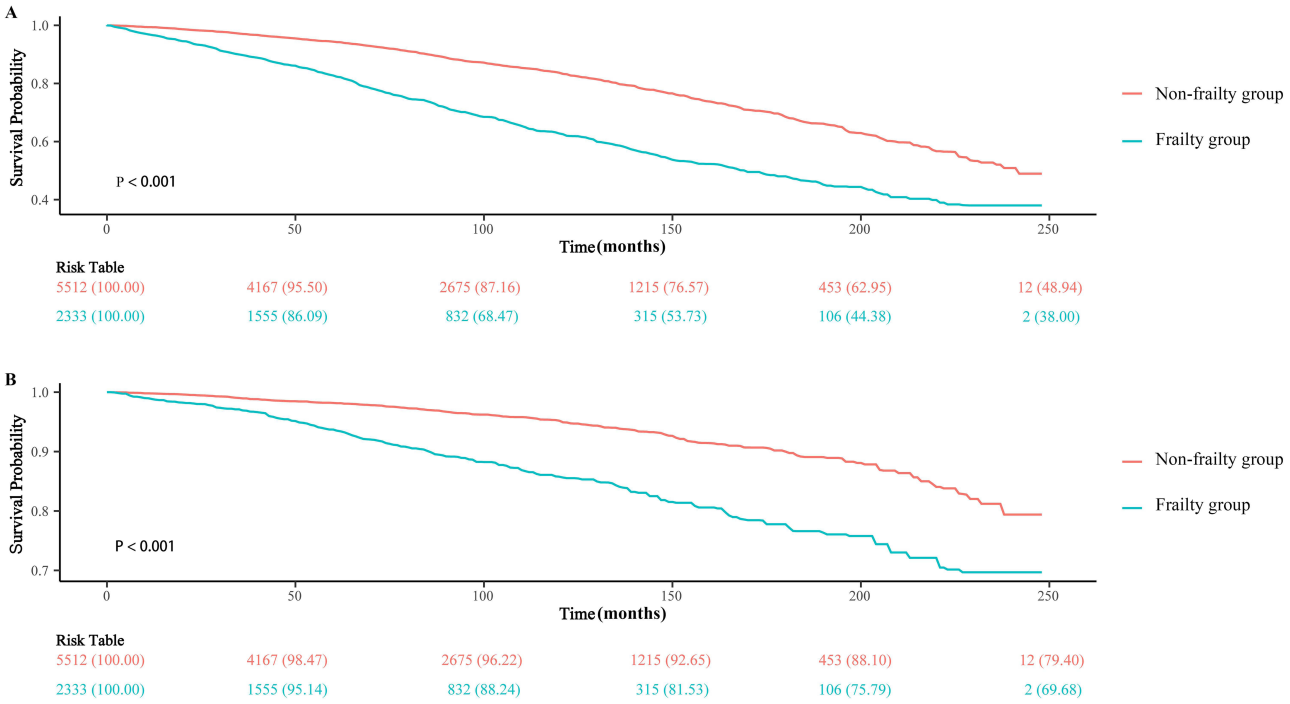

Figure 2 Kaplan-Meier curves showing the cumulative all-cause (**A**) and cardiovascular (**B**) mortality rate in prediabetic participants with and without frailty.

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Table 2 Associations Between Frailty Score, Frailty State and All-Cause or Cardiovascular Disease-Related Mortality in NHANES Participants with Prediabetes

	Crude Model		Model 1		Model 2	
All-cause mortality	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
Frailty score (every 0.01 point)	1.04 (1.04, 1.05)	<0.001	1.05 (1.04, 1.06)	<0.001	1.05 (1.04, 1.06)	<0.001
Frailty state (frailty vs non-frailty)	2.33 (2.03, 2.67)	<0.001	2.45 (2.12, 2.82)	<0.001	2.28 (1.89,2.76)	<0.001
CVD mortality	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
Frailty score (every 0.01 point)	1.05 (1.04, 1.05)	<0.001	1.05 (1.04, 1.06)	<0.001	1.06 (1.04, 1.08)	<0.001
Frailty state (frailty vs non-frailty)	2.68 (2.17, 3.31)	<0.001	2.78 (2.20, 3.51)	<0.001	2.84 (2.01, 4.02)	<0.001

Notes: Model 1 was adjusted for participants' age, sex, educational level, marital status and poverty-income ratio; Model 2 was further adjusted for drinking, smoking, physical activity, total cholesterol, triglyceride, and high-density lipoprotein, in addition to covariates listed for Model 1.
Abbreviations: CI, confidence interval; HR, hazard ratio.

all-cause (Figure 2A) and CVD (Figure 2B) mortality in the non-frailty group than in the frailty group (both P < 0.001). As shown in Table 2, a crude analysis showed that each 0.01 score increase in the frailty index was associated with a 4% and 5% increased risk of all-cause and CVD-related mortality, respectively. In the fully adjusted model 2, each 0.01 score increase in frailty index was still associated with a 5% and 6% increased risk of all-cause and CVD-related mortality, respectively. The multivariable adjusted model 2 suggested that frailty was significantly associated with elevated risks of all-cause (HR=2.28, 95% CI 1.89–2.76, P<0.001) and CVD-related (HR=2.84, 95% CI 2.01–4.02, P<0.001) mortality.

As shown in Figure 3A-B, the restricted cubic spline analysis indicated positive correlations of the frailty index with all-cause (P for nonlinearity = 0.26) and CVD-related (P for nonlinearity = 0.40) mortality.

Subgroup Analysis

Subgroup analyses stratified by participants' age, sex, body mass index, smoking, and medical comorbidities of hypertension, stroke, coronary heart disease, angina, congestive heart failure and heart attack showed that these factors did not modify the association between frailty and all-cause mortality (Figure 4A). However, the association between frailty and CVD mortality was observed only in never smokers and former smokers, but not in current smokers (Figure 4B).

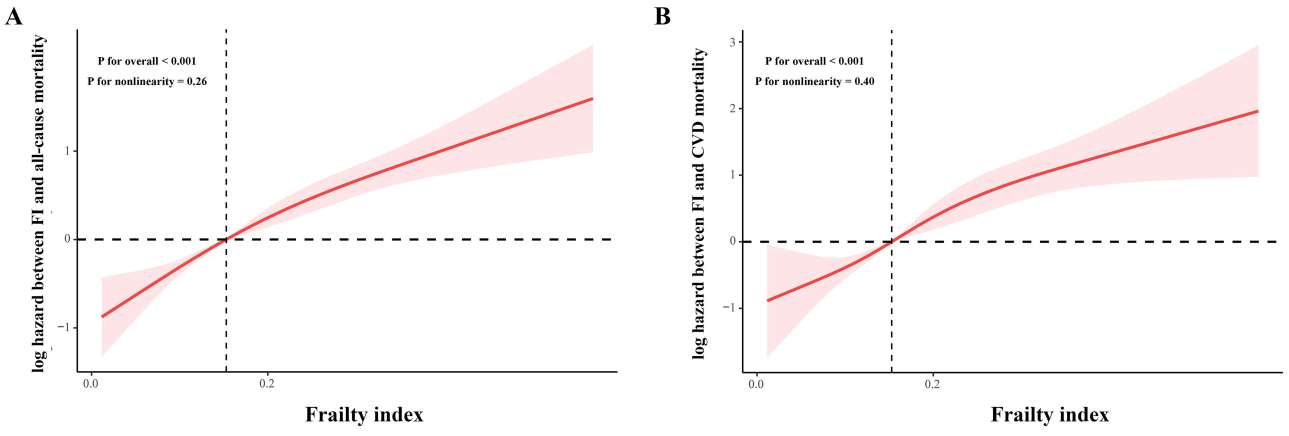

Figure 3 Restricted cubic spline analysis illustrating the dose-response relationship between the frailty index and log hazard ratio for all-cause (**A**) and cardiovascular mortality (**B**).

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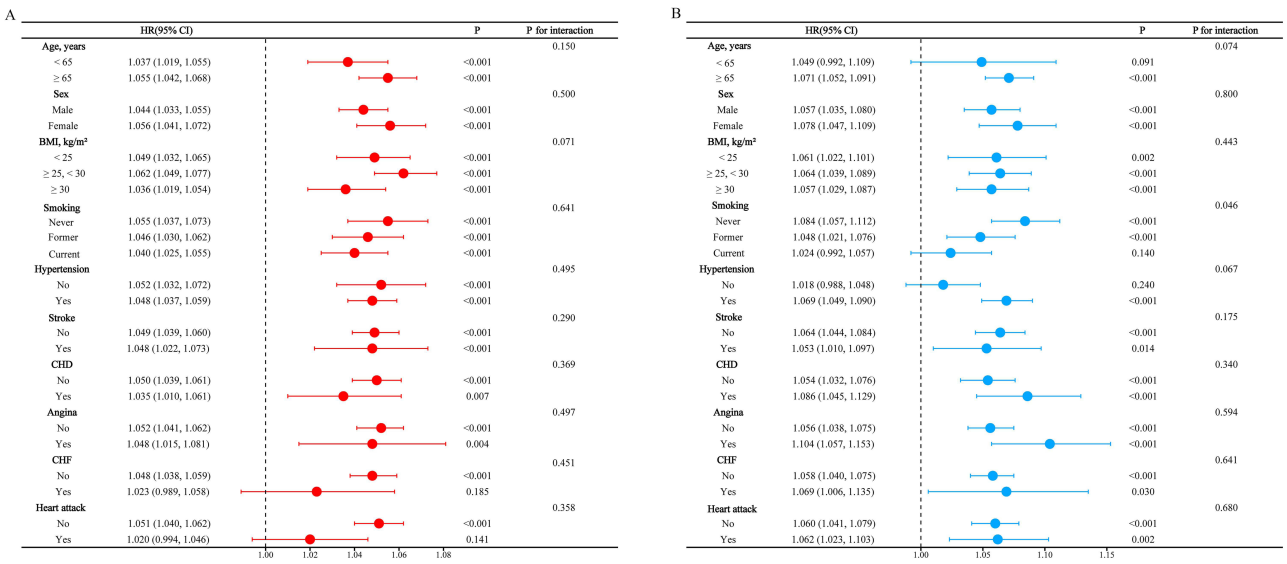

Figure 4 Forest plot for stratified analysis of the relationship between frailty and all-cause (**A**) or cardiovascular (**B**) mortality.

Sensitivity Analysis

The sensitivity analysis (Table 3) performed by excluding participants who died with a follow-up time of < 24 months also suggested a significantly increased all-cause or CVD-related mortality in prediabetic participants with frailty.

Discussion

Using nationally representative data, the present study showed that the frailty index was associated with elevated risks of both total and CVD mortality in individuals with prediabetes. Subgroup analysis showed that smoking status modified the association between frailty and CVD mortality.

Frailty is increasingly recognized as an important cause of markedly increased vulnerability to various adverse events, both in the general population and those with a wide range of medical conditions.[11,12] We are aware that the relationship between frailty and diabetes have been elucidated previously. Most researchers believe that the association between frailty and diabetes is bi-directional, in the sense that diabetes is involved in the development of frailty, and frailty may be an important driver of insulin resistance.[13] In an earlier meta-analysis, Hanlon et al showed that frailty was associated

Table 3 Sensitivity Analysis for the Associations Between Frailty Score, Frailty State and All-Cause or Cardiovascular Disease-Related Mortality in NHANES Participants with Prediabetes

	Crude Model		Model 1		Model 2	
All-cause mortality	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
Frailty score (every 0.01 point)	1.04 (1.03, 1.04)	<0.001	1.05 (1.04, 1.05)	<0.001	1.05 (1.04, 1.06)	<0.001
Frailty state (frailty vs non-frailty)	2.12 (1.84, 2.44)	<0.001	2.29 (1.97, 2.66)	<0.001	2.10 (1.74, 2.53)	<0.001
CVD mortality	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
Frailty score (every 0.01 point)	1.04 (1.03, 1.05)	<0.001	1.05 (1.04, 1.06)	<0.001	1.07 (1.05, 1.08)	<0.001
Frailty state (frailty vs non-frailty)	2.52 (2.00, 3.18)	<0.001	2.70 (2.09, 3.47)	<0.001	2.94 (2.13, 4.07)	<0.001

Notes: Model 1 was adjusted for participants' age, sex, educational level, marital status and poverty-income ratio; Model 2 was further adjusted for drinking, smoking, physical activity, total cholesterol, triglyceride, and high-density lipoprotein, in addition to covariates listed for Model 1.
Abbreviations: CI, confidence interval; HR, hazard ratio.

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with mortality in diabetics in 93% of studies.[14] Therefore, expert consensus recommends routine screening and assessment of frailty in the clinical management of elderly patients with diabetes.[15]

The associations between frailty and health outcomes in patients with prediabetes, to the best of our knowledge, have been rarely investigated. In the current study, prediabetic individuals with frailty were more likely to be female and had a higher prevalence of cardiovascular comorbidities. A meta-analysis by Gordon found that women had a higher frailty index than men in all age groups with longer lifespans, a phenomenon called the "frailty-mortality paradox".[16] The exact reasons for this sex difference are complicated and not fully understood. The significantly higher prevalence of cardiovascular morbidities is not surprising, as most of these are included in the calculation of the frailty index. Moreover, prior studies have indicated that frailty and CVD are interrelated, as those with CVD are more likely to be frail, and frail patients are at increased risk of developing various CVD.[17]

Our study demonstrated that even a 0.01 increase in the frailty risk was associated with a 4% and 5% increased risk of all-cause and CVD-related mortality, respectively, underscoring the critical importance of frailty assessment in prediabetic patients. A recent meta-analysis showed that frailty was associated with hypoglycemic events, microvascular and macrovascular complications, lower quality of life, and cognitive impairment in patients with diabetes.[14] Prediabetes serves as a critical stage for the early detection and intervention, as prediabetes is heterogeneous that can progress to overt diabetes or revert to normoglycemia. Interestingly, He et al showed that frailty, as defined by a 32-item frailty index, is an independent risk factor for the progression of prediabetes to diabetes.[6] Similarly, in an analysis of 38,950 prediabetic participants from the UK Biobank, Cao et al found that frailty, as defined by the Frailty Phenotype model, conferred a higher risk of progression to type 2 diabetes, CVD and all-cause mortality.[18]

Currently, the exact mechanisms underlying the associations between frailty, CVD and all-cause mortality are not completely understood. Undoubtedly, in addition to its role in the progression of prediabetes to diabetes, frailty is also associated with socioeconomic deprivation, lower health care utilization, and higher multi-morbidity, all of which may contribute to the elevated mortality in this patient population.[19] In addition, insulin resistance and inflammation, both hallmarks of prediabetes, have been linked to an increased risk of frailty through impaired muscle metabolism.[20]

Notably, subgroup analyses found that the smoking status modified the association between frailty and CVD mortality. The exact causes for current smoking to attenuate the association between frailty and CVD mortality remain poorly understood. Smoking has been demonstrated previously to be a potent risk factor for the development of various CVD and smoking cessation is beneficial in terms of reducing CVD mortality.[21] In addition, epidemiological and genetic studies have shown that smoking is a causal risk factor of frailty.[22] Therefore, a plausible explanation would be that current smoking may diminish the contribution of frailty to CVD mortality. Similarly, frailty would also modify the association between smoking and mortality, as frailer individuals are more susceptible to smoking-related mortality. Moreover, smoking cessation for over 10 years would minimize the mortality risk comparable to never smokers.[23]

The strength of our study lies in its national representativeness, large sample size, coupled with robust sensitivity analysis. More to the point, this study underscores that frailty assessment in prediabetic patients is also important in relation to patient mortality. Several limitations of this study should also be acknowledged. First, frailty status has been shown to be a dynamic process, and changes in frailty status might be more predictive of mortality than a simple assessment of frailty at baseline.[24] Second, there are currently a myriad of tools and operational definitions of frailty that can be broadly categorized into the frailty phenotype model and the deficit accumulation model.[25] Third, this retrospective analysis is unable to ascertain a causal relationship between frailty and mortality in prediabetic patients. It is recommended that prospective studies be conducted in the future to validate our findings and establish a cause-and-effect relationship between frailty and mortality in patients with prediabetes. Finally, although we have controlled for multiple covariates, the potential contributions of residual confounding or unmeasured factors cannot be completely excluded.

Conclusion

In conclusion, our study showed that the 49-item frailty index was positively associated with all-cause and CVD mortality in participants with prediabetes, highlighting that appropriate screening and management of frailty may help reduce mortality in patients with prediabetes.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical Approval and Consent to Participate

The study was approved by the Ethics Review Board of the National Center for Health Statistics, and all adult participants provided informed consent.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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