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Hierarchical Development of Physical Frailty and Cognitive Impairment and Their Association With Incident Cardiovascular Disease

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Abstract

BACKGROUND—Frailty and cognitive impairment (CI) are geriatric conditions that lead to poor health outcomes among older adults with cardiovascular disease. The association between their temporal patterns of development and cardiovascular risk is unknown.

OBJECTIVES—This study aims to examine the 5-year cardiovascular outcomes by the pattern of development of frailty and CI in older adults without a history of coronary artery disease.

METHODS—We used the National Health and Aging Trends Study, linked to Medicare data. Frailty was measured using the physical frailty phenotype. CI was measured using the AD8 Dementia Screening Interview, measured cognitive performance, or self-report by patient or caregiver for a diagnosis given by a physician. The primary outcome was incident major adverse cardiovascular event at 5 years.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

RESULTS—Of a total 2,189 study participants aged 65 and older, 38.5% were male. In this study population, 154 (7%) participants developed frailty first, 829 (38%) developed CI first, and 195 (9%) participants developed both simultaneously (frail-CI group). Those who developed frailty and CI simultaneously were older, more likely to be female, and had multiple chronic conditions. The frail-CI group had the highest risk of major adverse cardiovascular event (hazard ratio [HR]: 1.81; 95% CI: 1.47–2.23) followed by frail first (HR: 1.46; 95% CI: 1.17–1.81) and CI first (HR: 1.31; 95% CI: 1.15–1.50). Frailty first was associated with the greater risk of stroke (HR: 1.49; 95% CI: 1.06–2.09) compared to the intact group.

CONCLUSIONS—The simultaneous development of frailty and CI is associated with an increased risk of adverse cardiovascular outcomes including death compared with the development of each syndrome alone. Diagnostics to detect frailty and CI are critical in assessment of cardiovascular risk in the older population.

Keywords

cognitive impairment; coronary disease; frailty; older adults

In the developed world, the older adult population is expanding at a rapid pace. According to the U.S. Census Bureau, 16.5% of the United States population are older than 65 years of age,[1] and that figure is projected to grow to 20.3% by 2030.[2,3] Several geriatric conditions prevalent among older adult patients can impact the assessment of cardiovascular risk.[4] Physical frailty is defined as the loss of physiologic reserve, which leads to decreased resistance to stressors, increased vulnerability, and a progression to poor overall health outcomes. Cognitive impairment (CI), a progressive neurocognitive disorder, is commonly experienced in old age and is characterized as declines in brain functions such as memory, language, and problem-solving. The spectrum of both frailty and CI can greatly impact the quality of life and management of cardiovascular disease (CVD) in older patients. In this study, the spectrum of CI spans from age-related mild cognitive impairment to major neurocognitive disorder including dementia were studied. From a clinical perspective, dementia can have the most significant impact on clinical outcomes and management. The term “cognitive frailty” has been used to define the coexistence of frailty and CI and the addition of CI to the frailty criteria increases the predictive validity of the definition for adverse health outcomes in geriatric populations.[5] While these 2 syndromes can coexist in a minority of cases, the development of one condition can increase the risk of the development of the other.[6]

Previous research from the NHATS (National Health and Aging Trends Study) has shown that the incidences of death and major adverse cardiovascular events (MACEs) are increased in individuals classified as frail.[7] However, the incidences of CI, frailty, and their patterns of development over time among older adults at risk for coronary artery disease (CAD) are not yet understood. In this study, we aimed to: 1) evaluate the incidence of CI and frailty in an older adult population without known CAD; 2) examine the incidence and patterns of the temporal development of each geriatric syndrome during visit 1 and visit 2 of the study; and 3) assess their influence on MACE at 5 years of follow-up beyond visit 2 in the NHATS linked to Centers for Medicare & Medicaid Services data.

METHODS

THE SOURCE AND STUDY POPULATIONS.

We analyzed data from the 2011 NHATS baseline cohort.[7] Funded by the National Institute on Aging (U01AG032947), NHATS is a prospective cohort study that focuses on functioning of older patients. The source population is derived from a probabilistic sample of Medicare beneficiaries aged 65 years and older who were interviewed in 2011 during their baseline visit (visit 1) and annually reinterviewed to document the changes that occurred in their functional status as they grow older. Geriatric risks such as frailty, physical and cognitive functioning, ability to carry out activities of daily living (ADL), and environmental characteristics of each participant were collected. African Americans and very old participants were oversampled from the Medicare enrollment file. The data for each participant in the NHATS repository are linked to their Medicare data that were available to the investigators for analysis.

The study population included participants aged ≥65 years at enrollment who had no history of CAD prior to their 2011 NHATS baseline visit. Participants were assessed for frailty and CI at each subsequent visit and categorized into the following groups: 1) intact: those who did not develop either frailty or CI during the first 2 years of follow-up, ie, visit 1 or visit 2; 2) frail first: those who had physical frailty and not CI at visit 1 or those who were not found to have frailty and CI at visit 1 but had developed frailty at visit 2; 3) CI first: those who developed CI and had no frailty at visit 1 or those who were not found to have frailty and CI at visit 1 but had developed CI at visit 2; and 4) frail-CI: those who were found to have both frailty and CI on the same visit (either visit 1 or visit 2). Prior work addressed the temporal association between physical frailty and incident CVD in the NHATS study.[8] In this study, the same study subjects were used but measures of cognitive function were added to provide an additional layer of insight in the complex interplay between cognitive function, physical function, and incident CVD.[9]

DEFINITIONS OF PHYSICAL FRAILTY AND COGNITIVE IMPAIRMENT.

Physical frailty was defined using the framework provided by Fried et al[3] as a clinical syndrome characterized by increased vulnerability to stressors due to decline in reserve and function across multiple physiologic systems that occurs with age, leading to a compromised ability to manage everyday acute stress. Frailty in each patient in the NHATS study was assessed using the 5 domains of the Fried physical frailty phenotype: exhaustion, low physical activity, weakness, slowness, and shrinking.[10] If 3 or more of these 5 criteria were present based on previously published criterion,[11] the individual was categorized as frail and those with 1 or 2 of the 5 were categorized as ‘prefrail.’ Those without the presence of any criteria were categorized as ‘robust.’ If the grip or walking test was not done because of health/safety concerns, a value of 0 was assigned to indicate worst performance.

CI refers to a state of cognitive vulnerability often associated with vascular risk factors and with a higher risk of developing overt dementia.[3] Similar to Chu et al,[9] CI was assessed using measures of cognitive performance testing or by proxy reports.[9] Dementia was defined as a time independent variable, and was coded 1 when it was observed during visit 1 or

2, and 0 otherwise.[9] CI was determined by using 3 sources of information. Participants were classified as having CI if they had at least one of the following: 1) impairment in either 1 of 2 cognitive domains: executive function or memory; 2) if participant or proxy reported a diagnosis of CI or dementia given to them by their physician; or 3) a score ≥2 on the AD8 instrument. The AD8 Dementia Screening Interview is an 8-item battery of queries regarding an individual's cognitive status by assessing memory, temporal orientation, judgement, and functioning.[9] The main exposure in this study is the order of onset of physical frailty, CI, namely physical frailty first, CI first or co-occurrence within 1 year of each other in Medicare participants over 65 years of age.[9]

CARDIOVASCULAR OUTCOMES.

The primary outcome of this study is the time to first incident MACE, defined as a composite of death from any cause, acute myocardial infarction (AMI), any subsequent coronary heart disease, stroke, or peripheral vascular disease, whichever came first.[8,12] The length of follow-up for MACE was between visit 2 and visit 8 (ie, 5 years of follow-up).

GERIATRIC CONDITIONS.

Each participant's geriatric risks were assessed during follow-up visits which included level of functioning, ADL, instrumental activities of daily living (IADL), disability, and mobility disability. The Katz scale was used to assess for disability in: 1) self-care (ADL: bathing, dressing, eating, toileting); 2) household activities (IADL: doing laundry, preparing meals, shopping for groceries and for personal items, medication management, handling bills and banking); and 3) mobility (inside the home, going outside, getting out of bed).[11] Dementia status was determined using: 1) physician reports with a diagnosis of dementia or Alzheimer's disease; 2) a scoring administered to proxies indicating the participant has probable dementia; and 3) results from cognitive testing using the AD8 Dementia Screening Interview that evaluates memory, orientation, and executive function.[13] Disability was measured using the American Community Survey Disability Questions. Loss of independence was defined as participants reporting never or rarely ever going outside or having to use devices to go outside.[12]

DEMOGRAPHIC CHARACTERISTICS, MEDICAL CONDITIONS, AND HEALTH CARE UTILIZATION.

Each participant in the study was asked whether their physician had ever diagnosed them with the following medical conditions: high blood pressure, diabetes mellitus, stroke, any cardiac disorder, arthritis, lung disease, and CI or dementia. Hospitalization information for the past 12 months was also obtained.[8,12]

STATISTICAL ANALYSIS.

In a nationally representative sample, NHATS participants with a history of CAD were excluded at baseline. Similar to work by Chu et al,[9] participants were categorized according to the hierarchical development of frailty and CI during the first 2 years of the study, as follows: 1) frailty onset 1 year or longer before CI; 2) CI onset 1 year or longer before

frailty; 3) CI-frailty co-occurring within the same year; and 4) neither CI nor frailty occurred by visit 2.

Demographics, smoking status, comorbidity, hospitalizations, emergency department visits, falls, self-care, mobility, household activities, depression, anxiety, and CI at visit 2 were reported for the patterns of onset, namely: no frailty or CI, frailty onset before CI, CI onset before frailty, or CI-frailty co-occurrence. Percentages were calculated for categorical variables and mean ± SD for continuous variables. Data on self-care, mobility, and household activities are presented as cumulative proportions at 5 years for the 4 groups. Likelihood ratio chi-square and Kruskal-Wallis tests were used to assess the difference in sociodemographic health factors and incidence of cardiovascular outcomes among the CI/frailty groups. Proportional hazard models were used to assess the unadjusted association between the patterns of onset of frailty and CI on cardiovascular outcomes among older adults at 5-year follow-up. Patients were censored if they developed the cardiovascular outcomes of interest or if they were lost to follow-up. To address confounding by age, demographics, and other risk factors, we performed additional multivariable Cox models. Model 2 adjusted for age, gender, sex, race/ethnicity, census division, residence, income, body mass index, smoking status, diabetes, hypertension, number of comorbid diseases, and dependency status (as a surrogate measure for composite functional status). Those with prior stroke were excluded from the model because the rate of CI can be impacted by prior cerebrovascular events. The assumption for Cox proportional hazard models was checked by plotting the Schoenfeld residuals against survival time for each primary and secondary cardiovascular outcome by each of the 4 groups. We then applied a competing risk analysis to account for the potential impact of death on each component of MACE. We used the Fine and Gray proportional subdistribution hazard model, which is widely utilized in practice to analyze competing risk data.[14] The model allows for the estimation of subdistribution of hazard while accounting for competing risk of death.[14] All tests are 2-sided, and the statistically significant level is set at $P < 0.05$. Data analyses were conducted using SAS (version 9.4, SAS Institute Inc). The Johns Hopkins Medicine Institutional Review Board approved this study.

RESULTS

In the NHATS study, 2,189 community-dwelling participants had no history of CAD at baseline and hierarchical data on frailty and CI during visit 1 and 2 of follow-up. Of those, a total of 1,011 (46%) remained intact without frailty or CI; 154 (7%) had frailty-first; 829 (38%) had CI-first; and 195 (9%) had frailty-CI co-occurrence. The baseline demographic data and functional characteristics based on these patterns of hierarchical development of these geriatric syndromes are presented in Table 1. The mean age was 77.5 years and 61% of the cohort were ≥75 years of age. Female participants constituted 62% of the cohort and the majority enrolled were Whites or Caucasians. On average, the majority were overweight, and 48% of the cohort smoked at least 1 cigarette per day. More than one-half of the study population had at least 2 coexisting chronic medical conditions, and 11% of the cohort had 4 or more chronic comorbidities. The most prevalent medical conditions were hypertension, arthritis, and osteoporosis. Approximately 20% of the study population was living with diabetes mellitus and 9% had history of stroke at baseline.

Overall, those who had co-occurrence of frailty and CI simultaneously were older, more female, and belong to ethnic minority groups (Table 1). They had more help in self-care, mobility, household activities, and have a higher rate of disability. The presence and extent of disability were lower in the CI first group, as compared to the frailty-first group and CI-frailty groups. In addition, the proportion of those able to perform household activities and ADL or IADL without impairment were higher in the CI first group as compared to the frailty-first and CI-frailty groups.

The incidence of cardiovascular outcomes over the 5-year follow-up period is presented in Table 2. Overall, 25% of the participants died by 5-year follow-up and 59% suffered from a MACE, with CAD being the most common (30%). The frail-CI group had the highest incidence of all-cause mortality (60%) and developed more MACEs (87%) (Figure 1). The frail-CI group also had the highest incidence of peripheral vascular disease (PVD) (40%) and CAD (40%); however, the frail first group had the highest incidence of AMI (11%) and stroke (29%) (Table 2). In unadjusted Cox proportional hazards models, all 3 patterns of geriatric syndrome development, as compared with the intact group, were associated with incidence of death, MACEs and each individual component of MACEs: AMI, stroke, PVD, and CAD (Table 3). Frail-CI had a greater risk of MACEs, death, acute MI, PVD, and CAD as compared to frailty first and CI first.

After adjusting for age, gender, race/ethnicity, census division, residence and income, body mass index, smoking status, diabetes, hypertension, number of chronic diseases, and dependency status, the development of either frailty, CI or both simultaneously remained associated with a greater risk of MACE and death, as compared with the intact group, over the 5-year follow-up period (Table 3). When compared to the intact group, both geriatric syndromes and, regardless of the order of development, were associated with a greater risk of PVD and CAD. Frail-CI was associated with a greater risk of AMI (hazard ratio [HR]: 1.93; 95% CI: 1.07–3.47), whereas development of frailty first was associated with a greater risk of stroke (HR: 1.49; 95% CI: 1.06–2.09), and CI first and frail-CI were no longer statistically associated with a risk of stroke when compared to the intact group. Competing risk analysis is presented in Table 4. We found that after adjusting for potential confounders, the subdistribution HRs for frailty-first was associated with development of AMI during follow-up after accounting for the competing risk of death. The association between the CI-frailty group with MACEs was mostly explained by all-cause mortality during follow-up.

DISCUSSION

We examined the patterns of development of frailty and CI and their associations with cardiovascular outcomes among older adults in NHATS without prior known CAD during a 5-year follow-up. The major findings are as follows: 1) The highest proportion of participants developed cognitive frailty first (37.8%), followed by those who developed a combination of physical and cognitive frailty (8.9%), and then those who developed only physical frailty (7.0%); 2) participants who developed both CI and frailty simultaneously were older and had a high prevalence of multiple chronic conditions and baseline disability as compared with the other groups; and 3) as compared with participants who developed frailty first or CI first, participants who developed simultaneous CI and frailty had a

higher risk of developing MACEs, mostly attributed to mortality at 5-year follow-up, even after adjusting for demographic characteristics, traditional cardiovascular risk factors, and multimorbidity at baseline (Central Illustration).

In a previous study, we found that frailty in those without prior CAD was associated with MACE and mortality.[8] In addition, frail patients more frequently suffered from CI at baseline (26.8%) as compared with non-frail (2.6%), and 40% of those who were frail had probable dementia compared with just 3.5% of non-frail.[8] Previous research has shown that with the great degree of frailty, there is an increased for development of CI.[15] This suggested that the underlying mechanisms of CI and frailty are interrelated, and these may also increase the risk for cardiovascular events.

This study confirmed that CI, both with frailty and independent of frailty, was associated with a higher incidence of adverse cardiac events and mortality than those without CI. Outcomes were worse when CI and frailty developed simultaneously. These findings may be explained by CI causing inability to adhere to guideline directed medical therapy, difficulty managing cardiovascular risk factors, poor dietary habits, and overall worse physical health. Memory, attention, ability to learn, and follow executive functioning are all necessary to adhere to medical recommendations, care for oneself, and maintain good health.[16] Impairment in one or more of these domains of cognitive function can result in inability to follow care plans and follow-up with clinical recommendations, resulting in an increased likelihood for adverse cardiovascular outcomes and mortality. The combination of frailty and CI also exacerbates other clinical conditions because of impairment in health literacy and ability to follow recommendations resulting in worse health outcomes.[16]

CI is associated with worsened nutritional status, functional status, and mortality.[17] Additionally, during hospitalizations, CI is associated with increased risk of falls, longer length of stay, frequent discharge to nursing facilities, and higher inhospital mortality, with worse outcomes in those with severe CI.[18] Cognitive decline increases the risk of nonadherence to recommended lifestyle changes or medications to control cardiovascular risk factors, which increases cardiovascular risk. Cognitive decline can therefore lead to poor physical health because of difficulty with self-care, reduced physical activity due to muscle weakness fatigue or frailty, difficulty with mobility, and reduced ability to communicate with health care workers and caregivers. All these factors can contribute to poor overall physical health outcomes which can be manifested as falls, infections, and other health problems observed in older adults.

This study represents the most comprehensive study to date documenting the association of hierarchical development of CI and frailty with cardiovascular outcomes including AMI, CAD, PVD, and stroke, in those without CAD at baseline. Integration of screening tools for geriatrics risks in the cardiovascular practice will result in the identification of patients who may benefit from interventions to address geriatric risks and modify the approach for cardiovascular therapies. Multifaceted interventions to address physical function, nutritional status, and cognitive health are under investigation and may ultimately impact cardiovascular health.[19]

Cognitive frailty, physical frailty, and CVD are closely related. Cognitive frailty refers to the state of vulnerability in older adults characterized by the decline in cognitive functioning, memory, or executive function. When combined with physical frailty, signs like muscle weakness, fatigue, slowness, and gait impairment were associated with greater risk. Physical frailty is a well-established risk factor for CVD, and research suggests that cognitive frailty is also associated with an increased risk of cardiovascular events.[8,12] This is thought to be due to the complex interplay between cognitive and physical functioning with cardiovascular health.

This study has some limitations. First, MACE was diagnosed using Medicare claims data from hospital and outpatient encounters. Although this method is widely used when studying cardiovascular outcomes, the severity of each outcome cannot be ascertained using this method. Second, frailty and CI are dynamic processes which may reverse or change over time. In this study, we assessed both geriatric risks during the first and second clinic visits in NHATS. While this is important to acknowledge, the study results remain novel because the hierarchical association between frailty and CI in the context of CVD has not been studied to this extent. Third, when examining the CI-first vs frailty-first categories, the results might be influenced by different thresholds of dichotomous categorizations of continuous variables.[20] This can result in misclassification bias, which is sensitive to different thresholds of dichotomization.[20] While we prefer to evaluate variables as continuous, the categorization is often necessary for clinical decision making in practice when trying to decide whether an older adult is suffering from CI or frailty. Additionally, the instrument used to measure CI, the AD8 dementia screening interview, is subject to variability in reporting and may have resulted in misclassification bias. Despite this limitation, our estimates approximate other cohorts of older adults in the community, and this study represents the best approximation of CI and frailty in the study population.

Internal validity refers to the degree to which the results represent the true association between an exposure and an outcome in a particular study population. The main threats to internal validity of this study include selection bias, testing, and history. There could be preexisting clinical characteristics that are associated with patients who presented with both frailty and CI, as compared to those presenting with frailty alone or CI alone. To account for selection bias we have constructed a multivariable proportional hazard regression model to account for baseline differences between groups. After accounting for adjustments, the increase in MACE in patients with frailty and CI remains positive. While this is not a randomized study, our sample size is large enough to increase the internal validity by reducing the chance of random error associated with testing. Furthermore, the use of validated instruments and objective measures of frailty and CI minimize measurement error.

While there are specific criteria to diagnose dementia, outlined in the DSM (The Diagnostic and Statistical Manual of Mental Disorders)-5, the AD8 is one of many validated tools used to screen for CI in older adults.[21] While there are several advantages to using AD8 as a screening instrument, such as brevity, ease of use, high sensitivity, and specificity to capture dementia, it has important limitations. These include limited diagnostic accuracy, limited validation, dependency on the interviewer, and inability to distinguish between the types and forms of dementia. While AD8 may have underestimated the true prevalence of

CI in practice, there were still not an insignificant number of individuals in this cohort with CI, highlighting the importance of studying CI in this older population at risk for CAD. After a patient screens positive on any Alzheimer dementia screening tool, a comprehensive evaluation by a trained health care professional with experience in diagnosing and treating CI and dementia should be conducted. It is important to note that this study was not designed to differentiate between specific sub-types of dementia (eg, Alzheimer's disease, dascular dementia, etc) or the medications used to treat each phenotype of dementia.

CONCLUSIONS

In the NHATS study population, we found that the simultaneous development of frailty and CI is associated with significantly higher risk of MACEs and mortality than development of frailty first or CI first, even after controlling for cardiovascular risk factors. Assessment of frailty and CI in older adults should be part of their routine care, which may ultimately affect therapeutic choices and modify cardiovascular outcomes. Effective interventions to prevent and reverse these geriatric risks may improve cardiovascular outcomes in older population.

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ABBREVIATIONS AND ACRONYMS

ADL	activities of daily living
AMI	acute myocardial infarction
CAD	coronary artery disease
CI	cognitive impairment
CVD	cardiovascular disease
IADL	instrumental activities of daily living
MACE	major adverse cardiovascular event
PVD	peripheral vascular disease

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:

Older adults with CI and/or frailty are at greater risk for adverse cardiovascular outcomes than those who develop neither. Although most older adults develop CI first, followed by frailty, those who develop both simultaneously are at the highest risk for adverse cardiovascular outcomes.

TRANSLATIONAL OUTLOOK:

Screening for CI and frailty can identify patients at increased risk for poor cardiovascular outcomes. Biologic underpinnings responsible for these relationships should be studied.

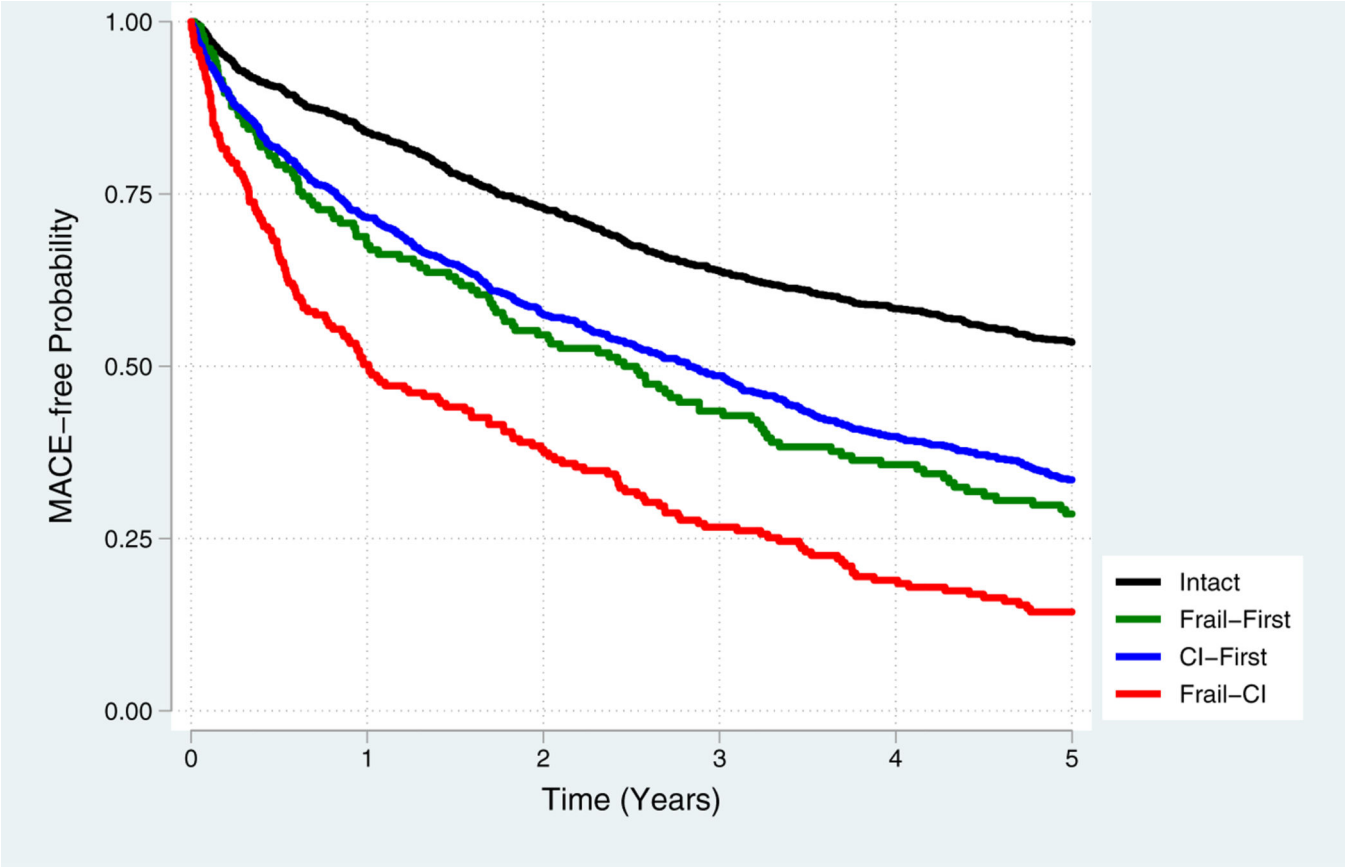
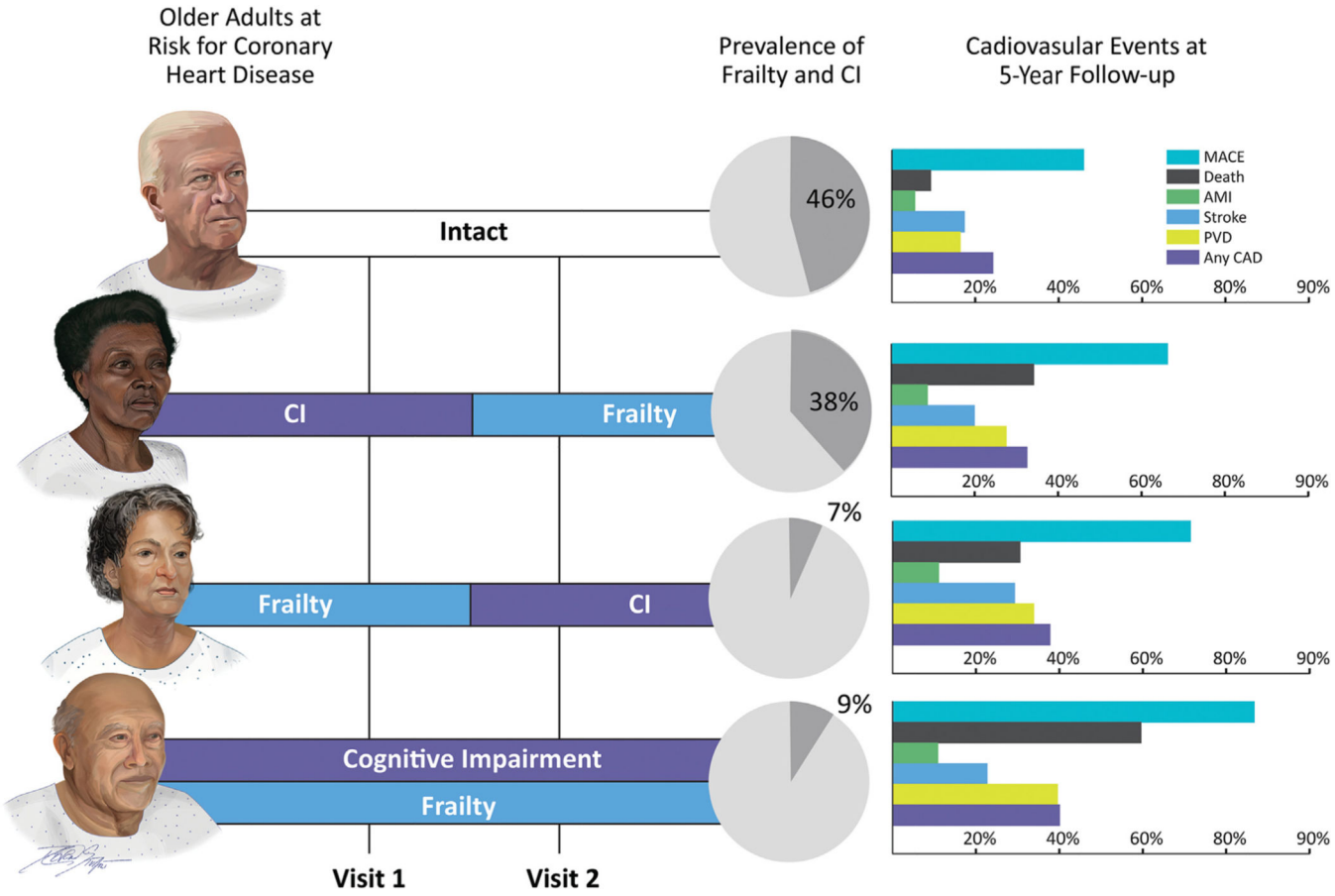


FIGURE 1. Kaplan-Meier Survival Curve of MACE at 5 Years by the Hierarchical Development of Frailty and Cognitive Impairment

Kaplan-Meier survival curve illustrating major adverse cardiovascular event-free survival over a 5-year follow-up by pattern of frailty and cognitive impairment development in the National Health and Aging Trends Study participants without a history of coronary artery disease (log-rank $P < 0.001$). Major adverse cardiovascular event was defined as acute myocardial infarction, stroke, peripheral vascular disease and coronary artery disease, and excluded mortality. CI = cognitive impairment; MACE = major adverse cardiovascular event.



CENTRAL ILLUSTRATION. This Figure Illustrates the Findings of This Study in Which 46% of the Participants Remained Intact Without Developing Either Cognitive Impairment or Frailty

These participants had the Lowest rate of major adverse cardiovascular events as illustrated in the bar graph to the right. A small percentage of participants (7%) developed frailty first, and this group had a significantly higher incidence of major adverse cardiovascular events than those who were intact. A large percentage of participants (38%) developed cognitive impairment first and the incidence of major adverse cardiovascular events as depicted on the bar graph to the right was greater than it was for those who remained intact, although less than it was for those who developed frailty first. Lastly, the group that developed cognitive impairment and frailty simultaneously comprised 9% of the participants and had the highest incidence of major adverse cardiovascular events. AMI = acute myocardial infarction; CAD = coronary artery disease; CI = cognitive impairment; MACE = major adverse cardiovascular event; PVD = peripheral vascular disease.

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TABLE 1

Characteristics of the Study Population of Participants Without a History of Coronary Heart Disease Enrolled in the NHATS by Patterns of Frailty and CI

	Total (N = 2,189)	Intact (n = 1,011)	Frail[a] First (n = 154)	CI First (n = 829)	Frail-CI (n = 195)	*P* Value
Age, mean	77.5	74.6	78.3	79.3	83.9	<0.001
Age, y						<0.001
65–69	18.6	26.8	15.6	12.3	4.6	
70–74	21.0	27.3	18.8	17.1	6.2	
75–79	20.8	21.3	18.2	21.5	17.4	
80–84	20.2	16.9	26.0	23.4	19.0	
85–89	12.0	6.0	14.9	14.2	30.8	
90+	7.5	1.7	6.5	11.5	22.1	
Sex						0.009
Female	61.5	59.4	68.2	60.9	70.3	
Male	38.5	40.7	31.8	39.1	29.7	
Race						<0.001
Non-Hispanic White	74.5	82.0	73.9	68.4	62.4	
Non-Hispanic Black	19.2	14.6	18.3	22.3	30.4	
Hispanic	4.1	2.1	5.2	6.1	5.2	
Other	2.2	1.4	2.8	3.3	2.1	
BMI, mean	27.1	27.7	27.6	26.4	26.5	<0.001
Smoking status						0.011
Smoke at least 1 cigarette/d	47.8	49.2	52.0	48.0	36.9	
Self-reported disease						
Arthritis	53.5	48.4	76.0	49.6	79.0	<0.001
Diabetes mellitus	20.0	17.2	27.3	19.9	28.7	0.0004
Hypertension	62.3	60.0	72.1	61.1	71.8	0.0006
Lung disease	12.5	11.9	22.1	11.0	14.4	0.0035
Osteoporosis	20.7	18.2	29.2	19.8	30.9	<0.001
Stroke	8.9	4.7	11.7	9.8	24.6	<0.001
Number of chronic diseases						<0.001
0–1	39.4	47.3	14.9	40.4	13.9	

	Total (N = 2,189)	Intact (n = 1,011)	Frail[a] First (n = 154)	CI First (n = 829)	Frail-CI (n = 195)	*P* Value
2–3	49.5	46.4	66.2	49.7	51.3	
4+	11.1	6.3	18.8	9.9	34.9	
Hospital stay past 12 mo	15.4	10.1	25.5	16.7	29.9	<0.001
Any fall past month	29.9	23.9	43.5	29.5	51.3	<0.001
Self-care disability						<0.001
No difficulty	76.7	89.0	58.4	76.1	29.7	
Difficulty but no help	11.2	7.6	23.4	11.7	18.5	
Help	12.1	3.4	18.2	12.2	51.8	
Mobility disability						<0.001
No difficulty	70.5	83.9	44.2	70.8	20.5	
Difficulty but no help	16.5	13.1	33.1	16.9	20.0	
Help	13.0	3.1	22.7	12.3	59.5	
Household activities disability						<0.001
No difficulty	64.7	81.6	36.4	61.5	12.8	
Difficulty but no help	12.5	12.5	26.0	10.7	9.7	
Help	22.8	5.9	37.7	27.7	77.4	
Overall disability level						<0.001
No difficulty	53.8	69.9	29.2	49.8	6.7	
Difficulty but no help	20.0	21.6	27.3	18.9	10.3	
Help	26.2	8.5	43.5	31.2	83.1	
Depression						
PHQ2 score ≥3	12.8	7.1	19.6	13.4	34.4	<0.001
Anxiety						
GAD2 score ≥3	10.5	5.6	17.0	11.4	26.6	<0.001
No. of ED visits						<0.001
0	77.3	82.5	68.8	76.0	62.1	
1	15.8	13.5	23.4	16.8	17.4	
≥2	7.0	4.1	7.8	7.2	20.5	
No. of hospitalizations						<0.001
0	89.0	92.4	83.8	89.6	73.3	
1	8.8	6.4	12.3	8.3	20.5	

	Total (N = 2,189)	Intact (n = 1,011)	Frail[a] First (n = 154)	CI First (n = 829)	Frail-CI (n = 195)	*P* Value
≥2	2.2	1.2	3.9	2.1	6.2	
Total LOS in hospital, mean	0.93	0.47	1.69	0.92	2.77	<0.001
Number of physician visits, mean	6.99	6.42	9.14	7.00	8.22	<0.001
Number of ADL impairment						<0.001
0	66.3	81.0	43.5	64.5	15.4	
1–2	20.7	15.4	28.6	24.1	26.7	
≥3	13.1	3.6	27.9	11.3	58.0	
Number of IADL impairments						<0.001
0	65.9	81.9	38.3	63.0	16.9	
1–2	20.9	15.8	37.7	23.3	23.6	
≥3	13.3	2.3	24.0	13.8	59.5	

Values are % unless otherwise indicated.

[a]Frailty was assessed by the physical frailty phenotype paradigm that is grounded in 5 criteria: exhaustion, low physical activity, weakness, slowness, and shrinking (www.nhats.org). Claims-based frailty index is a validated frailty tool with the physical frailty phenotype that utilizes claims data.

ADL = activities of daily living; BMI = body mass index; CI = cognitive impairment; ED = emergency department; GAD2 = generalized anxiety disorder 2-item; IADL = instrumental activities of daily living; LOS = length of stay; NHATS = National Health and Aging Trends Study; PHQ2 = patient health questionnaire-2.

TABLE 2

The Incidence of MACEs by Patterns of Frailty and CI Among Older Adults Without a History of Coronary Heart Disease in the NHATS During 5-year Follow-Up

	Total (N = 2,189)	Intact (n = 1,011)	Frail[a] First (n = 154)	CI First (n = 829)	Frail-CI (n = 195)	*P* Value
MACE	59.1	46.1	71.4	66.2	86.7	<0.001
Death	24.7	9.4	30.5	34.1	59.5	<0.001
AMI	7.6	5.6	11.0	8.6	10.8	0.008
Stroke	19.7	17.5	29.2	19.9	22.6	0.007
PVD	23.9	16.5	33.8	27.5	39.5	<0.001
Any CAD	29.7	24.3	37.7	32.5	40.0	<0.001

Values are % unless otherwise indicated.

[a]Frailty was assessed by the physical frailty phenotype paradigm that is grounded in 5 criteria: exhaustion, low physical activity, weakness, slowness, and shrinking (www.nhats.org).

AMI = acute myocardial infarction; CAD = coronary artery disease; CI = cognitive impairment; MACE = major adverse cardiovascular event; NHATS = National Health and Aging Trends Study; PVD = peripheral vascular disease.

TABLE 3

Proportional Hazards Regression Model Evaluating the Influence of Patterns of Frailty and CI on 5-Year Cardiovascular Outcomes Among Older Adults Without a History of Coronary Heart Disease in the NHATS

	MACE	Death	AMI	Stroke	PVD	CAD
Model 1[a]						
Frailty first[c]	1.99 (1.62–2.46)	3.65 (2.58–5.18)	2.27 (1.32–3.89)	1.91 (1.38–2.65)	2.38 (1.75–3.26)	1.88 (1.41–2.51)
CI first	1.75 (1.55–1.98)	4.24 (3.36–5.35)	1.80 (1.27–2.55)	1.25 (1.01–1.55)	1.98 (1.62–2.42)	1.58 (1.33–1.88)
Frail-CI	3.34 (2.80–3.99)	9.56 (7.27–12.5)	2.99 (1.81–4.94)	1.77 (1.27–2.46)	3.68 (2.80–4.82)	2.56 (1.98–3.30)
Model 2[b]						
Frail first[c]	1.46 (1.17–1.81)	2.62 (1.83–3.76)	1.73 (0.98–3.05)	1.49 (1.06–2.09)	1.74 (1.26–2.41)	1.43 (1.06–1.92)
CI first	1.31 (1.15–1.50)	2.65 (2.06–3.40)	1.43 (0.98–2.09)	1.01 (0.80–1.27)	1.52 (1.23–1.89)	1.35 (1.12–1.63)
Frail-CI	1.81 (1.47–2.23)	4.45 (3.23–6.13)	1.93 (1.07–3.47)	1.05 (0.71–1.54)	1.97 (1.43–2.70)	1.68 (1.25–2.26)

Values are HR (95% CI).

[a]Model 1 is unadjusted model.

[b]Model 2 was adjusted for age, gender, race/ethnicity, census division, residence and income, body mass index, smoking status, diabetes, hypertension, number of chronic diseases, and dependency status.

[c]Frailty was assessed by the physical frailty phenotype paradigm that is grounded in 5 criteria: exhaustion, low physical activity, weakness, slowness, and shrinking (www.nhats.org).

AMI = acute myocardial infarction; CAD = coronary artery disease; CI = cognitive impairment; MACE = major adverse cardiovascular event; NHATS = National Health and Aging Trends Study; PVD = peripheral vascular disease.

TABLE 4

Fine and Gray Competing Risk Analysis for Death on the Association Between Frailty First, CI First, and Both Frailty and CI on Cardiovascular Outcomes in the NHATS

	MACE	AMI	Stroke	PVD	CAD
Model 1[a]					
Frailty first[c]	1.17 (0.90–1.54)	2.28 (1.22–4.26)	1.29 (0.87–1.92)	1.58 (1.09–2.28)	1.21 (0.85–1.73)
CI first	0.86 (0.73–1.01)	1.06 (0.67–1.70)	0.73 (0.56–0.94)	1.17 (0.92–1.47)	0.93 (0.75–1.14)
Frail-CI	0.71 (0.S3–0.95)	1.24 (0.60–2.56)	0.57 (0.34–0.95)	1.03 (0.69–1.54)	0.86 (0.60–1.24)
Model 2[b]					
Frail first[c]	0.99 (0.75–1.31)	2.24 (1.18–4.24)	1.12 (0.74–1.71)	1.29 (0.88–1.89)	1.02 (0.71–1.48)
CI first	0.83 (0.70–1.00)	1.14 (0.66–1.96)	0.69 (0.51–0.93)	1.06 (0.82–1.38)	0.96 (0.76–1.22)
Frail-CI	0.57 (0.40–0.80)	1.40 (0.57–3.44)	0.42 (0.23–0.75)	0.74 (0.46–1.19)	0.78 (0.50–1.20)

Values are HR (95% CI).

[a]Model 1 is unadjusted model.

[b]Model 2 was adjusted for age, gender, race/ethnicity, census division, residence and income, body mass index, smoking status, diabetes, hypertension, number of chronic diseases, and dependency status.

[c]Frailty was assessed by the physical frailty phenotype paradigm that is grounded in 5 criteria: exhaustion, low physical activity, weakness, slowness, and shrinking (www.nhats.org).

AMI = acute myocardial infarction; CAD = coronary artery disease; CI = cognitive impairment; MACE = major adverse cardiovascular event; NHATS = National Health and Aging Trends Study; PVD = peripheral vascular disease.