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Research Article

Hierarchical Development of Frailty and Cognitive Impairment: Clues Into Etiological Pathways

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Abstract

Background: Frailty and cognitive impairment (CI) are associated and often coexist in older adults. Whether temporal patterns of occurrence reflect different etiologies remain unknown.

Methods: Participants from the National Health and Aging Trends Study were assessed annually (2011–2016) for frailty (Fried's criteria) and CI (bottom quintile of clock drawing test or immediate and delayed recall; proxy-report of dementia diagnosis or AD8 ≥ 2). We used the Fine & Gray model to identify correlates of frailty onset before CI, CI onset before frailty, and frailty-CI co-occurrence, accounting for death as a competing risk.

Results: Of 3,848 free of frailty, CI, and dementia at baseline, 2,183 (61.2%) developed neither frailty nor CI during the 5-year follow-up; 343 (8.3%) developed frailty first; 1,014 (24.4%) developed CI first; and 308 (6.0%) developed frailty-CI co-occurrence. Incident dementia, as a marker of underlying neuropathologies, was associated with greater likelihood of CI onset first (subdistribution hazard ratios [SHR] = 2.60, 95% confidence interval [ci] 2.09 to 3.24), and frailty-CI co-occurrence (SHR = 8.77, 95% ci 5.79 to 13.28), but lower likelihood of frailty onset first (SHR = 0.38, 95% ci 0.21 to 0.68). Number of comorbidities was only associated with frailty occurrence first (1 comorbidity: SHR = 2.51, 95% ci 1.15 to 5.47; 4+ comorbidities: SHR = 6.48, 95% ci 2.78 to 15.48).

Conclusions: Different patterns of frailty and CI occurrence exist, and dementia-related pathologies and comorbidities may be important correlates of order of emergence, potentially reflecting different etiologies. Future investigation into relationships between these patterns and dementia subtypes and related pathologies is needed to elucidate etiologic pathways and to provide new targets for prevention, intervention, and risk screening.

Keywords: Frailty, Cognition, Dementia, Comorbidities

Frailty and cognitive impairment (CI), among the most common geriatric conditions, have contributed to growing economic, medical, and social burdens affecting older adults worldwide. CI occurs in about 16% to 20% of older adults in the United States (1) and clinically manifests as a decline in cognitive functioning in at least one cognitive domain (memory, executive functioning, attention, language, and/or visuospatial ability). It is increasingly acknowledged as a prodromal phase of many types of later life dementias (1–4). Frailty is a syndrome (5–7) distinct from comorbidity and disability (8), occurring in about 10% to 15% of community-living older

adults (7,9). It is described by many as a deterioration in physiologic reserve and manifests as an inability to recover efficiently from chronic and acute stressors (5–7). Frailty and CI appear to be distinct but related conditions with shared antecedents, and associations with adverse outcomes (10,11). Unlike most dementias, frailty is potentially preventable or reversible as demonstrated by prior randomized clinical trials and cohort studies (12).

Epidemiologic and clinical studies have found that frailty is associated with poorer cognitive performance and steeper cognitive decline in older adults (10,11,13), and that the association may be stronger for executive function compared to memory (14). However, while some studies have found that greater frailty severity was predictive of cognitive decline (15–17), incident CI (18), and incident dementia, including non-Alzheimer's Disease (AD) (19) and AD Dementia (20), other studies have found that baseline cognitive performance was associated with incident frailty (21,22). Collectively, evidence suggests that many of the aging processes catalyzing frailty may also be responsible for brain aging and cognitive decline (10,11). However, the causal mechanisms underlying this association remain unclear.

Using data from the National Health and Aging Trends Study (NHATS), a nationally-representative sample of older adult U.S. Medicare beneficiaries, we (a) described the patterns of frailty and CI onset; and (b) investigated whether patterns of occurrence in frailty and CI are associated with different baseline socio-demographic factors, disease characteristics, and health events. Characterizing the profiles of individual-level characteristics associated with the different patterns of frailty and CI occurrence could inform whether temporal ordering matters with respect to identifying distinct underlying etiologies and pathways.

Method

Study Design

Data are from NHATS, a nationally-representative sample of U.S. Medicare beneficiaries aged 65 years and older. In 2011, the cohort was drawn from the Medicare enrollment file, with a response rate of 71% (n = 8,245) (23). All participants were followed annually for a maximum of 5 years (2011–2016), and data were collected via 2-hour, in-person interviews (23). Mortality was ascertained via reports by informants during attempts to contact the participant for their annual interview. NHATS is ongoing and approved by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board.

Study Population

The study population was restricted to older adults residing in community-dwelling or in non-nursing home, residential care settings (n = 7,609). We further dropped 112 individuals with insufficient data on frailty (<3 of 5 measures as described below). At baseline, we excluded 444 cases with prevalent frailty (5.8%), 2,302 cases with prevalent CI or dementia (30.3%), and 903 cases with both frailty and CI or dementia (11.9%). Among those with CI at baseline (n = 3,139), with or without frailty, 1,894 (57.2%) had prevalent dementia. Our final analytic sample comprised of 3,848 community-dwelling older adults free of frailty, CI, and dementia.

Measures

Frailty

In this study, frailty was measured using the physical frailty phenotype (PFP), which was previously operationalized in NHATS (9) using validated interview and performance measures of functioning (24) and guidance from prior studies (5,6). It is based on five criteria: exhaustion, low activity, weakness, slowness, and shrinking (Table 1) (5).

Each criterion was scored as 0 or 1 representing the absence or presence of the component, respectively. Consistent with recommended practice, participants were scored "0" for a criterion if they were not tested because of safety concerns, if they were ineligible due to recent surgery or pain, or if they were unable to complete a task (25,26). Criteria were summed to create a score ranging from 0 to 5; participants were defined as frail if they had a score of 3 or higher.

Table 1. Variables of Interest in the National Health and Aging Trends Study

Physical frailty	• *Exhaustion*: Self-reported low energy/easily exhausted, enough to limit activities • *Low Physical Activity*: Self-reported in the last month: (a) never walked for exercise and (b) never engaged in vigorous activities • *Unintentional weight loss*: Self-reported having lost 10+ lbs within prior year or had a BMI <18.5 kg/m^2 • *Slow Gait*: ≤20th percentile of time to walk 3 meters within four sex-by-height categories • *Weakness*: ≤ 20th percentile within 8 sex-by-BMI categories
Cognitive impairment	• Test performance in bottom quintile in at least 1 of 2 cognitive domains ○ Executive functioning (clock drawing test score <3 on a 0–5 scale) ○ Memory (summed scores of 10-item immediate and delayed recall batteries ≤ 5 • Proxy-reported doctor's diagnosis of dementia • AD8 administered to proxy not reporting a diagnosis (score ≥ 2)
Dementia	• Probable Dementia ○ Proxy-reported doctor's diagnosis of dementia ○ AD8 administered to proxy not reporting a diagnosis (score ≥ 2) ○ Self- and proxy-respondents not reporting a diagnosis with test performance score of <1.5 *SD* below the mean in at least two domains ▪ Executive functioning: clock drawing test (score range 0–5, cutoff ≤ 1) ▪ Memory: summed scores of 10-item immediate word recall and 10-item delayed word recall batteries (score range 0–20, cutoff ≤ 3) ▪ Orientation to Date and President and Vice-President naming (score range 0–8, cutoff ≤ 3) • Possible Dementia ○ Self- and proxy-respondents not reporting a diagnosis with test performance scores of <1.5 *SD* below the mean in 1 domain

Cognitive impairment

CI was assessed in two ways: cognitive performance testing or by proxy-reports (Table 1). Participants were classified with CI if at least one of the three criteria were met: (a) scored in the bottom quintile in at least one of the two cognitive domains: executive functioning (scoring <3 on a clock drawing test with a 0–5 scale, where lower values indicate poorer cognitive scores) and memory (scoring ≤ 5 on a summed score of the 10-item immediate and delayed recall batteries, where lower values indicating poorer cognitive scores); (b) self- or proxy-reported doctor's diagnosis of dementia; or (c) scored ≥ 2 on the AD8, an 8-item instrument administered to proxy respondents not reporting a diagnosis, which assesses memory, temporal orientation, judgment, and function (27). Self-respondents who refused a test, answered "do not know," or were unable to do a test were scored as 0 to indicate CI. A majority were self-respondents (98.8%).

Dementia

Dementia status was considered as a potential marker for the latent period of disease that manifests after decades of underlying progression (2). Dementia was treated as time-independent covariate that was binary coded as 1 if dementia onset was observed anytime during the follow-up, and 0 otherwise. The purpose of including dementia was to distinguish neurodegenerative pathologies from others underlying CI, based on the fact that the majority of dementia cases are AD-dementia, using the same logic from the definition of "cognitive frailty" given by the International Academy on Nutrition and Aging (IANA) and the International Association of Gerontology and Geriatrics (IAGG) in 2013, which requires the absence of dementia to try to exclude neurodegenerative etiologies (28). Participants were classified into three groups—probable dementia, possible dementia, and no dementia based on previously defined criteria in NHATS (29) (Table 1). "Probable dementia" was defined as any one of the three criteria derived from cognitive performance testing and self- or proxy- reports: (a) self- or proxy-report of doctor's diagnosis of dementia or AD, (b) a score of ≥ 2 on the AD8 administered to proxy-respondents not reporting a diagnosis, or (c) self- and proxy-respondents not reporting a diagnosis with test performance scores > 1.5 *SD* below the mean in at least two of three domains (memory, orientation, and executive functioning). "Possible dementia" was defined for self- and proxy-respondents not reporting a diagnosis with test performance scores > 1.5 *SD* below the mean in one domain. Self-respondents who refused a test, were unable to do a test, or answered "do not know," were scored 0.

Participant characteristics

Demographic factors including age, sex, race/ethnicity, highest level of educational attainment, residence, and annual household income were considered (30). History of medical conditions was self-reported, which has been shown to be reasonably accurate against medical records (31); participants were asked whether a doctor had ever told them they had: arthritis, diabetes, heart disease, high blood pressure, lung disease, osteoporosis, and stroke. Healthcare utilization, including ever having an overnight hospitalization stay or surgery (back, heart, knee, hip) in the past year was also based on self-reports. Subjective well-being (32), depressive symptoms (33–35), activities of daily living (ADLs) (24), and instrumental activities of daily living (IADLs) (24) were also considered. Additionally, measures of gait speed, memory function, and executive function at baseline were also considered as markers for distinct underlying latent disease processes, such as Alzheimer's Disease and Vascular Dementia (36,37).

Statistical analysis

Nationally-representative descriptive statistics were generated by different individual-level patterns of onset: (a) frailty onset 1 year or more before CI, (b) CI onset 1 year or more before frailty, (c) CI-frailty co-occurrence (within the same year), and (d) neither CI nor frailty anytime during follow-up.

We used the Fine & Gray competing risks model (38) to estimate subdistribution hazard ratios (SHR) and identify correlates of the patterns of onset, namely: frailty onset before CI, CI onset before frailty, or CI-frailty co-occurrence. The model treated these patterns as mutually exclusive outcomes while accounting for death and other respective patterns of occurrence as competing risks (38). Follow-up time was calculated as time (in years) since baseline. In Model I, we only included baseline age, sex, race, income, education, and residence. To better control for age, we used natural splines with knots at 75, 85, and 95 years. In Model II, we explored all correlates included in Model I, as well as ADLs, depression, well-being, number of comorbidities, slow gait (<0.8 m/s), history of hospitalization in the past year, history of surgery in the past year, current smoking status, clock drawing test score, and immediate and delayed word recall sum score measured at baseline, as well as incidence of dementia anytime during follow-up. In Model III, we explored all above-mentioned correlates, except instead of number of comorbidities, we incorporated history of specific medical conditions. NHATS sampling weights of the sample design were incorporated in all models (39).

We conducted a series of sensitivity analyses to determine whether coefficients remained similarly associated with the different patterns of occurrence. First, we excluded individuals with incident probable and possible dementia, and secondly, we excluded individuals who were severely depressed (score PHQ-2 score of ≥5); by conducting these analyses, we aimed to assess whether associations remained robust independently of related etiologies. Thirdly, we conducted analyses stratified by white and black race to assess whether associations remained the same by race; associations among Hispanics were not examined due to insufficient power. All analyses were performed using Stata version 14.0.

Results

Patterns of Frailty and CI Occurrence

Of 7,497 community-dwelling participants, 3,848 (59.4%) were free of frailty and CI/dementia at baseline with a median follow-up of 5 years (IQR = 4). Among those without frailty and CI/dementia at baseline, 2,183 (61.2%) developed neither during the 5-year follow-up, of which 167 (6.2%) died during follow-up before any of the outcomes could occur; 343 (8.3%) developed frailty first, of which 58 (15.8%) developed subsequent CI; 1,014 (24.4%) developed CI first, of which 84 (7.4%) developed subsequent frailty; and 308 (6.0%) developed frailty-CI co-occurrence (Table 2). A majority of individuals for whom CI and frailty co-occurred had developed dementia sometime during the follow-up period (63.0%), and over a third (35.0%) of those who developed CI first developed dementia sometime during the follow-up period. However, only 9.1% of those who developed frailty first developed dementia sometime during the follow-up period (Table 2).

Determinants of Distinct Patterns of Frailty and CI Occurrence

In Model I, females were at greater risk of developing frailty first (SHR = 1.52, 95% confidence interval [ci] 1.19 to 1.95), but had

Table 2. Nationally-Representative Estimates of Baseline Population Characteristics by Order of Cognitive Impairment (CI) or Frailty Onset (n = 3,848)[a]

	Overall 3,848 (100)	Neither CI nor Frailty 2,183 (61.2)	Incident CI Before Frailty 1,014 (24.4)	Incident Frailty Before CI 343 (8.3)	CI-Frailty Co-occurrence 308 (6.0)
Age	73.2 (6.8)	72.2 (6.2)	74.3 (6.9)	74.9 (6.8)	77.7 (7.2)
Female	2,178 (55.5)	1,210 (54.1)	555 (53.9)	228 (66.6)	185 (60.1)
Race					
White, non-Hispanic	2,963 (86.9)	1,722 (88.3)	755 (84.4)	273 (87.7)	213 (81.7)
Black, non-Hispanic	638 (5.9)	332 (5.3)	183 (6.7)	51 (5.8)	72 (9.8)
Hispanic	144 (4.2)	66 (3.4)	51 (6.0)	11 (4.1)	16 (6.0)
Income					
1st quartile	719 (17.7)	386 (15.2)	232 (20.0)	69 (19.9)	105 (30.4)
4th quartile	974 (29.9)	617 (32.9)	237 (27.1)	67 (21.9)	53 (21.6)
Incident Dementia	619 (13.4)	11 (0.5)	378 (35.0)	34 (9.1)	196 (63.0)
Depression	350 (8.6)	158 (6.6)	93 (9.2)	48 (15.0)	51 (18.3)
Activities of daily living					
Moderate disability	737 (18.2)	200 (15.0)	347 (19.3)	100 (31.2)	90 (27.9)
Severe disability	207 (4.5)	40 (3.1)	80 (3.5)	36 (10.0)	51 (15.7)
Current smoker	318 (16.0)	189 (16.4)	64 (12.0)	39 (21.5)	26 (20.3)
Gait speed < 0.8 m/s	1,845 (42.5)	930 (37.9)	499 (43.3)	212 (61.0)	204 (61.3)
History of surgery	1,438 (37.1)	741 (33.9)	375 (37.3)	172 (50.4)	150 (51.4)
Hospitalization	620 (14.9)	290 (12.5)	172 (15.9)	84 (23.8)	74 (;22.7)
Number of comorbidities					
0	759 (21.3)	516 (25.1)	187 (19.5)	25 (7.0)	31 (10.1)
1	1,251 (32.8)	743 (34.2)	350 (34.7)	83 (24.0)	75 (23.6)
2	1,040 (26.0)	551 (24.5)	282 (26.5)	119 (34.5)	88 (27.9)
3	519 (13.1)	259 (11.6)	126 (12.5)	61 (18.1)	73 (23.5)
4 or more	279 (6.8)	114 (5.5)	69 (6.7)	55 (16.4)	41 (15.0)
History of cancer	1,034 (26.5)	558 (25.1)	272 (27.3)	107 (29.7)	97 (33.1)
History of hip fracture	117 (2.5)	41 (1.5)	28 (3.5)	14 (3.0)	24 (7.6)
History of heart disease	586 (14.6)	300 (13.4)	143 (13.5)	74 (21.5)	69 (21.9)
History of high blood pressure	2,495 (61.6)	1,258 (59.2)	651 (61.0)	253 (72.4)	233 (73.4)
History of arthritis	1,967 (49.9)	1,014 (45.5)	508 (49.3)	247 (73.5)	198 (65.4)
History of osteoporosis	735 (19.5)	380 (17.7)	192 (19.8)	94 (29.6)	69 (23.3)
History of diabetes	828 (19.9)	410 (17.0)	228 (21.9)	102 (29.7)	88 (28.4)
History of lung disease	537 (13.9)	290 (13.0)	120 (11.8)	73 (22.6)	54 (18.7)
History of stroke	288 (6.6)	114 (4.6)	85 (7.4)	40 (11.4)	49 (16.1)
Subjective well-being (range 0–22)	17.9 (2.9)	18.0 (2.8)	17.9 (2.8)	16.9 (3.3)	17.3 (3.3)
Years of follow-up	3.4 (2.0)	2.8 (2.2)	4.3 (1.4)	4.3 (1.2)	4.4 (1.1)

Note: [a]Raw numbers and weighted percentages (%) for categorical characteristics, as well as weighted means and raw standard deviations (*SD*) for continuous characteristics are presented, except for years of follow-up, where median and interquartile range is provided.

lower risk of developing CI first (SHR = 0.85, 95% ci 0.74 to 0.98). Both Hispanics (SHR = 1.64, 95% ci 1.21 to 2.21) and blacks (SHR = 1.33, 95% ci 1.12 to 1.60) were at higher risk of developing CI before frailty than whites; blacks were also at higher risk of CI-frailty co-occurrence than whites (SHR = 1.95, 95% ci 1.43 to 2.67). Higher educational attainment had a dose-response, protective association with developing CI first and CI-frailty co-occurrence. Income and residence were not strongly associated with any patterns (Table 3).

In Model II, being female remained strongly associated with developing frailty first (SHR = 1.45, 95% ci 1.05 to 2.03); however, was no longer associated with developing CI first (SHR = 1.00, 95% ci 0.82 to 1.21). Race and education lost strong significance; however, higher income was associated with a lower risk of developing CI-frailty co-occurrence (SHR = 0.73, 95% ci 0.59 to 0.89). Current smokers had greater risk of developing frailty first (SHR = 1.98, 95% ci 1.30 to 2.99) and CI-frailty co-occurrence (SHR = 1.99, 1.25 to 3.18), and borderline lower risk of developing CI first (SHR = 0.74, 95% ci 0.55 to 1.01). Interestingly, persons who developed possible or probable dementia by the end of follow-up were at 2.60 times greater risk of developing CI before frailty (95% ci 2.09 to 3.24) and were at 8.77 times greater risk of CI-frailty co-occurrence compared to those without dementia (95% ci 5.79 to 13.28). Conversely, those with incident dementia were about 62% less likely to develop frailty before CI (SHR = 0.38, 95% ci 0.21 to 0.68). Additionally, number of comorbidities was positively associated with frailty occurrence before CI, but neither CI before frailty nor CI-frailty co-occurrence; specifically, those with one comorbidity were at 2.51 times greater risk (SHR = 2.51, 95% ci 1.15 to 5.47), and those with 4+ comorbidities were at 6.48 times greater risk of developing frailty first (SHR = 6.48, 95% ci 2.71 to 15.48) (Table 4).

In Model III, being female was no longer associated with elevated risk of developing frailty first (SHR = 1.42, 95% ci 0.98 to 2.04). As in Model II, race and education were not strongly associated with any patterns of occurrence, though higher income was associated with a lower risk of CI-frailty co-occurrence (SHR = 0.74,

Table 3. Model I: Demographic Correlates of Different Patterns of Incident Frailty-Cognitive Impairment (CI) Occurrence in Community-Dwelling Older Adults (n = 3,848)[a]

	Outcome 1: CI first Competing Risks: Frailty First, Co-occurrence, Death	Outcome 2: Frailty first Competing Risks: CI First, Co-occurrence, Death	Outcome 3: Co-occurrence Competing Risks: CI First, Frailty First, Death
Baseline age (knots at 75, 85, and 95 y)			
Age spline covariate 1	1.028 (1.013, 1.042)**	1.044 (1.019, 1.070)**	1.108 (1.076, 1.141)**
Age spline covariate 2	0.976 (0.935, 1.019)	0.948 (0.876, 1.026)	0.950 (0.891, 1.013)
Female	0.848 (0.738, 0.975)**	1.519 (1.185, 1.948)**	1.009 (0.773, 1.316)
Race			
White	Ref	Ref	Ref
Black	1.333 (1.120, 1.587)**	1.078 (0.778, 1.492)	1.954 (1.431, 2.667)**
Hispanic	1.636 (1.210, 2.213)**	1.054 (0.531, 2.091)	1.333 (0.742, 2.394)
Other minority	1.423 (0.942, 2.150)	1.175 (0.530, 2.601)	1.358 (0.590, 3.126)
Education			
8th Grade or Less	Ref	Ref	Ref
9th–12th Grade (no diploma)	0.914 (0.659, 1.267)	0.872 (0.452, 1.683)	0.705 (0.423, 1.175)
High School Diploma or Equivalent	0.895 (0.670, 1.196)	1.138 (0.630, 2.057)	0.499 (0.317, 0.785)**
Some College but no Degree	0.757 (0.562, 1.020)	0.876 (0.477, 1.608)	0.583 (0.365, 0.931)**
Associates or Bachelor's Degree	0.693 (0.505, 0.952)**	0.776 (0.403, 1.492)	0.343 (0.199, 0.590)**
Graduate Degree	0.507 (0.356, 0.722)**	0.684 (0.338, 1.381)	0.353 (0.188, 0.665)**
Residence (Residential Care, non-nursing home vs. Community)	0.828 (0.546, 1.255)	0.623 (0.310, 1.256)	1.199 (0.668, 2.152)
Income	0.961 (0.894, 1.033)	0.963 (0.846, 1.095)	0.870 (0.751, 1.008)

Note: [a]Subdistribution hazard ratios (95% confidence intervals) are presented from a Fine & Gray competing risks model, which treated each of the patterns of incident frailty/CI occurrence as mutually exclusive outcomes, accounting for mortality and other respective patterns of occurrence, where ** $p < .05$.

Table 4. Model II: Health Correlates of Different Patterns of Incident Frailty-Cognitive Impairment (CI) Occurrence in Community-dwelling Older Adults (n = 3,848)[a]

	Outcome 1: CI first Competing Risks: Frailty first, Co-occurrence, Death	Outcome 2: Frailty first Competing Risks: CI first, Co-occurrence, Death	Outcome 3: Co-occurrence Competing Risks: CI first, Frailty first, Death
Incident dementia[b]	2.604 (2.094, 3.240)**	0.375 (0.208, 0.677)**	8.770 (5.794, 13.275)**
Memory (Immediate & Delayed Word Recall Sum Score)	0.906 (0.865, 0.950)**	0.997 (0.930, 1.069)	0.970 (0.885, 1.063)
Executive functioning (Clock Drawing Score)	0.766 (0.665, 0.882)**	1.535 (1.204, 1.957)**	0.893 (0.693, 1.151)
Ever had surgery	0.914 (0.752, 1.111)	1.210 (0.873, 1.675)	1.441 (1.002, 2.071)**
Current smoker	0.742 (0.547, 1.006)	1.974 (1.304, 2.988)**	1.992 (1.248, 3.179)**
Depression	0.979 (0.687, 1.395)	0.976 (0.593, 1.607)	1.443 (0.902, 2.309)
ADL			
No disability	Ref	Ref	Ref
Moderate disability	0.996 (0.782, 1.268)	1.766 (1.235, 2.525)**	1.309 (0.828, 2.067)
Severe disability	0.642 (0.380, 1.084)	1.527 (0.806, 2.895)	2.231 (1.267, 3.928)**
Gait Speed ≤ 0.8	0.889 (0.734, 1.077)	1.275 (0.892, 1.824)	1.158 (0.801, 1.673)
History of hospitalization	1.004 (0.769, 1.311)	1.291 (0.900, 1.853)	0.725 (0.437, 1.204)
Number of comorbidities			
0	Ref	Ref	Ref
1	0.914 (0.688, 1.215)	2.508 (1.151, 5.468)**	0.990 (0.535, 1.834)
2	0.889 (0.665, 1.188)	4.575 (2.116, 9.890)**	1.094 (0.595, 2.011)
3	1.002 (0.710, 1.414)	2.390 (0.994, 5.747)	1.616 (0.851, 3.070)
4 or more	0.746 (0.474, 1.175)	6.480 (2.712, 15.481)**	1.409 (0.675, 2.939)
Subjective well-being	1.006 (0.970, 1.042)	0.935 (0.883, 0.990)**	0.991 (0.933, 1.052)

Notes: ADL = activities of daily living.

[a]Subdistribution hazard ratios (95% confidence intervals) are presented from a Fine & Gray competing risks model, which treated each of the patterns of incident frailty/CI occurrence as mutually exclusive outcomes, accounting for mortality and other respective patterns of occurrence, where ** $p < .05$. Model is adjusted for age, sex, race, education, income, and residence. [b]Incident dementia comprises of both "Probable" and "Possible" dementia developed anytime during the follow-up period after baseline (2012–2016).

Table 5. Model III: Health Correlates of Different Patterns of Incident Frailty-Cognitive Impairment (CI) Occurrence by Specific Comorbidities (n = 3,848)[a]

	Outcome 1: CI first Competing Risks: Frailty first, Co-occurrence, Death	Outcome 2: Frailty first Competing Risks: CI first, Co-occurrence, Death	Outcome 3: Co-occurrence Competing Risks: CI first, Frailty first, Death
Incident dementia	2.616 (2.103, 3.254)**	0.366 (0.202, 0.665)**	8.997 (5.979, 13.538)**
Memory (Immediate & Delayed Word Recall Sum Score)	0.909 (0.868, 0.952)**	1.000 (0.932, 1.074)	0.963 (0.878, 1.056)
Executive functioning (Clock Drawing Score)	0.775 (0.673, 0.892)**	1.506 (1.174, 1.932)**	0.900 (0.685, 1.183)
Ever had surgery	0.931 (0.758, 1.142)	1.179 (0.833, 1.668)	1.422 (0.982, 2.060)
Current smoker	0.744 (0.550, 1.007)	2.115 (1.371, 3.262)**	1.867 (1.144, 3.049)**
Depression	0.969 (0.673, 1.394)	0.988 (0.590, 1.656)	1.350 (0.805, 2.266)
ADL			
No disability	Ref	Ref	Ref
Moderate disability	0.990 (0.777, 1.262)	1.713 (1.188, 2.468)**	1.312 (0.830, 2.074)
Severe disability	0.604 (0.353, 1.034)	1.329 (0.687, 2.571)	2.450 (1.373, 4.372)**
Gait Speed ≤ 0.8	0.891 (0.734, 1.083)	1.269 (0.884, 1.820)	1.164 (0.805, 1.681)
History of hospitalization	1.033 (0.791, 1.350)	1.303 (0.888, 1.914)	0.683 (0.411, 1.136)
History of cancer	1.114 (0.906, 1.369)	1.104 (0.772, 1.579)	1.270 (0.880, 1.832)
History of hip fracture	1.431 (0.861, 2.380)	0.830 (0.325, 2.118)	1.712 (0.786, 3.729)
History of heart disease	0.848 (0.646, 1.113)	1.074 (0.702, 1.642)	1.093 (0.690, 1.730)
History of high blood pressure	0.858 (0.705, 1.044)	1.354 (0.939, 1.953)	1.047 (0.706, 1.554)
History of arthritis	0.946 (0.804, 1.113)	1.859 (1.279, 2.702)**	0.997 (0.691, 1.439)
History of osteoporosis	1.122 (0.861, 1.463)	1.264 (0.849, 1.882)	0.892 (0.551, 1.444)
History of diabetes	0.908 (0.718, 1.147)	1.463 (1.006, 2.127)**	0.924 (0.614, 1.390)
History of lung disease	0.911 (0.701, 1.183)	1.426 (0.963, 2.111)	1.246 (0.780, 1.990)
History of stroke	1.035 (0.731, 1.464)	1.274 (0.785, 2.068)	1.481 (0.861, 2.550)
Subjective well-being	1.004 (0.968, 1.041)	0.943 (0.890, 1.000)**	0.992 (0.934, 1.053)

Notes: ADL = activities of daily living.

[a]Subdistribution hazard ratios (95% confidence intervals) are presented from a Fine & Gray competing risks model, which treated each of the patterns of incident frailty/CI occurrence as mutually exclusive outcomes, accounting for mortality and other respective patterns of occurrence, where ** $p < .05$. Model is adjusted for age, sex, race, education, income, and residence. [b]Incident dementia comprises of both "Probable" and "Possible" dementia developed anytime during the follow-up period after baseline (2012–2016).

95% ci 0.60 to 0.90). Consistent throughout Model III, incident dementia was strongly associated with higher risk of developing CI first (SHR = 2.62, 95% ci 2.10 to 3.25), and CI-frailty co-occurrence (SHR = 9.00, 95% ci 5.98 to 13.54), and was strongly associated with lower risk of developing frailty first (SHR = 0.37, 95% ci 0.20 to 0.67) (Table 5). A history of some conditions was associated with frailty first, including arthritis (SHR = 1.86, 95% ci 1.28 to 1.70), diabetes (SHR = 1.46, 95% ci 1.01 to 2.13), and lung disease (SHR=1.43, 95% ci 0.96 to 2.11); none were associated with CI first or CI-frailty co-occurrence (Table 5).

Sensitivity Analyses

Across sensitivity analyses, inferences remained consistent for associations related to incident dementia and number of comorbidities. Specifically, number of comorbidities remained strongly and positively associated with developing frailty first when we excluded 619 participants with possible and probable dementia (1 comorbidity: SHR=2.88, 95% ci 1.18 to 7.00; 4+ comorbidities: SHR=8.35, 95% ci 2.11 to 22.44) or when we excluded 350 participants with severe depressive symptoms (1 comorbidity: SHR = 2.35, 95% ci 1.06 to 5.20; 4+ comorbidities: SHR = 6.48, 95% ci 2.66 to 15.80). Among participants free of severe depressive symptoms, those with incident dementia had a higher risk of developing CI first (SHR = 2.79, 95% ci 2.21 to 3.51) and an even greater risk of developing CI-frail co-occurrence (SHR = 9.14, 95% ci 5.77 to 15.49), but had a reduced risk of developing frailty first (SHR = 0.46, 95% ci 0.25 to 0.85). Similarly, direction and magnitude of associations for number of comorbidities and incident dementia were robust after stratification by white and black race. Despite direction and magnitudes remaining similar among blacks, due to smaller sample sizes, the association between dementia and frailty before CI was not statistically significant, nor was the association between number of comorbidities and developing frailty first among blacks.

Discussion

In this study, different patterns of frailty and CI occurrence were documented and found to be associated with different correlates. Of note, results related to incident dementia and comorbidities with regard to patterns were consistent. Specifically, incident dementia anytime during the follow-up period, as a surrogate of underlying neurodegenerative pathologies, was strongly associated in all models with a high risk of developing CI before frailty (SHR = 2.60 95% ci 2.09 to 3.24), and an even higher risk of CI-frailty co-occurrence (SHR = 8.77 95% ci 5.79 to 13.28), as well as a reduced risk of developing frailty before CI (SHR = 0.38, 95% ci 0.21 to 0.68). Comorbidities were consistently associated with developing frailty first, but not CI first or CI-frailty co-occurrence.

Our findings suggest that order of occurrence may indicate varying underlying etiologic processes with distinct pathological trajectories. Dementia is a syndrome that develops over decades and manifests with severe cognitive deficits across multiple cognitive domains, ultimately affecting daily function (40). AD is recognized as the most common type of dementia among older adults in the United States (41–43), followed by vascular dementia (44), though growing evidence suggests that individuals are likely to have mixed pathologies (44,45). In this study, CI-frailty co-occurrence was the pattern most strongly associated with incident dementia. It is possible that these participants were already on the dementia pathway at the time co-occurring CI and frailty were observed. Similarly, CI before frailty occurrence demonstrated a positive association with incident dementia, although to a lesser degree. Unlike with other patterns of frailty-CI occurrence, participants with incident dementia anytime during the study period had a reduced risk of frailty onset before CI. We hypothesize that dementia and other age-associated pathologies are important influences on the emergence of frailty when CI co-occurs or precedes frailty. We further hypothesize that frailty onset before CI represents a pathway that is distinct from other onset patterns with etiologies that may be vascular or inflammatory in nature given its relation to history of arthritis, diabetes, and lung disease. Furthermore, CI that develops subsequent to frailty may differ in terms of etiology from CI in other patterns.

There are several notable limitations to this study. We would be remiss not to mention the potential biases introduced by measurement error. However, the non-trivial sample sizes for all three groups makes it unlikely that the different patterns of associations were primarily driven by measurement error. Additionally, using cognitive performance measures to screen for impairment is particularly challenging. Measures with higher sensitivity to impairment (eg, Mini-Mental State Examination) are not designed to discriminate well at higher levels of cognitive function. The clock drawing test was selected in NHATS for its wide-spread use as screening tools for dementia, and compared to the Mini-Mental State Examination, the clock drawing test is known to have less education bias and language barrier (46,47), greater sensitivity to AD-related cognitive decline, and is better able to identify executive dysfunction among people with normal Mini-Mental State Examination (48). Therefore, it is suitable for a variety of evaluation settings where speed and ease of assessment are essential in this large, heterogeneous sample. Additionally, NHATS lacks any biomarker data or data on dementia sub-types and related pathologies, both of which would help assess underlying mechanisms associated with different patterns of frailty-CI onset. Furthermore, issues regarding overlapping operational definitions of CI and dementia (ie, endogeneity) in analyses examining both dementia and CI, could be a notable limitation. However, our goal was not to model dementia relative to CI as a time-dependent outcome; instead, dementia was treated as time-independent covariate, whose purpose was to distinguish neurodegenerative pathologies from others underlying CI, using the same logic from the definition of cognitive frailty given by IAGG/IANA, which requires the absence of dementia to try to exclude neurodegenerative etiologies (28). We are aware of the difficulty of "pinpointing" etiology without the use of diagnostic neuroimaging tools (volume, default mode network) or genetic markers (eg, ApoE4), which would be cost-prohibitive in large survey studies such as NHATS. To address this issue by taking full advantage of all available information, we used a "temporal criterion" as recently recommended in the definition of "cognitive frailty" (49). The validity of the "temporal criterion" hinges on the assumption that the order by which physical and CIs manifest clinically matches their underlying sequence of pathological development, which may or may not be true.

Notwithstanding these limitations, this study provides useful etiological insights for the next generation of research to inform future, targeted use of more costly imaging methods. Several strengths support the validity of these findings. The use of this heterogeneous, nationally-representative sample of U.S. Medicare beneficiaries aged 65 years and older provides sufficient power and supports generalizability of these findings to older adults nationwide. Secondly, NHATS provided up to 5 years of longitudinal data, providing sufficient time to assess temporal ordering of frailty and CI occurrence.

Recently, with increased attention on the frailty syndrome and its relationship to cognitive aging, consensus papers have suggested

expanding the definition of frailty to include cognition (28). This novel construct, "cognitive frailty," represents the presence of both frailty and CI in the absence of dementia (13,28), and was proposed with the goal of identifying individuals with "reduced cognitive reserve" that is a potentially reversible consequence of frailty rather than the result of neurodegenerative disorders (28). Growing evidence suggests that frailty may be preventable and modifiable as indicated by prior randomized clinical trials and cohort studies (7,12), which provides a promising avenue for developing better-targeted interventions to prevent CI related to reduced cognitive reserve caused by frailty. We hypothesize that unlike those who develop CI before frailty or CI-frailty co-occurrence, persons who develop frailty before CI represent this "cognitive frailty" group who might benefit most from interventions designed to target CI caused by reduced physiologic reserve. Whether this hypothesis holds or not, our findings emphasize the importance of assessing temporal ordering of frailty and CI in the study of causal mechanisms, improving upon the cross-sectional definition of cognitive frailty, and validating it as a potentially useful clinical entity (50), as well as highlighting the potential value in targeting interventions to improve care in older adults.

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Conflict of interest statement

None declared.

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