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Accumulation of Deficits as a Key Risk Factor for Cardiovascular Morbidity and Mortality: A Pooled Analysis of 154 000 Individuals

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Background—Frailty is associated with higher mortality in individuals at high cardiovascular disease (CVD) risk. We hypothesize that frailty is a more important prognostic factor than CVD risk factors and aim to determine the prognostic value of a cumulative deficit frailty index in patients with or at high risk for CVD.

Methods and Results—We conducted an individual-level pooled analysis of participants with or at risk for CVD, recruited in 14 multicenter clinical trials. The cumulative deficit index was calculated as the proportion of 26 deficits exhibited. Individuals were categorized as nonfrail, prefrail, or frail if they had indexes of ≤0.1, >0.1 to 0.21, or >0.21, respectively. CVD risk was assessed using the Framingham score. Outcomes included CVD event (new or recurrent myocardial infarction, stroke, or heart failure) and mortality. We studied 154 696 patients (mean age, 70.8 years; 63% men) with median follow-up of 3.2 years. There were 17 535 CVD events and 15 067 deaths. The frail group (n=13 872) had higher risk of a CVD event (incidence rate ratio, 1.97; 95% CI, 1.85–2.08), all-cause mortality (hazard ratio, 1.91; 95% CI, 1.79–2.03), and CVD mortality (hazard ratio, 1.91; 95% CI, 1.77–2.05) than the nonfrail group (n=101 343). Associations remained unchanged after adjusting for CVD risk factors. The index statistically outperformed the Framingham score in its ability to discriminate CVD events (C-statistic, 0.60 [95% CI, 0.60–0.61] versus 0.58 [95% CI, 0.57–0.58], respectively; *P*<0.001).

Conclusions—In individuals with or at high risk of developing CVD, the cumulative deficit index is associated with increased CVD events and mortality, independent of CVD risk factors, and adds incremental prognostic value. (***J Am Heart Assoc***. 2020;9: e014686. DOI: 10.1161/JAHA.119.014686.)

Key Words: cardiovascular outcomes • deficit accumulation • frailty • mortality

Despite important advances in strategies to prevent the development of cardiovascular disease (CVD), and therapeutic strategies after the development of manifest CVD, CVD remains the leading cause of death worldwide. Traditional risk scores, such as the Framingham risk score, were developed decades ago, and although subsequently revised, these scores still feature traditional risk factors almost exclusively. However, we are witnessing a major epidemiologic shift because of the aging population. With aging, there is an increase in the proportion of individuals who survive with more morbid conditions. These conditions are closely associated with frailty, a multifactorial syndrome that may result in an increased vulnerability to stressors, such as an acute cardiovascular event.[1]

Multisystem dysfunction is an important indicator of frailty. Mitnitski et al have described an "accumulation of deficits" model of frailty, wherein symptoms, abnormal laboratory test results, and physical examination findings over multiple organ systems are combined to create a cumulative deficit frailty index.[2] Although studies to date have described an association between frailty and mortality in those with established CVD,[3,4] it is unknown whether being frail predisposes to CVD events and whether the increase in the risk of death observed among frail individuals is caused by CVD or other causes.

The objectives of this article are to do the following: (1) determine the prognostic value of a cumulative deficit frailty index and (2) understand how frailty, as measured by deficit accumulation, leads to premature mortality in patients with or at high risk of CVD. We will accomplish this by describing the relationship between the cumulative deficit index and

Clinical Perspective

What Is New?

- In patients with or at high risk for cardiovascular disease, nontraditional risk factor estimation using a cumulative deficit frailty index is associated with increased adverse cardiovascular events, independent of traditional risk factors.

What Are the Clinical Implications?

- Measuring frailty by deficit accumulation in high-risk patients adds incremental prognostic value to traditional risk scores.
- With an aging population, the burden of frailty is expected to increase, and researchers should consider incorporating measures of frailty when designing future clinical trials in cardiovascular disease.

CVD events, cardiovascular death, and noncardiovascular death.

Methods

Study Design and Participants

We conducted a participant-level pooled analysis of prospective clinical trials coordinated by the Population Health Research Institute, McMaster University (Hamilton, Canada). All studies conducted by the Population Health Research Institute that had individual patient data available for post hoc analysis were screened. Studies were included if they recorded cardiovascular and all-cause mortality as prespecified primary or secondary outcomes and had ≥6 months' follow-up. Fourteen studies were included: ACTIVE (Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events), APOLLO (Aliskiren Prevention Of Later Life Outcomes), AVERROES (Apixaban versus acetylsalicylic acid to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment), CURE (Clopidogrel in Unstable angina to prevent Recurrent Events), DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication), HOPE (Heart Outcomes Prevention Evaluation), HOPE-3, OASIS-5 (Fifth Organization to Assess Strategies in acute Ischemic Syndromes), ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial), ORIGIN (Outcome Reduction with an Initial Glargine INtervention), RE-LY (Randomized Evaluation of Long-term anticoagulation therapY), TIMACS (TIMing of intervention in Acute Coronary Syndrome), TRANSCEND (Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease), and WAVE (Warfarin Antiplatelet Vascular Evaluation).[5–18] The selected studies were all randomized controlled trials of various cardiovascular therapeutic strategies, and they were approved by respective institutional review boards. These trials primarily enrolled community-dwelling adults, with or at high risk for CVD. Three trials enrolled hospitalized patients presenting with acute coronary syndromes.[8,12,16] A description of each study is included in Table S1. The protocol of this study was approved by the Hamilton Integrated Research Ethics Board of McMaster University. Informed consent was obtained from participants at enrollment for use of their data in future research. Baseline and outcome data were collected using standard case report forms and were deidentified.

Cumulative Deficit Frailty Index

The cumulative deficit frailty index was constructed using an approach developed by Searle et al.[19] Variables included in the index were diseases, symptoms, signs, or laboratory measures. Each was age related, did not saturate too early (ie, not found in all individuals at an early age), was associated with adverse outcomes, and covered several bodily systems. Baseline visit case report forms were reviewed for all trials by one author (M.A.M.F.), and variables that met these criteria for use in the cumulative deficit index were extracted and reviewed by a second author (D.P.L.). A total of 34 variables were considered for the primary analysis. Of these variables, 8 were traditional CVD risk factors: history of myocardial infarction (MI), stroke, heart failure, diabetes mellitus, hypertension, peripheral arterial disease, elevated body mass index, and high cholesterol; these traditional CVD risk factors were not incorporated into the cumulative deficit index. Rather, the cumulative deficit index was constructed using the remaining 26 deficits that were not traditional CVD risk factors (Table S2). Each variable was polychotomized or dichotomized and mapped to the interval 0 to 1. For example, for the question, "rate your health," the response included excellent=0, very good=0.25, good=0.5, fair=0.75, and poor=1. The cumulative deficit index was calculated as a ratio of deficits present/the total number of deficits considered. Each study included common variables that were incorporated into the cumulative deficit index and included additional variables unique to the study that were also included in the cumulative deficit index. Table S2 details each cumulative deficit index variable and its score.

Outcomes

The primary outcomes were as follows: (1) CVD events (defined as new or recurrent MI, stroke, or hospitalization for heart failure, (2) mortality (CVD and non-CVD), and (3) CVD case fatality. MI was diagnosed when 2 of the following 3 criteria were present: typical symptoms, increased cardiac enzymes (at least twice the upper limit of normal), and diagnostic ECG

changes. Stroke was defined as a neurologic deficit lasting >24 hours that was confirmed on computed tomographic imaging. Hospitalization for heart failure required evidence of clinical and radiologic signs of congestion. CVD deaths were defined as follows: unexpected deaths presumed to be caused by ischemic CVD and occurring within 24 hours of symptom onset without evidence of another cause; deaths from MI or stroke that occurred within 7 days after the event; and deaths from congestive heart failure, dysrhythmia, pulmonary embolism, or ruptured abdominal aortic aneurysm. Secondary outcomes included nonfatal MI, nonfatal stroke, and hospitalization for heart failure. All outcomes were adjudicated by adjudicators blinded to the participant allocation. Adjudicators were trained to apply standardized outcome event definitions.

Statistical Analysis

Statistical analyses were performed using STATA, version 15 (Stata Corporation, College Station, TX). The cumulative deficit frailty index was expressed as both a continuous variable (in 0.1 increments) and was categorized into nonfrail, prefrail, and frail groups based on previously reported thresholds: nonfrail (cumulative deficit index ≤0.1), prefrail (0.10<cumulative deficit index≤0.21), and frail (cumulative deficit index >0.21).[20,21] Differences in baseline characteristics were compared between the groups using the χ^2 test for categorical variables, by analysis of variance for normally distributed continuous variables, and by the Kruskal-Wallis test for nonnormally distributed continuous variables. We estimated the risk of CVD events by calculating incidence rate ratios using Poisson regression. The relationship between the cumulative deficit index and mortality was evaluated by Kaplan-Meier time-to-event curves. Time-to-event models were constructed using Cox proportional hazards models. To mitigate within-study clustering, we used shared frailty models in our time-to-event analysis, in which the study was modeled as a random effect. The assumption of the proportionality of hazards was evaluated by visual inspection of the log-log plots. Adjustment in all models was made for age, sex, ethnicity, and smoking history. The relationship between the cumulative deficit index and the hazard ratio for death was displayed using a spline curve with 5 knots. CVD case fatality was calculated using the method of Ghani et al, wherein a parametric mixture model was used to estimate cumulative incidence and mortality statistics at single time points.[22] To determine the incremental prognostic value of the cumulative deficit frailty index, we performed 3 analyses: First, the primary analysis was further adjusted for the following traditional CVD risk factors: baseline history of MI, stroke, heart failure, diabetes mellitus, hypertension, peripheral arterial disease, elevated body mass index, and high cholesterol. Second, the respective C-statistics of the cumulative

deficit index and the Framingham risk score were compared using the method of Hanley and McNeil.[23] Third, population attributable risks were calculated to evaluate the impact of the cumulative deficit frailty index on mortality, compared with traditional CVD risk factors, such as smoking, hypertension, and the presence of CVD at baseline (defined as a history of MI or stroke).

To evaluate if missing data influenced the final results, a sensitivity analysis was performed excluding participants with <11 recorded frailty variables (the minimum number of variables considered appropriate to predict mortality when constructing a cumulative deficit frailty index[24]). In the sensitivity analysis, we also performed multiple imputation for hypercholesterolemia because hypercholesterolemia was not recorded in several trials per protocol. Subgroup analyses were performed for the following: age (stratified by tertile), sex, ethnicity, baseline CVD, and history of diabetes mellitus. The aggregate data that support the findings of this study are available from the corresponding author on request.

Results

Baseline Characteristics

In total, 154 696 participants (37% women; mean age, 70.8 years) were included in the analysis: 101 343 participants (65.5%) were classified as nonfrail, 39 481 participants (25.5%) were classified as prefrail, and 13 872 participants (9.0%) were classified as frail. The median (25th–75th percentile) cumulative deficit score was 0.056 (0.014–0.13). Baseline CVD was present in 46 685 participants (32.0%). The median Framingham risk score was similar in all 3 groups (median [IQR], 17 [14–20]; 17 [14–21]; and 17 [13–20] for nonfrail, prefrail, and frail, respectively). *P* values for trend were <0.01 for all baseline variables, indicating consistent differences between the nonfrail, the prefrail, and the frail groups for all covariates collected. Participants' baseline characteristics are described in Table 1.

Accumulation of Deficits and CVD Event Risk

The median (25th–75th percentile) follow-up duration was 3.2 (1.0–5.0) years. MI occurred in 6408 participants (4.5% of cohort; 2088 of these [33%] were fatal MIs), stroke occurred in 5249 participants (3.7% of cohort; 1903 of these [36%] were fatal strokes), and heart failure occurred in 5878 participants (5.0% of cohort; 2369 of these [40%] were fatal events) throughout the follow-up period. Unadjusted analyses are shown in Table S3. Participants classified as frail were 1.97 (95% CI, 1.85–2.08) times more likely to have a CVD event and 2.69 (95% CI, 2.43–2.97) times more likely to have a fatal CVD outcome compared with nonfrail participants,

Table 1. Baseline Characteristics

Characteristics	Nonfrail	Prefrail	Frail
Total	101 343 (65.5)	39 481 (25.5)	13 872 (9.0)
Age, y	69.7±9.6	72.1±9.4	74.6±9.3
Female sex	32 907 (32)	16 759 (42)	7289 (53)
Ethnicity			
White	65 432 (66)	26 744 (69)	9683 (73)
East Asian	11 817 (12)	3222 (8)	790 (6)
South Asian	4705 (5)	1742 (5)	432 (4)
Black	1572 (2)	796 (2)	239 (2)
Latino	12 097 (12)	4985 (13)	1386 (10)
Other	2351 (3)	1245 (3)	706 (5)
Highest level of education			
No school	2731 (4)	1514 (5)	432 (7)
Primary school	21 449 (31)	9023 (32)	2214 (33)
Secondary school	21 055 (30)	8241 (29)	1967 (29)
Trade school	10 330 (15)	3572 (13)	773 (11)
College/university	13 805 (20)	5797 (21)	1369 (20)
Smoking history			
Never smoker	40 940 (43)	16 469 (45)	6057 (48)
Ex-smoker	38 895 (40)	15 403 (42)	5281 (42)
Current smoker	16 573 (17)	4939 (13)	1299 (10)
Alcohol intake			
<1 Drink/wk	34 853 (67)	18 467 (68)	7090 (70)
>1 Drink/wk	16 848 (33)	8756 (32)	3062 (30)
Myocardial infarction	25 044 (26)	8297 (22)	2787 (21)
Stroke	7944 (8)	3871 (10)	1647 (12)
Heart failure	7062 (17)	5674 (28)	3518 (34)
Diabetes mellitus	27 063 (27)	11 839 (31)	4770 (35)
Cancer	798 (1)	4019 (11)	3094 (25)
BMI, kg/m^2	28.1±4.9	28.6±5.7	29.0±6.2
Systolic BP, mm Hg	137±19	135±21	131±21
Resting heart rate, bpm	70±12	73±16	77±17
Creatinine, μmol/L	88 (75–101)	88 (76–106)	96 (80–120)
Total cholesterol, mmol/L	5.3±3.1	5.2±1.2	5.3±4.4
Cognitive function			
MMSE score	29 (26–30)	28 (25–30)	28 (24–29)
Cardiovascular risk			
Framingham risk score	17 (14–20)	17 (14–21)	17 (13–20)
Patients classified as high risk on the basis of the Framingham risk score (>30% 10-y CVD risk)	44 070 (44)	16 059 (40)	4718 (34)

Data presented as mean±SD, median (interquartile range), or count (column percentage), unless otherwise noted. *P* value for trend was <0.01 for all baseline characteristics from ANOVA (for continuous normally distributed variables), the Kruskal-Wallis test (for continuous nonnormally distributed variables), or the χ^2 test (for dichotomous variables). Percentage represents column percentage. BMI indicates body mass index; BP, blood pressure; bpm, beats per minute; CVD, cardiovascular disease; MMSE, Mini-Mental State Examination.

Table 2. CVD Events Adjusted for Baseline Characteristics and CVD Risk Factors

Variables	Model	Nonfatal Outcome			Fatal Outcome			Fatal or Nonfatal Outcome		
		Nonfrail	Prefrail	Frail	Nonfrail	Prefrail	Frail	Nonfrail	Prefrail	Frail
Myocardial infarction	A	1	0.85 (0.79–0.91)	0.69 (0.61–0.78)	1	0.98 (0.87–1.11)	1.34 (1.14–1.56)	1	0.88 (0.83–0.94)	0.86 (0.78–0.95)
	B	1	1.05 (0.95–1.16)	1.17 (0.97–1.42)	1	1.32 (1.06–1.65)	2.12 (1.57–2.87)	1	1.09 (0.99–1.20)	1.36 (1.16–1.59)
Stroke	A	1	1.24 (1.14–1.34)	1.32 (1.18–1.48)	1	1.45 (1.28–1.64)	1.73 (1.47–2.04)	1	1.29 (1.21–1.38)	1.44 (1.31–1.58)
	B	1	1.21 (1.06–1.39)	1.25 (0.98–1.59)	1	1.73 (1.21–2.49)	1.78 (1.00–3.15)	1	1.27 (1.12–1.44)	1.31 (1.04–1.63)
Heart failure	A	1	1.50 (1.39–1.62)	1.87 (1.66–2.11)	1	1.69 (1.51–1.89)	2.76 (2.37–3.22)	1	1.58 (1.48–1.69)	2.31 (2.10–2.53)
	B	1	1.37 (1.21–1.55)	1.80 (1.49–2.18)	1	1.57 (1.17–2.10)	2.46 (1.66–3.63)	1	1.40 (1.25–1.56)	1.91 (1.61–2.26)
Any CVD event	A	1	1.27 (1.20–1.32)	1.59 (1.48–1.71)	1	1.54 (1.43–1.66)	2.69 (2.43–2.97)	1	1.35 (1.30–1.41)	1.97 (1.85–2.08)
	B	1	1.17 (1.09–1.25)	1.33 (1.18–1.51)	1	1.46 (1.23–1.73)	2.27 (1.80–2.89)	1	1.20 (1.13–1.29)	1.48 (1.16–1.65)

Incidence rate ratios and 95% CIs for nonfatal and fatal myocardial infarctions, strokes, heart failure, and combined cardiovascular events. Model A represents adjustment made for age, sex, ethnicity, and smoking history. Model B represents adjustment made for baseline characteristics (age, sex, ethnicity, and smoking history) and traditional cardiovascular disease risk factors (history of myocardial infarction, stroke, heart failure, diabetes mellitus, hypertension, peripheral arterial disease, elevated body mass index, and high cholesterol). CVD indicates cardiovascular disease.

after adjusting for age, sex, ethnicity, and smoking history (Table 2). The cumulative deficit index discriminates fatal CVD events more strongly than nonfatal events; incident rate ratio for fatal events was 2.69 (95% CI, 2.43–2.97) versus 1.59 (95% CI, 1.48–1.71) for nonfatal events. A graded relationship was seen in prefrail patients for all CVD events, except nonfatal MIs, which were less likely to occur in frail patients. The additional adjustment for traditional CVD risk factors did attenuate the effect size; however, frailty was still predictive for incident events (Table 2). The respective incident rate ratios for any CVD event and for fatal CVD were 1.48 (95% CI, 1.33–1.65) and 2.27 (95% CI, 1.80–2.89), respectively.

Accumulation of Deficits and Mortality

Death occurred in 15 067 participants (9.7%) during the 3.2 years' follow-up. Of these deaths, 9432 (62.6%) were cardiovascular and 5639 (37.4%) were noncardiovascular. The overall, CVD, and non–CVD mortality rates per 100 person–years were 3.2 (95% CI, 3.2–3.3), 2.0 (95% CI, 2.0–2.1), and 1.2 (95% CI, 1.2–1.2), respectively. After a CVD event (new or recurrent MI, stroke, or heart failure), the case-fatality rates at 3.2 years in the nonfrail, prefrail, and frail groups were 26.3% (95% CI, 25.3%–27.2%), 33.0% (95% CI, 31.5%–34.5%), and 41.7% (95% CI, 39.2%–44.2%), respectively. In the frail group, the age-, sex-, ethnicity-, and smoking history–adjusted hazard ratios for all-cause mortality, CVD mortality, and non–CVD mortality were 1.91 (95% CI, 1.79–2.03), 1.91 (95% CI, 1.77–2.05), and 1.90 (95% CI, 1.71–2.10), respectively. These associations were unchanged after adjusting for 8 traditional CVD risk factors (Table 3). Kaplan-Meier survival curves for all-cause and CVD and non–CVD mortality are shown in Figure 1. A monotonic relationship was seen between the cumulative deficit frailty index and death (Figure 2).

Additional Prognostic Value of the Cumulative Deficit Frailty Index

The frail group, which accounted for 9% of the study cohort, had a population attributable risk of death of 19.3% (95% CI, 18.4%–20.2%) and of cardiovascular death of 19.4% (95% CI, 18.3%–20.4%). In comparison, the presence of individual CVD risk factors at baseline had a smaller impact on rates of death. The population attributable risk of death for smoking was 8.68% (95% CI, 2.70%–14.3%); for hypertension, it was 11.6% (95% CI, 1.98%–20.2%); and for the presence of CVD at baseline, it was 7.89% (95% CI, 8.60%–21.8%). Similar results were seen for cardiovascular mortality (Table S4). Population attributable risk of death for the prefrail group was 6.7% (95% CI, 5.9%–7.6%). The cumulative deficit frailty index exhibited greater discriminatory performance to the Framingham risk score for incident CVD events (C-statistic, 0.60 [95% CI,

Table 3. Hazard Ratios for Mortality Outcomes

Frailty Status	Unadjusted			Adjusted for Baseline Characteristics			Adjusted for Baseline Characteristics and Traditional CVD Risk Factors		
	All-Cause Mortality	Cardiovascular Mortality	Noncardiovascular Mortality	All-Cause Mortality	Cardiovascular Mortality	Noncardiovascular Mortality	All-Cause Mortality	Cardiovascular Mortality	Noncardiovascular Mortality
Frailty index (per 0.1-unit increase)	1.46 (1.44–1.48)	1.44 (1.40–1.46)	1.50 (1.46–1.54)	1.27 (1.24–1.29)	1.26 (1.23–1.29)	1.28 (1.24–1.33)	1.35 (1.28–1.41)	1.32 (1.25–1.40)	1.43 (1.29–1.60)
Nonfrail	1	1	1	1	1	1	1	1	1
Prefrail	1.48 (1.43–1.53)	1.46 (1.40–1.53)	1.50 (1.42–1.59)	1.27 (1.21–1.32)	1.24 (1.18–1.32)	1.30 (1.21–1.40)	1.41 (1.27–1.57)	1.39 (1.23–1.57)	1.50 (1.24–1.83)
Frail	2.81 (2.68–2.95)	2.79 (2.62–2.96)	2.86 (2.64–3.10)	1.91 (1.79–2.03)	1.91 (1.77–2.05)	1.90 (1.71–2.10)	2.18 (1.89–2.51)	2.06 (1.76–2.42)	2.60 (1.92–3.52)

Unadjusted and adjusted hazard ratios with 95% CIs using shared frailty models. Baseline characteristics included in the initial adjustment model: age, sex, ethnicity, and smoking history. Cardiovascular disease risk factors included in the subsequent adjustment model: history of myocardial infarction, stroke, heart failure, diabetes mellitus, hypertension, peripheral arterial disease, elevated body mass index, and high cholesterol. CVD indicates cardiovascular disease.

0.60–0.61] versus 0.58 [95% CI, 0.57–0.58], respectively; $P<0.001$). Combining the cumulative deficit frailty index and the Framingham risk score improved discrimination further (C-statistic, 0.66; 95% CI, 0.66–0.67). These data indicate that the cumulative deficit index and the Framingham risk score provide complementary and additional information and that the 2 together are likely to provide better discriminatory value than either 1 of the 2 approaches.

Subgroup and Sensitivity Analysis

There was a significant interaction between the cumulative deficit index and age, sex, smoking status, and diabetes mellitus with respect to mortality. The index was associated with increased mortality in all subgroups. However, the risk of death among the frail group was highest among those aged <65 years, smokers, and Asians (Figure 3). Further analyses of these subgroups revealed that they were more likely to die from cardiovascular deaths if frail compared with their counterparts. Subgroup analysis using the cumulative deficit index per 0.1-unit increase is included in Figures S1 and S2. The sensitivity analysis excluding patients with <11 frailty variables demonstrated that the cumulative deficit frailty index was still predictive of incident or recurrent CVD events and mortality (Tables S5 and S6).

Discussion

Our results show that in adults with or at high risk of developing CVD, a cumulative deficit frailty index that does not contain any traditional CVD risk factors is associated with adverse CVD outcomes and provides incremental prognostic value to traditional CVD risk factors. Individuals identified as frail using this index were almost twice as likely to develop incident or recurrent CVD, had a 59% relative risk increase in fatality rates if a CVD event occurs, had a 1.6-fold increase in non-CVD mortality, and had a 1.7-fold increase in CVD mortality. An intermediate relationship was seen in prefrail participants, with risks of these outcomes between those of frail and nonfrail individuals.

Relationship Between Deficit Accumulation, Frailty, and CVD Events

Previous studies have shown conflicting results about the relationship between frailty and CVD events. One observational study of 5294 community-dwelling adults (mean age, 71 years; 56% women) from the ELSA (English Longitudinal Study of Ageing) found that a deficit accumulation frailty model using a 40-item index was not significantly associated with CVD events over 7 years (sex-adjusted hazard ratio, 1.7; 95% CI, 0.8–3.4).[25] In this study, CVD events were defined as
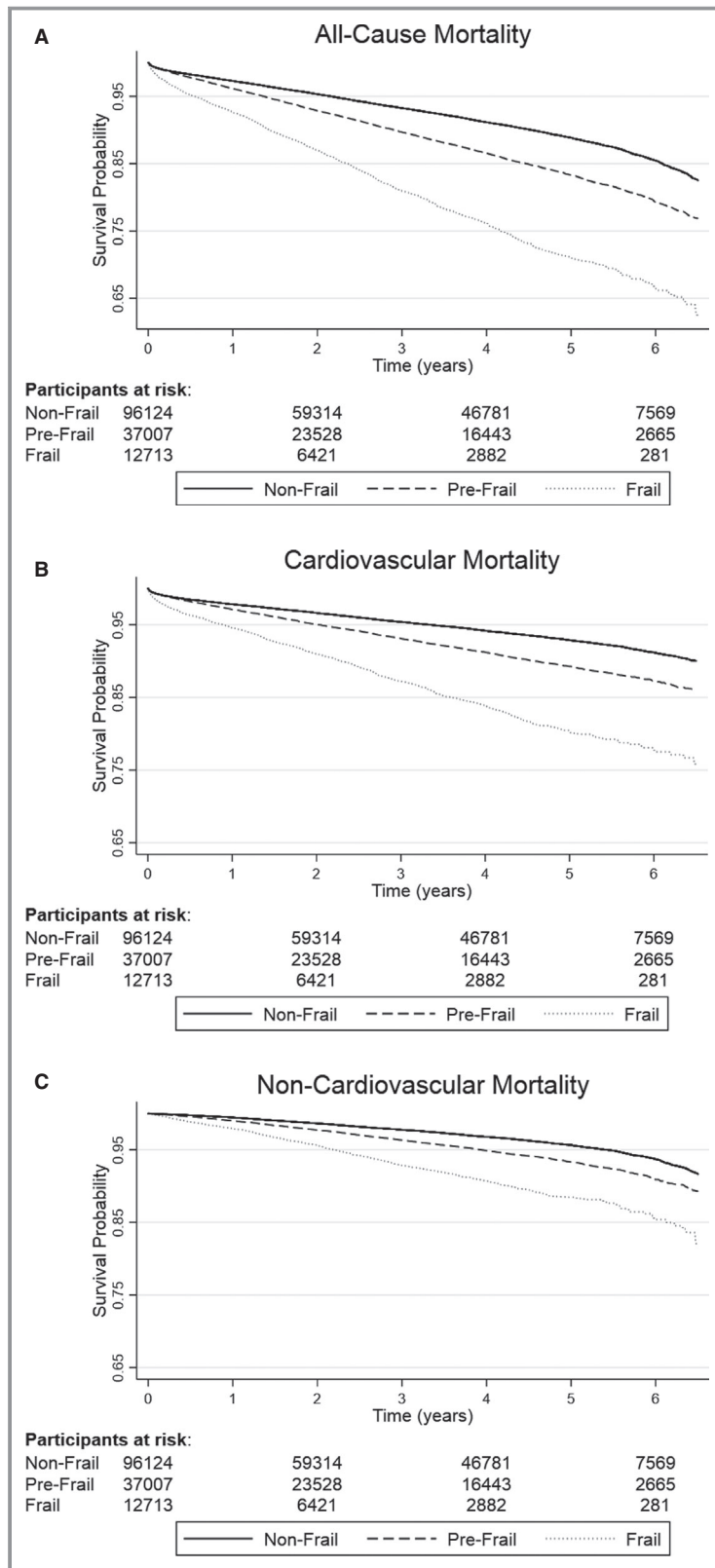
Figure 1. Kaplan-Meier curves for all-cause mortality (**A**), (Gerstein) cardiovascular mortality (**B**), and noncardiovascular mortality (**C**).
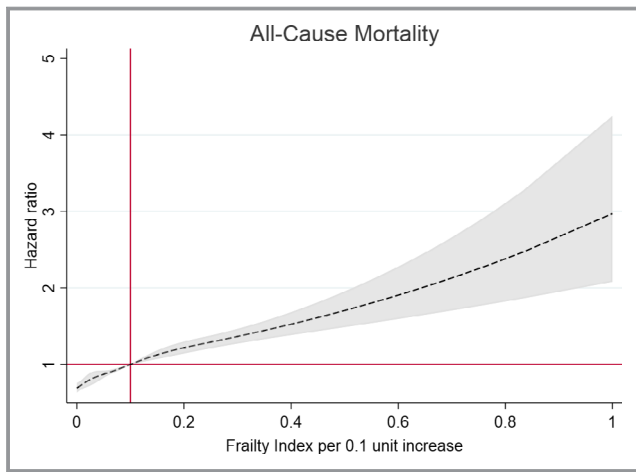
Figure 2. Spline graph adjusted for baseline characteristics and cardiovascular disease risk factors. Shaded area represents 95% confidence limits. Vertical red line represents frailty index value of 0.1 (cutoff for nonfrail). Horizontal red line represents a hazard ratio of 1.

the diagnostic codes for "ischemic heart disease" in the first 4 positions of the discharge summary.[26] These studies are limited by reporting bias, as they used patient self-report or registry data to identify outcome events. In contrast, information on outcome events in our study was systematically elicited, and when identified, events were independently adjudicated using supporting documentation.

There is biologic plausibility to suggest a possible causal relationship between the accumulation of deficits, frailty, and CVD events. Multisystem dysfunction is closely associated with the frailty syndrome[27]; frail patients are functionally limited and concurrent medical comorbidities are associated with chronic systemic inflammation, loss of muscle mass, and decreased functional reserve, all of which increase CVD risk. Our study suggests that among those with or at high risk for developing CVD, the accumulation of deficits, a proxy measure of frailty, further enhances the risk of CVD events, and performs better than traditional CVD risk estimates, such as the Framingham risk score (C-statistic, 0.60 for the cumulative deficit frailty index compared with 0.58 for the Framingham risk score for discriminating CVD events; $P<0.001$). The C-statistic is known to be insensitive to incremental discriminatory value of new indexes.[28,29] Despite this, the cumulative deficit index and the Framingham risk score have complementary and additive information and the 2 together have a C-statistic of 0.66. We also found that frail individuals were more likely to have fatal MIs than nonfatal ones, which indicates that if a frail individual develops an MI,

self-reported MI, stroke, or heart failure. In comparison, a second observational study of 2195 community-dwelling adults (mean age, 47 years; 52% women) from the Nova Scotia Health Survey found that a 17-item index that did not include any traditional CVD risk factors was significantly associated with CVD events over 10 years (age- and sex-adjusted hazard ratio, 1.35; 95% CI, 1.16−1.58). This study determined CVD events as any hospitalization that reported
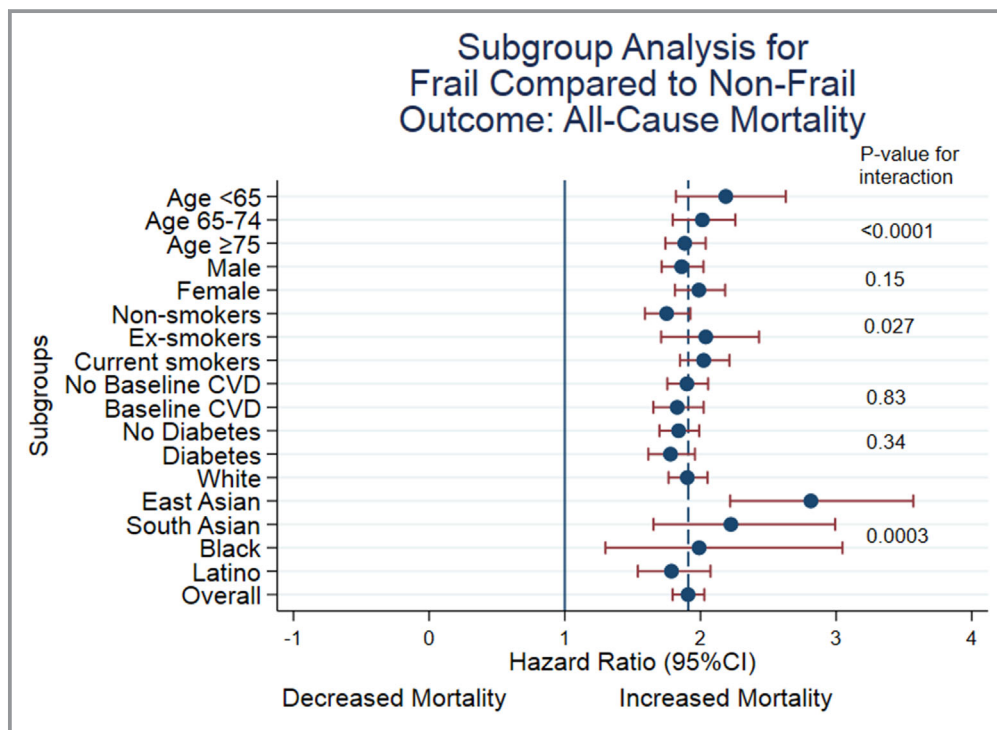

Figure 3. Subgroup analysis for all-cause mortality. CVD indicates cardiovascular disease.

it is more likely to be fatal than an MI in a nonfrail person. This is consistent with the construct that frail patients are more "vulnerable" to stressors, such as CVD events.

Relationship Between Deficit Accumulation, Frailty, and Mortality

Frailty is associated with increased mortality[30]; however, it was unknown whether frailty predisposes to death by an association with further CVD events, or whether the cause of death in frail individuals with CVD is predominantly noncardiovascular. This is relevant because if frail individuals die predominantly of non-CVD causes, they are unlikely to benefit as much from CVD treatments as they may die from competing non-CVD risks before they can derive benefits from such treatments. Our results show that among those with or at high risk for developing CVD, participants identified as frail are equally likely to die cardiovascular deaths compared with noncardiovascular deaths. This perhaps indicates that the cumulative deficit index is a marker of a generalized impairment and is not disease specific. We also found that when frail patients develop a CVD event, they are 59% more likely to die than their nonfrail counterparts. This increased risk of death associated with the accumulation of deficits is seen in all subgroups who were studied, with a higher risk in certain subgroups including younger individuals (age <65 years), smokers, and Asians. When comparing population attributable risks of all-cause and cardiovascular death, frailty is associated with twice as many deaths as smoking, 1.5 times as many deaths as hypertension, and twice as many deaths as a history of CVD (baseline history of MI, stroke, or heart failure). Studies show that only 70% of the population attributable fraction of CVD is accounted for by conventional risk factors.[31] Frailty may help fill the remaining 30%. Given the higher absolute mortality risk in individuals with frailty, one can hypothesize that they may benefit more (in absolute terms) from CVD prevention than nonfrail individuals. However, it is unknown whether frail individuals respond to therapeutic strategies in the same way as nonfrail individuals, and it is possible that frailer patients may be more vulnerable to adverse effects of preventative treatments and intervention. Therefore, further research to understand the net clinical benefit of CVD treatments is needed in frail populations.

Strengths and Limitations

Our study explores the relationship between frailty, as determined by the cumulative deficit frailty index, and CVD in a large, prospectively studied population that included patients both with and without baseline CVD, using data from rigorously conducted randomized controlled trials with adjudicated outcomes. Despite these strengths, our study has a few limitations. We used a 26-variable cumulative deficit index that has not been specifically validated in other studies. However, multiple variations of Rockwood's cumulative deficit frailty index have been studied, and its association with mortality remains robust when variables are used that cover a broad range of systems. Not every study included in this analysis had all 26 variables in its data sets; however, a sensitivity analysis using only participants with ≥11 frailty index variables was conducted, which showed that the cumulative deficit frailty index was still predictive for adverse CVD events. Prior studies have shown an association with mortality with as few as 11 variables.[24] We used the Framingham risk score as a traditional risk estimate as this was the only validated cardiovascular risk score we could measure from the data available among the included studies. We recognize that Framingham risk score is mainly used as an estimate of incident CVD events and that its discriminatory ability in our study may be reduced when compared with population estimates (C-statistic, 0.79 for men and 0.83 for women) as, by definition, our data set includes high-CVD risk patients.[32] Finally, we acknowledge that clinical trial participants are highly selected patients and the generalizability of our results may be limited.

Conclusions

Despite advances in CVD prevention and treatment, frail patients represent an important subgroup that remains at high risk for adverse cardiovascular events and CVD-related death. The cumulative deficit frailty index can provide incremental prognostic value when added to traditional measures of CVD risk. An evaluation of frailty may help identify those with established CVD or CVD risk factors who are at especially high risk of adverse outcomes. Researchers should consider incorporating measures of frailty when designing future clinical trials in CVD.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Description of included studies.

STUDY ACRONYM	COMPLETE NAME	KEY INCLUSION CRITERIA MANDATORY	ADDITIONAL	KEY EXCLUSION CRITERIA	INTER-VENTION	MEAN FOLLOW-UP	EVENTS RECORDED
ACTIVE	Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events	Atrial fibrillation	Established or at high-risk for CVD (CAD, stroke, TIA, PVD, CHF, DM, HTN)	High bleeding risk (PUD, previous ICH, thrombocytopenia)	Clopidogrel plus ASA versus oral anticoagulation	3.6 years	Death, MI, stroke, hospitalization for heart failure
APOLLO	The Aliskiren Prevention of Later Life Outcomes	Age >65 + HTN	Established CVD (CAD, stroke, TIA, PVD), or at high risk for CVD (dyslipidemia, smoking, obesity, DM, CKD, LVH)	Severe HTN, symptomatic heart failure, recent (in 3 months) stroke or ACS	Aliskiren vs placebo	6 months	Death, MI, stroke, hospitalization for heart failure
AVERROES	Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment)	Atrial fibrillation and unable to tolerate or have failed vitamin K antagonist	Established or at high-risk for CVD (CAD, stroke, TIA, PVD, CHF, DM, HTN)	High bleeding risk (PUD, previous ICH, thrombocytopenia)	Apixaban vs Aspirin	1.1 years	Death, MI, stroke
CURE	The Clopidogrel In Unstable Angina to Prevent Recurrent Events Trial	NSTEMI within 24 hours		High bleeding risk (on oral anticoagulation, previous ICH, thrombocytopenia)	Clopidogrel vs placebo	9 months	Death, MI, stroke, hospitalization for heart failure
DREAM	Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication	Impaired fasting glucose		DM, established CVD	Ramipril vs placebo and Rosaglitazone vs placebo	3 years	Death, MI, stroke, hospitalization for heart failure
HOPE	The Heart Outcomes Prevention Evaluation Study	Established CVD (CAD, stroke, TIA, PVD)	Additional risk factor for CVD (dyslipidemia, smoking, obesity, DM, CKD, LVH)	Heart failure	Ramipril vs placebo	5 years	Death, MI, stroke, hospitalization for heart failure
HOPE-3	The Heart Outcomes Prevention Evaluation - 3	Risk factor for CVD (dyslipidemia, smoking, obesity, DM, CKD, LVH)		Established CVD	Rosuvastatin or Candesartan + hydrochlo	5.6 years	Death, MI, stroke, hospitalization for heart failure

					rthiazide vs placebo		
OASIS-5	The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes	NSTEMI within 24 hours		High bleeding risk (on oral anticoagulation, previous ICH, thrombocytopenia), Creatinine >3mg/dl	Fondaparinaux vs Enoxaparin	6 months	Death, MI, stroke, hospitalization for heart failure
ONTARGET	The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial	Established CVD (CAD, stroke, TIA, PVD)		Heart failure, Creatinine >3mg/dl	Ramipril vs Telmisartan vs Ramipril + Telmisartan	4.7 years	Death, MI, stroke, hospitalization for heart failure
ORIGIN	Investigators in the Outcome Reduction with an Initial Glargine Intervention	Impaired fasting glucose	Risk factor for CVD (dyslipidemia, smoking, obesity, DM, CKD, LVH)	Type 1 diabetes, Severe T2DM (A1c >9%)	Glargine and n-3 fatty acids vs placebo	6.2 years	Death, MI, stroke, hospitalization for heart failure
RE-LY	Randomized Evaluation of Long-Term Anticoagulation Therapy	Atrial fibrillation	Established or at high-risk for CVD (CAD, stroke, TIA, PVD, CHF, DM, HTN)	High bleeding risk (PUD, previous ICH, thrombocytopenia)	Dabigatran vs Warfarin	2 years	Death, MI, stroke
TIMACS	Investigators in the Timing of Intervention in Acute Coronary Syndrome	NSTEACS within 24 hours		Not suitable candidate for revascularization	Early PCI (≤24 hours of randomization) vs late PCI (≥36 hours after randomization)	6 months	Death, MI, stroke, hospitalization for heart failure
TRANSCEND	The Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease	Established CVD (CAD, stroke, TIA, PVD) and intolerant to ACE inhibitors		Heart failure, Creatinine >3mg/dl	Telmisartan vs placebo	4.7 years	Death, MI, stroke, hospitalization for heart failure
WAVE	The Warfarin Antiplatelet Vascular Evaluation Trial	PVD		High bleeding risk (on oral anticoagulation, previous ICH, thrombocytopenia)	Antiplatelet + warfarin vs warfarin alone	2.9 years	Death, MI, stroke, hospitalization for heart failure

CVD (cardiovascular disease), CAD (coronary artery disease), TIA (transient ischemic attack), PVD (peripheral vascular disease), CHF (congestive heart failure), DM (diabetes), HTN (hypertension), PUD (pepric ulcer disease), ICH (intracranial hemorrhage), CKD (chronic kidney disease), LVH (left ventricular hypertrophy), ACS (acute coronary syndrome), PCI (percutaneous coronary intervention), ACE (angiotensin converting enzyme)

Table S2. Variables included in the cumulative deficit frailty index.

Variables	Scoring
Non-CVD Comorbid conditions	
Self reported history of thyroid disease	Yes = 1, No = 0
Self reported history of cancer	Yes = 1, No = 0
Self reported history of laser retinopathy	Yes = 1, No = 0
Self reported history of foot infection requiring antibiotics	Yes = 1, No = 0
Self reported history of amputation	Yes = 1, No = 0
Self reported history of proteinuria	Yes = 1, No = 0
Self reported history of fractures in the last 5 years	Yes = 1, No = 0
Self reported history of urinary incontinence	Yes = 1, No = 0
Self reported history of falls in the last year	Yes = 1, No = 0
Self reported history of orthostatic symptoms or syncope	Yes = 1, No = 0
Mood	
Self reported history of depression (question: "do you feel sad or depressed?")	Yes = 1, No = 0
Cognition	
MMSE score*	<10=1
	≥10 and <18 =0.75
	≥ 18 and <20 = 0.5
	≥20 and <24 = 0.25
	>24 = 0
Functional Assessment	
Pill burden	Scored continuously, with #pills/10 = FI score. If >10 pills taken, score was considered = 1
Mobility	"I have no problems walking about" = 0
	"I have some problems walking about" = 0.5
	"I am confined to bed" = 1
Self-care	"I have no problems with self-care" = 0

	"I have some problems with washing or dressing myself" = 0.5
	"I am unable to wash or dress myself" = 1
Ability to perform usual activities (work, study, housework, family or leisure activities)	"I have no problems with performing my usual activities" = 0
	"I have some problems with performing my usual activities" = 0.5
	"I am unable to perform my usual activities" = 1
Pain/discomfort	"I have no pain or discomfort" = 0
	"I have moderate pain or discomfort" = 0.5
	"I have extreme pain or discomfort" = 1
"Rate the state of your health today" scored from 0 (worst state imaginable) to 100 (best state imaginable)	<20 = 1
	20-39 = 0.75
	40-59 = 0.5
	60-79 = 0.25
	80-100 = 0
Physical examination parameters	
Low BMI (kg/m^2)	<18.5 = 1
Baseline hypotension	sBP <100 = 1
	sBP ≥100 = 0
Elevated resting heart rate (beats/min)	≥100 = 1
	<60=0
Lab values	
Anemia (Hemoglobin, g/L)	<90 =1
	90-120 = 0.5
	>120 = 0
Thrombocytopenia (Platelet count, x10^9/L)	<150 =1
	>150 =0
Elevated creatinine (μmol/L)	>110 for men and >90 for women = 1
	<=110 and <-90 for women = 0
Low albumin (g/L)	≤35 = 1
	>35 = 0
Abnormal LFTs (AST or ALT, U/L)	≥100=1
	50-99=0.5

	<50=0

*MMSE only recorded in 5 studies (ACTIVE, APOLLO, ONTARGET, ORIGIN and TRANSCEND)

MMSE: Mini-mental state examination, BMI: body mass index, LFT: liver function test

Table S3. Unadjusted CVD events analysis.

	Nonfatal outcome			Fatal outcome			Fatal or non-fatal outcome		
	Non-frail	Pre-frail	Frail	Non-frail	Pre-frail	Frail	Non-frail	Pre-frail	Frail
Myocardial Infarction	1	0.84 (0.78-0.90)	0.70 (0.62-0.79)	1	1.11 (1.01-1.23)	1.43 (1.25-1.63)	1	0.92 (0.87-0.97)	0.92 (0.84-1.00)
Stroke	1	1.27 (1.18-1.37)	1.49 (1.34-1.66)	1	1.69 (1.53-1.87)	2.28 (2.00-2.59)	1	1.41 (1.33-1.50)	1.75 (1.61-1.90)
Heart failure	1	1.70 (1.58-1.82)	2.27 (2.04-2.52)	1	1.96 (1.79-2.14)	3.54 (3.15-3.97)	1	1.82 (1.72-1.92)	2.86 (2.65-3.10)
Combined	1	1.29 (1.23-1.34)	1.65 (1.55-1.77)	1	1.74 (1.64-1.84)	3.05 (2.82-3.30)	1	1.44 (1.39-1.49)	2.14 (2.03-2.25)

Incidence rate ratios and 95% confidence intervals for non-fatal and fatal myocardial infarctions, strokes, heart failure, and combined cardiovascular events. Unadjusted analysis. CVD: cardiovascular disease

Table S4. Population attributable risk analysis for cardiovascular death.

Variable	Population attributable risk (%) with 95% CI*
High-morbidity status	19.3 (18.3-20.4)
Intermediate-morbidity status	6.26 (5.19-7.32)
Smoking	2.27 (-3.53-7.74)
Diabetes	19.3 (13.2-25.1)
Hypertension	19.2 (7.47-29.5)
Myocardial infarction	9.42 (-0.38-21.0)

Table S5. Sensitivity analysis for CVD events.

	Model	Nonfatal outcome			Fatal outcome			Fatal or non-fatal outcome		
		Non-frail	Pre-frail	Frail	Non-frail	Pre-frail	Frail	Non-frail	Pre-frail	Frail
Myocardial Infarction	A	1	1.05 (0.95-1.16)	1.17 (0.97-1.42)	1	1.32 (1.06-1.65)	2.12 (1.57-2.87)	1	1.09 (0.99-1.20)	1.36 (1.16-1.59)
	B	1	0.97 (0.87-1.07)	0.86 (0.69-1.07)	1	0.91 (0.75-1.10)	1.27 (0.95-1.71)	1	0.95 (0.87-1.04)	0.97 (0.82-1.16)
Stroke	A	1	1.21 (1.06-1.39)	1.25 (0.98-1.59)	1	1.73 (1.21-2.49)	1.78 (1.00-3.15)	1	1.27 (1.12-1.44)	1.31 (1.04-1.63)
	B	1	1.06 (0.96-1.18)	1.26 (1.05-1.50)	1	1.21 (1.01-1.42)	1.49 (1.15-1.91)	1	1.10 (1.00-1.20)	1.32 (1.14-1.53)
Heart failure	A	1	1.37 (1.21-1.55)	1.80 (1.49-2.18)	1	1.57 (1.17-2.10)	2.46 (1.66-3.63)	1	1.40 (1.25-1.56)	1.91 (1.61-2.26)
	B	1	1.26 (1.15-1.38)	1.40 (1.21-1.63)	1	1.38 (1.20-1.59)	1.65 (1.34-2.03)	1	1.29 (1.20-1.40)	1.48 (1.31-1.67)
Any CVD event	A	1	1.17 (1.09-1.25)	1.33 (1.18-1.51)	1	1.46 (1.23-1.73)	2.27 (1.80-2.89)	1	1.20 (1.13-1.29)	1.48 (1.33-1.65)
	B	1	1.10 (1.04-1.17)	1.17 (1.05-1.30)	1	1.22 (1.10-1.35)	1.47 (1.26-1.72)	1	1.13 (1.07-1.19)	1.25 (1.15-1.37)

Incidence rate ratios and 95% confidence intervals for non-fatal and fatal myocardial infarctions, strokes, heart failure, and combined cardiovascular events. Model A: Primary analysis with adjustment made for baseline characteristics (age, sex, ethnicity and smoking history) and traditional cardiovascular disease (CVD) risk factors (history of myocardial infarction, stroke, heart failure, diabetes, hypertension, peripheral arterial disease, elevated BMI and high cholesterol). Model B: Sensitivity analysis done after excluding participants with <11 frailty variables and imputing values for hypercholesterolemia, using the same adjustment variables.

Table S6. Sensitivity analysis for mortality.

Frailty status	Model	Unadjusted			Adjusted for baseline characteristics			Adjusted for baseline characteristics and traditional CVD risk factors		
		All-cause mortality	Cardiovascular mortality	Non-cardiovascular mortality	All-cause mortality	Cardiovascular mortality	Non-cardiovascular mortality	All-cause mortality	Cardiovascular mortality	Non-cardiovascular mortality
Frailty Index (per 0.1 unit increase)	A	1.46 (1.44-1.48)	1.44 (1.40-1.46)	1.50 (1.46-1.54)	1.27 (1.24-1.29)	1.26 (1.23-1.29)	1.28 (1.24-1.33)	1.35 (1.28-1.41)	1.32 (1.25-1.40)	1.43 (1.29-1.60)
	B	1.70 (1.66-1.73)	1.74 (1.69-1.79)	1.63 (1.57-1.68)	1.36 (1.32-1.41)	1.35 (1.29-1.41)	1.38 (1.31-1.45)	1.23 (1.18-1.29)	1.21 (1.15-1.28)	1.33 (1.24-1.42)
Non-frail		1	1	1	1	1	1	1	1	1
Pre-frail	A	1.48 (1.43-1.53)	1.46 (1.40-1.53)	1.50 (1.42-1.59)	1.27 (1.21-1.32)	1.24 (1.18-1.32)	1.30 (1.21-1.40)	1.41 (1.27-1.57)	1.39 (1.23-1.57)	1.50 (1.24-1.83)
	B	1.65 (1.59-1.72)	1.72 (1.63-1.82)	1.56 (1.46-1.67)	1.32 (1.24-1.39)	1.28 (1.19-1.39)	1.35 (1.25-1.48)	1.17 (1.09-1.26)	1.12 (1.02-1.23)	1.35 (1.20-1.51)
Frail	A	2.81 (2.68-2.95)	2.79 (2.62-2.96)	2.86 (2.64-3.10)	1.91 (1.79-2.03)	1.91 (1.77-2.05)	1.90 (1.71-2.10)	2.18 (1.89-2.51)	2.06 (1.76-2.42)	2.60 (1.92-3.52)
	B	3.19 (3.01-3.38)	3.36 (3.12-3.62)	2.95 (2.69-3.24)	1.89 (1.74-2.05)	1.85-1.67-2.06)	1.97 (1.73-2.24)	1.61 (1.44-1.79)	1.54 (1.34-1.76)	1.76 (1.48-2.11)

Unadjusted and adjusted hazard ratios with 95% confidence intervals using shared frailty models. Baseline characteristics included in the initial adjustment model: age, sex, ethnicity and smoking history. Cardiovascular disease (CVD) risk factors included in the subsequent adjustment model: history of myocardial infarction, stroke, diabetes, hypertension, peripheral arterial disease, and elevated BMI. Model A: Primary analysis. Model B: Sensitivity analysis done after excluding participants with <11 frailty variables and imputing values for hypercholesterolemia.

Figure S1. Subgroup analysis for cardiovascular mortality.
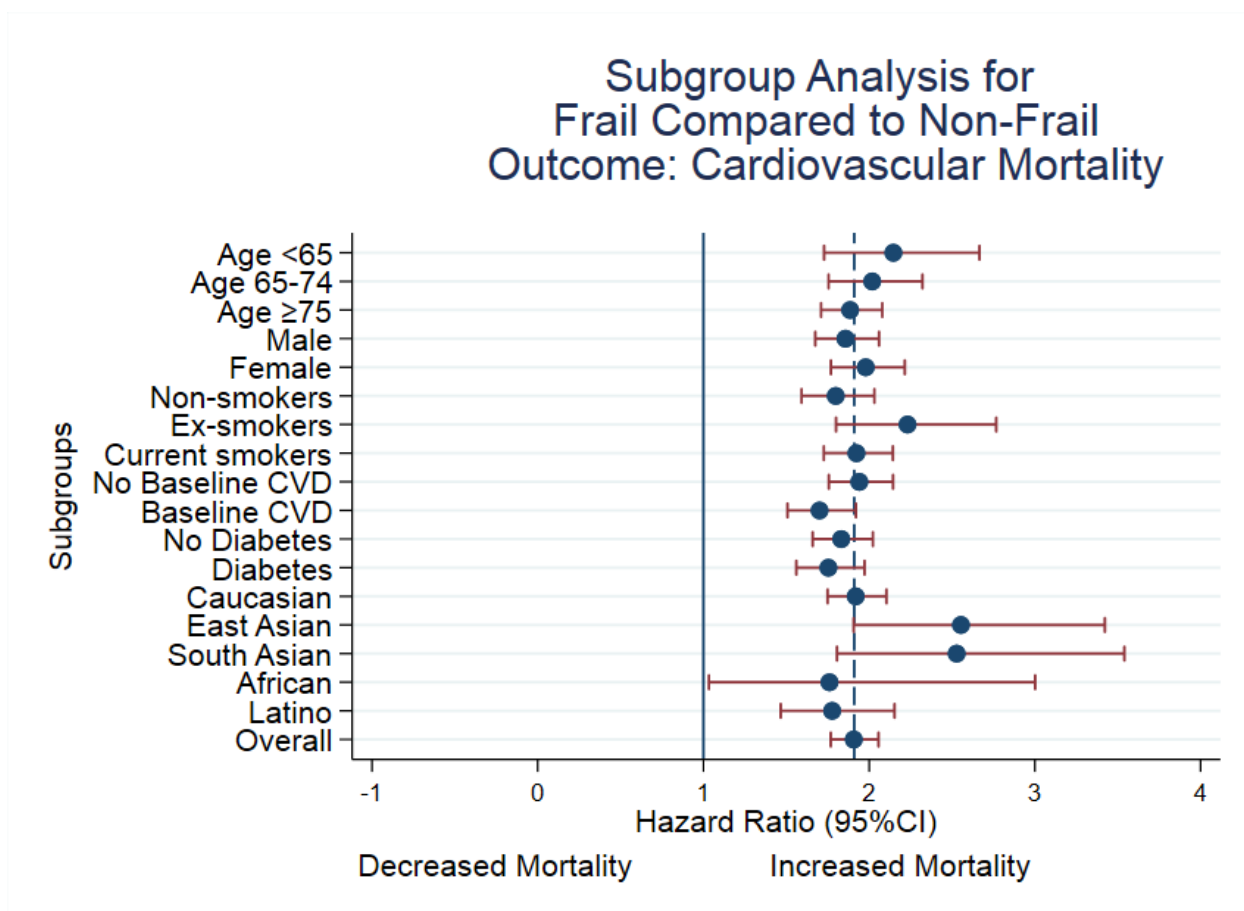
P-values for interaction significant for age (p=0.0002), smoking (p=0.02) and ethnicity (p=0.0007).
CVD: cardiovascular disease

Figure S2. Subgroup analysis for mortality per 0.1 unit increase in cumulative deficit index. CVD: cardiovascular disease.