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Mortality Risk Along the Frailty Spectrum: Data from the National Health and Nutrition Examination Survey 1999 to 2004

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Abstract

OBJECTIVES—To determine the relationship between frailty and overall and cardiovascular mortality.

DESIGN—Longitudinal mortality analysis.

SETTING—National Health and Nutrition Examination Survey (NHANES) 1999–2004.

PARTICIPANTS—Community-dwelling older adults aged 60 and older (N = 4,984; mean age 71.1 ± 0.19, 56% female).

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article

MEASUREMENTS—We used data from 1999–2004 cross-sectional NHANES and mortality data from the National Death Index, updated through December 2011. An adapted version of Fried's frailty criteria was used (low body mass index, slow walking speed, weakness, exhaustion, low physical activity). Frailty was defined as persons meeting 3 or more criteria, prefrailty as meeting 1 or 2 criteria, and robust (reference) as not meeting any criteria. The primary outcome was to evaluate the association between frailty and overall and cardiovascular mortality. Cox proportional hazard models were used to evaluate the association between risk of death and frailty category adjusted for age, sex, race, smoking, education, coronary artery disease, heart failure, nonskin cancer, diabetes, and arthritis.

RESULTS—Half (50.4%) of participants were classified as robust, 40.3% as prefrail, and 9.2% as frail. Fully adjusted models demonstrated that prefrail (hazard ratio (HR) = 1.64, 95% confidence interval (CI) = 1.45–1.85) and frail (HR = 2.79, 95% CI = 2.35–3.30) participants had a greater risk of death and of cardiovascular death (prefrail: HR = 1.84, 95% CI = 1.45–2.34; frail: HR = 3.39, 95% CI = 2.45–4.70).

CONCLUSION—Frailty and prefrailty are associated with increased risk of death. Demonstrating the association between prefrail status and mortality is the first step to identifying potential targets of intervention in future studies.

Keywords

frailty; prefrailty; mortality; cardiovascular

Frailty is a decline in the body's physiological reserve and a reduced ability to maintain homeostasis among life's constant stressors.[1] It has been associated with functional losses, disability, greater healthcare use, and higher healthcare costs.[2–7] Although a standardized definition of frailty has not been agreed upon, its concept has evolved to be a complex relationship of physical, psychological, and social factors.[7] Fried's landmark study demonstrated a way to operationalize frailty collectively as a phenotype defined according to a set of variables: unintentional weight loss, self-reported exhaustion, slow gait speed, low energy expenditure and weak grip strength (frail ≥3; prefrail 2).[8] By this definition the prevalence of frailty is estimated to be 10.7% while prefrailty is 41.6% in community-dwelling older adults.[9] It is thought that prefrailty has similar associations with the negative outcomes of frailty. As frailty is a dynamic process, prefrail individuals are more likely to maintain prefrail status or revert back to a robust state than frail individuals.[10] This makes prefrailty an intermediary, possibly reversible phase that should be investigated separately from frailty in its associations and potential interventions.

Frailty is a known risk factor for mortality.[11–14] A metaanalysis demonstrated 50% greater mortality in individuals with frailty than in robust subjects and that this risk escalates with each additional phenotypic frailty component.[15] Frailty is also thought to have quadruple the risk of cardiovascular mortality,[16] but evidence of prefrailty's association with overall and cardiovascular mortality is less clear, with conflicting studies demonstrating various relationships between prefrailty and survival. The aim of this study was to evaluate mortality in prefrail individuals to determine whether it is an important entity in itself. We

hypothesized that the risk of all-cause and cardiovascular death in prefrail individuals would be significantly greater than robust participants.

METHODS

Study Design and Participants

Participants included in the analysis were identified from the 1999 to 2004 cross-sectional National Health and Nutrition Survey (NHANES). NHANES is a multistage probability survey conducted by the National Center for Health Statistics designed to assess the health and nutritional status of adults and children in the United States. The survey focuses on noninstitutionalized persons and oversamples non-Hispanic blacks, Mexican Americans, and persons aged 60 and older. Full details are available at http://www.cdc.gov/nchs/nhanes.html.

The total sample in NHANES consisted of 38,077 participants. Of these, 29,402 were interviewed and examined in a mobile examination center. We aimed to include only those aged 60 and older (n = 7,729) who had full body composition data (n = 4,984) in our secondary analysis. Trained field staff interviewed participants in English or Spanish, and data collection was automated. Respondents completed questionnaires directly or, if unable, by proxy. The local institutional review board at Dartmouth college exempted this study from review because of the de-identified nature of the data.

Mortality Data

Mortality was evaluated using the 2015 public-use linked mortality files, which include mortality data from the time of the study through December 31, 2011. These data were obtained from the National Death Index, a service of the National Center for Health Statistics that serves as a centralized database of death record information in state vital statistics offices. These data are linked to the NHANES data using a unique study identifier. Full details are available at https://www.cdc.gov/nchs/ndi/index.htm. Time to death was calculated in days from the date of death, and overall and cardiovascular mortality were assessed. Cardiovascular mortality was defined using *International Classification of Disease* codes.

Study Variables

We applied the Fried definition of frailty to our study sample using data from participant self-reported questionnaires and objective measures. The 5 criteria of frailty from the Cardiovascular Health Study[8,17] were adapted, as has been done previously with NHANES data[18]: unintentional weight loss of 10 pounds or more in a year: low body mass index (BMI)<18.5 kg/m^2; self-reported exhaustion: difficulty walking between rooms; weakness: difficulty lifting or carrying 10 lbs; slow walking speed: gait speed <0.8 m/s; and low physical activity: reduced physical activity compared to others your age. Frailty was defined as meeting 3 or more of the five criteria, prefrailty as meeting 1 or 2 criteria, and robust as meeting 0 of the 5 criteria.

Covariates

Demographic variables included self-reported age, sex, race, marital status, education, smoking status, and ethnicity. We categorized respondents as non-Hispanic white, non-Hispanic black, Hispanic, or other. We ascertained self-reported comorbidities such as diabetes, arthritis, coronary artery disease, congestive heart failure, and non-skin cancer if participants answered the question "Has a doctor ever told you have [disease state]?" Participants were classified as smokers if they had smoked at least 100 cigarettes in their lifetime.

Weight was measured in kilograms on an electronic digital scale. Height was measured using a stadiometer. Subjects were asked a number of self-perception questions regarding limitations in activities of daily living (ADLs) and instrumental activities of daily living (IADLs). All activities were self-reported, and subjects noted on scale from 1 to 4 their degree of difficulty in performing these tasks. We classified subjects as having difficulty if they indicated a response of anything other than "no difficulty." Of the 7 well-accepted IADLs,[19] NHANES included managing money, performing household chores, preparing meals, and handling routine needs. We defined ADL disability as difficulty getting in and out of bed or inability to dress or eat. NHANES did not include assessment of bathing or toileting.[20]

Statistical Analysis

All data were merged into one file for this analysis. All analyses accounted for the complex, stratified nature of NHANES and incorporated primary sampling units, weighting, and strata, according to analytical guidelines. Continuous variables are represented as means and standard errors and categorical variables as counts and weighted percentages. Analysis of variance and chi-square tests were used to assess differences in baseline characteristics according to frailty group. Because gait speed was not assessed in NHANES 2003–04, we used multiple imputation analyses to account for missing values. Multiple imputations were conducted using R version 3.3.2 and the package *mice*, which operates by creating plausible data values from a distribution specifically designed for each data point. We generated 5 imputed data sets using predictive mean matching. The correction variables used were age, sex, education, protein, race, diabetes, arthritis, congestive heart failure, cancer, and lean mass percentage. The 5 data sets were averaged, resulting in a final imputed data set used for analysis. To test the quality of the imputation, analyses were run on the full imputed data set and on a subset excluding the imputed variables.

The primary outcome was mortality risk, and the primary predictor was frailty category. Three separate Cox proportional hazard models were created to evaluate the risk of death. Model 1 was unadjusted and included frailty categories as the sole predictors; Model 2 included age, sex, race, education, and smoking; and Model 3 included the covariates in Model 2 and additionally adjusted for comorbidities such as diabetes, heart failure, cancer, coronary artery disease, and arthritis. All-cause and cardiovascular mortality were assessed and are presented in the results as hazard ratios (HRs) with 95% confidence intervals (CIs). Kaplan-Meier survival curves for overall and cardiovascular mortality are presented in Figure 1. As an exploratory analysis, mortality modeling was stratified according to age

group (60–69, 70–79, ≥80). As a comparison to our imputed gait speed model, frailty rates were calculated using a 4-component model by removing the gait speed criteria: robust meeting 0 criteria, prefrail meeting 1–2 criteria, frail meeting 3–4 criteria. The above models were replicated (not shown). Data analysis was conducted using Stata version 12 (Stata Corp., College Station, TX). $P < .05$ was considered statistically significant.

RESULTS

The mean age of the selected study sample of 4,984 participants was 71.1 ± 0.19, and they had a mean BMI of 28.2 ± 0.10 kg/m^2. The majority of the participants were non-Hispanic white (Table 1). Participants with higher frailty status were more likely to be female, have a higher BMI, and be older. Frail and prefrail participants were more likely to have concurrent comorbidities such as diabetes, coronary artery disease, arthritis, stroke, chronic kidney disease, and chronic obstructive pulmonary disease and significantly more likely to have dysfunction in at least one IADL or ADL. There were few observed differences in baseline characteristics between those with complete frailty variable data and those without complete frailty data. Those with incomplete data were slightly older, had lower BMI, and more ADL and IADL limitations at baseline (Table S1).

Table 2 presents a breakdown of each frailty component; the number of components participants in the study fulfilled; and overall rates of participants who were robust, prefrail, and frail. Robust and frail rates differed between our 5- and 4-component models mostly at the extremes, with 50.4% and 65.4% classified as robust and 9.2% and 4.5% as frail, respectively. The frailty component seen at the highest rate was low walking speed (31.3%), followed by weakness (27.1%). Few participants met all 5 criteria (<1%).

Over the course of follow-up 1,901 participants died, with 521 (27.4%) dying from cardiovascular causes. Median follow-up time was 95.8 months (interquartile range 78–124). Overall and cardiovascular mortality analyses along the frailty spectrum are outlined in Table 3. The adjusted models suggest a 64% higher mortality rate (HR = 1.64, 95% CI = 1.45–1.85) in prefrail individuals than in those who were robust and a rate nearly 3 times as high in frail individuals (HR = 2.79, 95% CI = 2.35–3.30). Similar estimates were observed for cardiovascular mortality (prefrail: HR = 1.84, 95% CI = 1.45–2.34; frail: HR = 3.39, 95% CI = 2.45–4.70). Figures 1 and 2 depict the Kaplan Meier survival curves for overall mortality and cardiovascular mortality. As an exploratory analysis, we stratified trail participants mortality rates according to age group (Table S2). Prefrailty rates and overall mortality according to age group demonstrated a trend toward greater risk than robust for all geriatric age groups (60–69: HR = 1.65, 95% CI = 1.31–2.09; 70–79: HR = 1.77, 95% CI = 1.45–2.17; ≥80: HR = 1.57, 95% CI = 1.28–1.92). We found similar results examining prefrailty and cardiovascular mortality compared to robust (60–69: HR = 1.52, 95% CI = 0.95–2.44; 70–79: HR = 2.42, 95% CI = 1.61–3.65; ≥80: HR = 1.88, 95% CI = 1.25–2.81).

DISCUSSION

This study demonstrates that, although frailty has a larger association with overall and cardiovascular mortality than prefrailty, the association between prefrailty and mortality is

meaningful and noteworthy. Specifically, prefrail participants were 64% more likely than robust participants to die.

Few studies have focused on the relationship between prefrailty and mortality. A systematic review[15] evaluating the association between mortality and frailty did not examine the relationship specifically with prefrailty. The Cardiovascular Health Study demonstrated the relative risk of mortality in prefrail individuals over a 4 year time period to be 1.67, (95% CI = 1.29–2.15),[17] and another study[21] that evaluated men aged 65 and older found prefrail participants were 36% more likely to die than robust individuals. Other studies such as the Crystal study[22] and The Three-City Study[6] challenge this association, with their findings failing to show statistically significant greater mortality in prefrail participants, making this relationship unclear.

Evidence for a strong association between frailty and cardiovascular disease exist while prefrailty's relationship is less defined.[11,23–26] The Progetto Veneto Anziani Study found that low energy expenditure, exhaustion, and slow gait speed were predictive of new cardiovascular events, and prefrailty appeared to be an independent predictor of cardiovascular disease.[25] A metaanalysis examining the relationship between frailty and mortality found that prefrail participants were 3 times as likely to die from cardiovascular disease over a median 4.4-year follow-up,[16] although that analysis was based on 2 studies not representative of community-dwelling elderly adults; one focused on posthospital discharge mortality after a myocardial infarction,[24] and the other evaluated individuals without baseline cardiovascular disease.[25]

Determining this association is important in clarifying prefrailty as an important diagnostic entity in itself versus another early disease state. Although some preconditions such as prehypertension have been well defined, no association has been found between prehypertension and overall mortality.[27] This is unlike other precondition states such as prediabetes, for which a metaanalysis demonstrated an associated greater risk of all-cause and cardiovascular mortality when defined according to fasting glucose as low as 5.6 mmol/L.[28] This demonstrates that not all preconditions are equal in their associated risks.

Another important argument for early recognition of prefrailty outside its own associated risks is its higher likelihood of reversibility. One study of the transitions of frailty found that 57.6% of participants had at least one transition in the 54-month follow-up.[10] Transition to greater frailty was 43.3%, versus 23% to less frailty. Rates of transition from frail to robust were negligible (≤0.9%), and the longer participants were classified as frail, the greater their chance of remaining frail and the higher their mortality, but if participants entered the study prefrail, the chances of remaining prefrail or transitioning to robust over 36 months was 78.4%. Those starting prefrail had higher rates of transitioning back to robust in the first 36 months, although chances were lower, and mortality was greater for those remaining prefrail over this 54-month period. This demonstrates that recognizing prefrailty and intervening reduces not only the chances of frailty progression, but also the higher mortality risk of remaining prefrail.

Our study of a large, nationally representative sample provides further support for a significant association between mortality and prefrailty. These results highlight the importance of identifying individuals across the frailty spectrum. Few studies have explored the most mutable risk factors aimed at preventing transitions to higher frailty states. One trial[29] assessed the effect of an exercise and nutritional intervention on quality of life and physical performance over 12 weeks in prefrail women. Significant improvements in handgrip strength, subjective pain, and emotional well-being with exercise were observed but not maintained at 6-month follow-up. A larger study, the Lifestyle Interventions and Independence for Elders Pilot Study,[30] completed over 12 months, examined older adults at risk of disability and demonstrated that 150 min/wk of activity plus balance training led to faster walking speed. These studies indicate that interventions can reverse prefrailty, but studies showing maintenance of these benefits over time are lacking.

Our study had a number of strengths, including large sample size and use of self-reported and biometric measurements and of a validated tool for frailty classification, which makes our findings relevant. Or study also had several important limitations. First, the variables present in NHANES to operationalize Fried's frailty criteria required us to modify some of the original definitions, but the prevalence rates of each component were comparable with those in other studies.[8,15,31] Second, because walking speed was missing for 3,645 participants, we performed multiple imputations to maximize our data analysis. We used multivariate imputation by chained equations for our missing data, a robust method that generates multiple predictions for each missing value, taking the uncertainty of the imputations into account and yielding accurate standard errors.[32] We did not use data without imputed gait speed for conclusion data, but baseline characteristics of those with gait speed information were compared with characteristics of those with imputed gait speed to show that they were similar populations. Third, a number of the frailty components are based on self-reported data and are subject to recall bias. Fourth, although we demonstrated greater mortality risk by age, we caution the reader on generating conclusions from this data because of the sample sizes in the age subgroups. Because our study sample included only community-dwelling adults, this could have led to some selection bias, particularly for those aged 80 and older, which probably made our results more conservative than if institutionalized elderly adults had been included. Also, because of the increasing literature on the association between valvular heart disease and frailty, we caution the reader on the limitation of our dataset to correct for this variable in our analysis.[33,34] In addition, medical care and culture have changed since early the 2000s, and mortality rates continue to decline from heart disease, stroke, and cancer, whereas diabetes and obesity rates have increased, according to several U.S. studies.[35,36] The decline in rates cardiovascular mortality seems to have slowed, probably because of incremental advances in prevention and treatment, along with the increasing aging population's high on rates of heart disease and mortality.[37,38] A limitation in Fried's frailty model is its lack of cognitive and psychosocial factors in determining frailty status. There is increasing evidence that inclusion of these factors could improve predictive ability for adverse health outcomes.[39] The deficit accumulation model that Rockwood and colleagues defined encompasses cognitive changes as part of defining frailty. Although frailty rates vary according to definition (9.9% for physical frailty and 13.6% for physical and psychosocial frailty),[9] when evaluating mortality, as we aimed to do

here, both models have shown comparable results.[40,41] Lastly, with any epidemiology-based analysis, causality cannot be inferred, and future longitudinal, interventional studies are needed.

The large number of prefrail and frail individuals will continue to grow as our society continues to age.[42] Prefrailty and frailty should be ascertained because an estimated 3% to 5% of deaths of older adults could be delayed with frailty prevention.[43] The implementation of interventions targeting the most common deficits in the frailty spectrum (gait speed and weakness) has a large potential to improve function: reduce hospitalization, institutionalization, and unneeded healthcare spending while improving quality of life.[8,15,26] Recognizing prefrailty as its own entity is essential because of its association with overall and cardiovascular mortality, as well as its window of opportunity for reversibility in delaying frailty progression. Knowledge of prefrailty's association of mortality allows providers to see the value of aggressive primary and secondary prevention through optimizing medication management and health promotion efforts. With this relationship known, research efforts can examine potential interventions and their ability to improve long-term outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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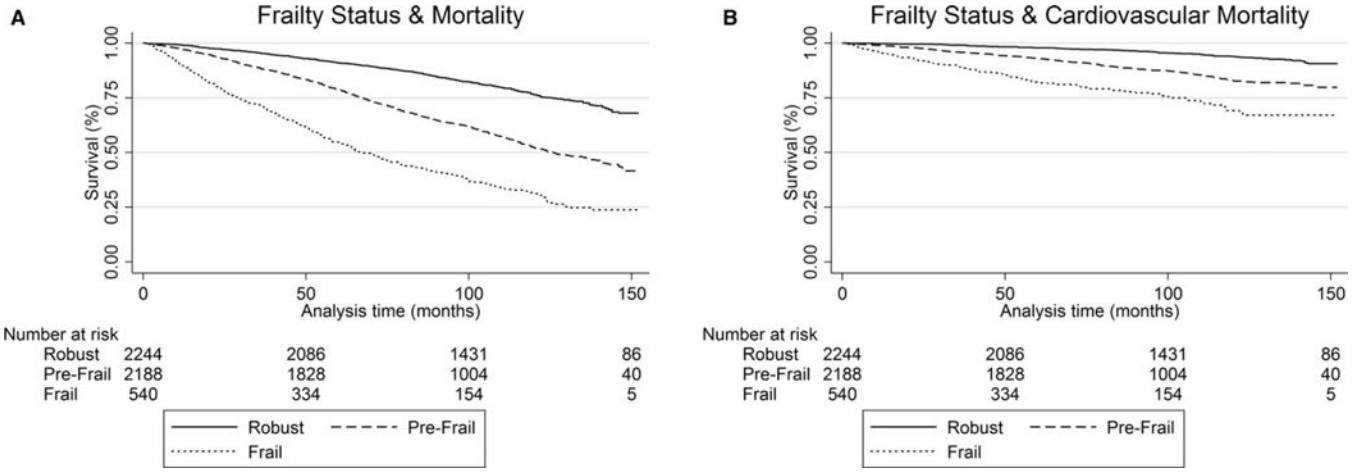

Figure 1.

Kaplan Meier survival curve for (A) all-cause and (B) cardiovascular mortality of robust, prefrail, and frail participants demonstrating a significant trend toward greater death from all-cause and cardiac causes with greater frailty status.

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Table 1

Participant Baseline Characteristics

Characteristics	Total, N = 4,984	Robust, n = 2,246	Prefrail, n = 2,195	Frail, n = 541	P-Value
Age, mean (SE)	71.1 (0.19)	68.7 (0.22)	73.3 (0.23)	74.9 (0.45)	<.001
Sex, n (%)					
Female	2,531 (56.6)	949 (47.2)	1,244 (65.6)	336 (68.1)	<.001
Male	2,453 (43.5)	1,297 (52.8)	951 (34.4)	205 (31.9)	<.001
Race and ethnicity, n (%)					<.001 *
Non-Hispanic white	2,846 (81.2)	1,387 (86.1)	1,203 (77.4)	256 (70.5)	
Non-Hispanic black	811 (8.3)	281 (5.5)	403 (10.3)	127 (15.8)	
Hispanic	1,202 (7.2)	533 (5.9)	522 (8.1)	146 (10.8)	
Other	125 (3.2)	45 (2.4)	67 (4.2)	12 (3.0)	
≥College education, n (%)	1,676 (40.6)	986 (50.4)	585 (32.3)	105 (23.4)	<.001
Smoker, n (%)					.02 *
Never	2,327 (46.7)	1,004 (44.2)	1,052 (49.1)	271 (50.3)	
Former	2,035 (41.4)	948 (43.9)	889 (39.6)	198 (35.5)	
Current	611 (11.9)	288 (11.9)	254 (11.4)	69 (14.3)	
Body mass index, kg/m^2, mean (SE)	28.2 (0.10)	27.8 (0.12)	28.3 (0.18)	30.7 (0.49)	<.001
≥1 activity of daily living limitations	2,423 (47.3)	576 (25.3)	1,320 (63.5)	527 (96.8)	<.001
≥1 instrumental activity of daily living limitations	1,751 (32.6)	248 (10.2)	988 (46.4)	515 (94.5)	<.001
Comorbidities, n (%)[a]					
Diabetes mellitus	1,060 (18.3)	356 (13.2)	499 (21.0)	205 (34.5)	<.001
Heart failure	373 (7.1)	47 (1.9)	211 (10.1)	115 (22.9)	.34
Nonskin cancer	916 (21.7)	418 (22.1)	395 (20.8)	103 (22.9)	.49
Coronary artery disease	870 (18.3)	297 (14.2)	421 (20.1)	152 (30.9)	<.001
Arthritis	2,379 (50.2)	786 (38.3)	1,228 (59.8)	363 (73.6)	<.001
Hypertension	2,326 (87.7)	892 (87.0)	1,123 (87.7)	311 (90.1)	.34
Stroke	405 (7.6)	101 (4.5)	192 (8.3)	112 (21.1)	<.001

Characteristics	Total, N = 4,984	Robust, n = 2,246	Prefrail, n = 2,195	Frail, n = 541	P-Value
Chronic obstructive pulmonary disease	496 (11.8)	130 (6.8)	269 (15.9)	97 (21.4)	<.001
Chronic kidney disease	81 (4.2)	22 (2.5)	39 (4.8)	20 (11.5)	.03

[a] Self-reported at initiation of screening.

SE = standard error.

* P value for overall in group.

Table 2

Frailty Components and rates

	Five-Component Model	Four-Component Model[a]
Frailty Components	**n (weighted %)**	
Difficulty walking between rooms	586 (10.0)	
Body mass index <18.5 kg/m^2	59 (1.3)	
Less activity than peers	735 (14.1)	
Gait speed <0.8 m/s[b]	1,865 (31.3)	n/a
Difficulty lifting 10 pounds	1,455 (27.1)	
Number of components		
0	2,246 (50.4)	3,063 (67.0)
1	1,486 (27.7)	1,026 (21.7)
2	709 (12.6)	414 (7.8)
3	371 (6.4)	189 (3.4)
4	167 (2.7)	5 (0)
5	3 (0)	n/a
Frailty status		
Robust	2,246 (50.4)	3,158 (65.4)
Prefrail	2,195 (40.3)	1,561 (30.2)
Frailty	541 (9.2)	263 (4.5)

[a]Defining frailty according to 4-component model: robust = 0 criteria, prefrail = 1–2 criteria, frailty = 3–4 criteria.

[b]Imputed and nonimputed.

Table 3

Association Between Frailty and Overall and Cardiovascular Mortality

	Model 1	Model 2	Model 3
Mortality	**Hazard Ratio (95% Confidence Interval)**		
Overall			
Prefrail	2.40 (2.16–2.67)	1.79 (1.60–2.01)	1.64 (1.45–1.85)
Frail	4.97 (4.34–5.69)	3.89 (3.36–4.51)	2.79 (2.35–3.30)
Cardiovascular			
Prefrail	2.82 (2.28–3.48)	2.07 (1.65–2.60)	1.84 (1.45–2.34)
Frail	3.72 (2.85–4.87)	4.79 (3.61–6.34)	3.39 (2.45–4.70)

Model 1: unadjusted.

Model 2: adjusted for age, sex, race, education, smoking.

Model 3: adjusted for Model 2 covariates and diabetes, heart failure, cancer, coronary artery disease, arthritis.

Reference: robust.