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Association of Longitudinal Trajectories of Physical Frailty With Dementia Status in Older Adults: A National Cohort Study

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ABSTRACT

Background and Objectives: The longitudinal patterns of change in physical frailty and their associations with the subsequent dementia risk remain unclear. This study aimed to (1) explore the long-term trajectories of physical frailty over a 6-year period in older adults without dementia at baseline; (2) identify the socio-demographic and health-related factors associated with different physical frailty trajectories; and (3) examine the longitudinal relationships between different physical frailty trajectories and subsequent risk of dementia.

Research Design and Methods: This national cohort study used data from the National Health and Aging Trends Study (NHATS) conducted in the United States from 2015 to 2021 and included adults aged ≥ 65 without dementia ($n = 2245$) at baseline in 2015. Group-based trajectory modeling was used to describe the longitudinal changes. Socio-demographic and health-related characteristics were compared across the identified physical frailty trajectories using bivariate analyses, employing Rao–Scott chi-square tests for categorical variables and design-based F-tests for continuous variables. Multinomial logistic regression analyses were conducted to examine the relationships between different frailty trajectories and subsequent dementia status.

Results: Three frailty trajectories were identified: low-stable (74.00%), low-increasing (21.14%), and high-level (4.86%). Participants in the low-increasing and high-level groups were predominantly older, female, minorities, unmarried, and less educated and had a lower income, more comorbidities, and greater anxiety and depression symptoms ($p < 0.001$). Compared with the low-stable group, older adults in the low-increasing group had higher risk of possible dementia (RRR: 2.37, 95% CI: 1.41–3.97, $p < 0.001$) and probable dementia (RRR: 1.71, 95% CI: 1.08–2.73, $p = 0.02$); similarly, older adults in the high-level group had higher risks of possible dementia (RRR: 4.24, 95% CI: 1.74–10.36, $p < 0.001$) and probable dementia (RRR: 2.99, 95% CI: 1.32–6.76, $p = 0.01$). No significant differences were found in the risk of dementia between the high-level frailty group and the low-increasing frailty group ($p > 0.05$).

Conclusion and Implications: This study highlighted the importance of regular frailty monitoring for early detection and informed future interventions that could delay frailty progression and potentially reduce dementia risk.

Fen Ye and Weijiao Zhou made equal contributions to this manuscript.

Summary

- Three frailty trajectories were identified: low-stable (74.00%), low-increasing (21.14%), and high-level (4.86%), with increasing frailty linked to a higher dementia risk.
- Key predictors of worsening frailty included older age, minority status, lower socioeconomic status, more comorbidities, and greater mental health burdens (anxiety and depression).
- The low-increasing and high-level frailty groups were at significantly greater risk of developing possible and probable dementia compared to the low-stable group.
- Early identification of frailty trajectories offers opportunities for targeted interventions to slow frailty progression, reduce dementia risk, and improve health outcomes.

1 | Background

Dementia is a progressive and heterogeneous syndrome that significantly compromises cognitive function and daily living activities, leading to significant dependency, disability, and broad societal impacts [1]. Over 55 million people worldwide are living with dementia, and the number is expected to increase to 78 million by 2030 and 139 million by 2050 [1, 2]. The prevalence of dementia among older adults aged 65 years and older is as high as 10% and increases with age [3], and 91% of patients manifest symptoms after the age of 65 [1]. Population aging, with the growing prevalence of dementia and compounded by the current lack of a definitive cure, contributes to the global health burden and causes high medical, social, and informal care costs; the care costs were reported to be US$1.3 trillion in 2019, approximately 1.5% of the global GDP, and are estimated to rise to US$2.8 trillion by 2030 [1, 4]. Given the limited efficacy of existing pharmacological treatments, identifying and managing modifiable risk factors (e.g., frailty) is critical for dementia prevention or delaying its progression [1]. A 2020 report on dementia prevention, intervention, and care revealed that approximately 40% of global dementia cases could be prevented or delayed by addressing modifiable risk factors throughout an individual's life course [5]. Notably, frailty has been identified as a moderator in the relationship between Alzheimer's disease pathology (e.g., amyloid protein deposition) and dementia, potentially amplifying the effects of certain risk factors and accelerating cognitive decline [5]. This underscores the importance of prevention as a strategy to reduce the global dementia burden, emphasizing proactive management over treatment after onset.

Frailty, a complex and multifaceted condition associated with aging, is a dynamic concept that integrates both biomedical and psychosocial elements (e.g., physical, sensory, social, cognitive, psychological, and nutritional aspects) [6, 7]. It can be defined either as a unidimensional physical phenomenon characterized by exhaustion, low physical activity, shrinking, low walking speed, and weakness or as a broader multidimensional deficit accumulation model [8, 9]. The physical frailty model is particularly linked to various forms of cognitive impairment and dementia, including Alzheimer's disease, highlighting its importance in predicting dementia risk [9, 10]. Physical frailty (hereafter referred to as frailty) is characterized by reduced physiological reserves and resistance to stressors resulting from cumulative declines across multiple physiological systems [11]. It affects approximately 10% of community-dwelling older adults and up to 50% of long-term care residents [12–14]. This condition significantly impacts an individual's health and quality of life, leading to an increased risk of cognitive impairment and dementia [7, 15, 16]. This may be due to factors such as reduced neural reserve and increased vulnerability to systemic and cerebral pathologies that impair cognitive functions [10]. A meta-analysis involving 14,302 individuals indicated that frailty alone was significantly associated with the incidence of dementia (hazard ratio [HR]: 1.47, 95% confidence interval [CI]: 0.89–2.40) [17]. This relationship was further substantiated by a large-scale prospective study involving a cohort of 143,215 participants from the UK Biobank dataset [18]. However, the study relied on single measurements to ascertain the frailty status at certain points in time and overlooked the dynamic nature of frailty, although heterogeneity in frailty progression was identified [19]. Such cross-sectional or infrequent longitudinal measurements fail to fully capture the continuous and nuanced changes that individuals may experience in their frailty status over time. The observed heterogeneity in frailty progression—indicating that frailty does not progress in a linear manner or evolve uniformly across all individuals—poses significant research challenges and raises questions about the correlations between different patterns of frailty trajectories, characterized by specific patterns and rates of change, and the risk of subsequent dementia [19, 20].

Notably, frailty is not an inevitable result of aging but a potentially reversible condition [21]. Evidence suggests that with targeted interventions, such as physical activity, nutritional support, and comprehensive healthcare management, the decline in physiological systems can be addressed, potentially restoring some level of function and mitigating the progression to more severe outcomes associated with frailty [21]. Moreover, Petermann-Rocha, Lyall, Gray, et al. found that frailty is linked to an increased risk of dementia even before the onset of cognitive symptoms and that this risk is present in both older and middle-aged adults, highlighting the need for early management of frailty as a preventive measure against dementia [18]. Understanding the relationships between varying patterns of frailty trajectories over time and the risk of developing dementia is crucial for developing targeted early intervention strategies and warrants further investigation. Thus, this study aimed to (1) investigate the long-term trajectories (6 years) of frailty among older adults without dementia at baseline using data from the National Health and Aging Trends Study (NHATS); (2) identify socio-demographic and health-related factors associated with different physical frailty trajectories; and (3) elucidate the relationship between frailty trajectories and the risk of subsequent dementia.

2 | Methods

2.1 | Data Sources and Study Population

The NHATS is an annual, nationally representative longitudinal study of Medicare beneficiaries aged 65 years and older [22].

Data are collected annually through in-home interviews conducted by trained professionals. Participants share detailed information on various aspects of their lives, including health status, physical and cognitive abilities, daily activities, medical conditions, and social support. These interviews incorporate both self-reported data and performance-based evaluations. NHATS began in 2011 (Round 1), with the sample was replenished in 2015 to maintain its nationally representative (Round 5). In both Rounds 1 and 5, participants were selected using a stratified 3-stage sample design with oversampling of individuals aged 90 years and older and non-Hispanic Blacks [22]. The weighted response rates in these rounds were 71.5% and 96%, respectively. The NHATS was approved by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board, and all participants provided informed consent.

This study used data from 2015 to 2021 (6 survey rounds, excluding the 2020 round due to unavailable data) and included participants (1) without possible/probable dementia (the measurement of dementia status was detailed in Measures) in 2015, (2) who had frailty in the first 3 or more rounds (2015–2017), and (3) who had a dementia status (including no, possible, or probable dementia) recorded in the 2021 survey round. Among 5823 older adults with no dementia in 2015, 2611 participants were excluded for the following reasons; 846 had missing data on frailty in 2015, 1076 had missing data on frailty (583 were deceased or lost to follow-up) in 2016 and 689 had missing data on frailty (354 were deceased or lost to follow-up) in 2017. In total, 3212 participants were included in the trajectory group modeling of frailty. Of these, 929 participants were deceased or lost to follow-up in 2021, 12 were excluded for missing dementia data in 2021, and 26 were excluded for missing covariate data. The final cohort for analysis comprised 2245 participants (see Figure 1).

2.2 | Measures

2.2.1 | Frailty (Collected From 2015 to 2021, Rounds 5–11)

Following an approach published elsewhere [23], frailty was assessed using the Fried Frailty Phenotype (FFP) paradigm, with 5 criteria obtained from self-report and physical measures, namely exhaustion, low physical activity, shrinking, low walking speed, and weakness [8]. Each item was coded as "1" when the participant met the item requirements; the sum score of these five items was calculated. Participants with a sum score of 0–2 were classified as "non-frail," and those with a sum score of 3–5 were classified as "frail" (see Supporting Information S1: Tables S1–S3).

2.2.2 | Dementia Status (Collected in 2021, Round 11)

The NHATS classified participants as having no dementia, possible dementia, and probable dementia using a validated algorithm (sensitivity: 85.7%; 95% CI: 69.7–95.2) [24] based on the following information: cognitive testing (memory, orientation, executive function), self- or proxy-reported dementia diagnosis, and AD8 Dementia Screening Interview score (see Supporting Information S1: Tables S4 and S5). Probable dementia in the NHATS was determined by a reported diagnosis, AD8 criteria fulfillment (proxy reports only), or scores below 1.5 standard deviations in two or more domains (orientation ≤ 3, memory ≤ 3, executive functioning ≤ 1). Possible dementia was determined by a score below 1.5 standard deviations in one domain. All other participants were classified as having no dementia.

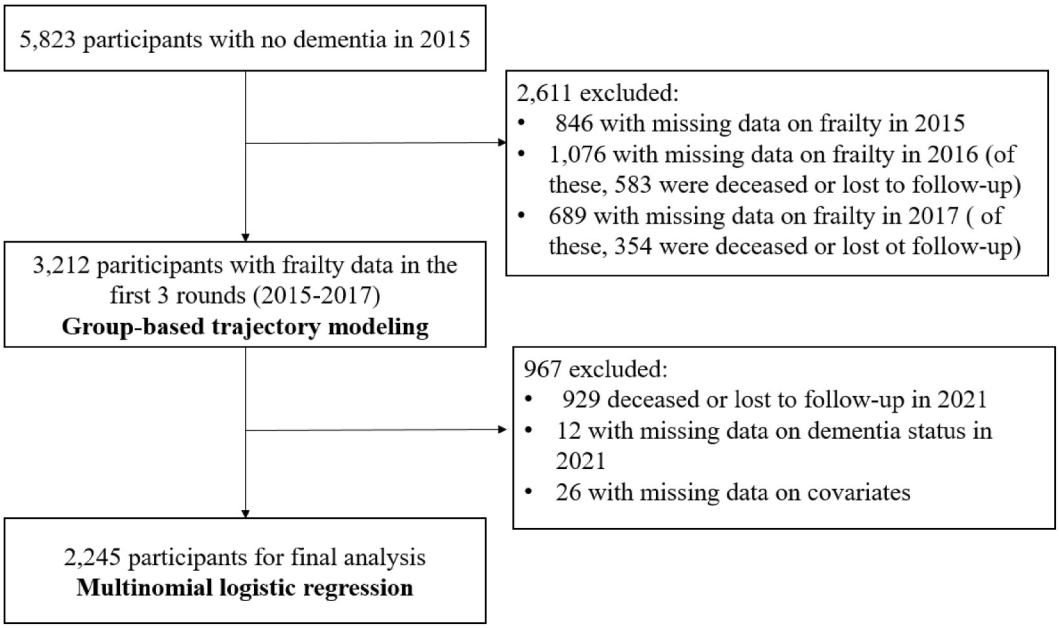

FIGURE 1 | Participants selection flowchart. Of the 3212 participants included for GBTM, there were 2050 in the low-stable group, 827 in the low-increasing group, and 335 in the high-level group. The dotted lines indicate 95% CIs.

2.2.3 | Covariates (Collected in 2015, Round 5)

Covariates were selected based on clinical experiences and established factors influencing the relationship between frailty and dementia [5, 25, 26]. The socio-demographic characteristics were age (categorized in 5-year increments), sex, race and ethnicity, marital status, education status, and annual income. Health-related characteristics encompassed a spectrum of chronic conditions, ascertained via a self-reported medical history of heart disease, heart attack, lung disease, hypertension, diabetes mellitus, arthritis, osteoporosis, stroke, and cancer (the number of comorbidities ranged from 0 to 9). Furthermore, depression and anxiety symptoms were quantified using an aggregate score of the Generalized Anxiety Disorder-2 scale and Patient Health Questionnaire-2 [27, 28], each comprising 2 items scored from 1 (not at all) to 4 (nearly every day), with total scores ranging from 4 to 16 and a higher score indicating severer depression and anxiety symptoms.

2.3 | Statistical Analysis

Group-based trajectory modeling (GBTM) was conducted to describe frailty trajectories [29]. First, it was assumed that the frailty trajectories of older adults would be categorized or follow 2 to 6 groups with consideration of the model brevity and clinical practice. The optimal number of trajectories was selected based on the Bayesian Information Criterion (BIC) values (a smaller BIC indicates a better fit) [29, 30]. Second, the optimal number of trajectories was fixed, and different polynomial forms for each group were tested by intercept only or by linear, quadratic, or cubic terms [31]. The optimal functional form was defined using the χ^2 test. The GBTM was used to calculate the likelihood of participants belonging to each trajectory group. The following indices were used to determine the goodness of model fit: average group posterior probabilities (AvePP) > 70%, odds of correct classification (OCC) ≥ 5 [32], and a minimum sample size > 10% [29].

Once the frailty trajectories were determined, the following analyses were conducted while controlling for the complex sample design and weights. Taylor series linearization methods were used for variance estimation. Descriptive statistics (percentages for categorical variables, means and standard errors for continuous variables) were calculated to summarize the baseline characteristics. Bivariate analyses were used to compare the socio-demographic and health-related characteristics of different trajectories' affiliations. Rao–Scott chi-square tests for categorical variables and design-based F-tests for continuous variables were used to assess bivariate differences. Multinomial logistic regression was used to examine the socio-demographic and health-related characteristics associated with different trajectories. To investigate the associations between distinct trajectories and dementia status, multinomial logistic regression analyses were conducted while controlling for socio-demographic and health-related factors. The relative risk reduction (RRR) and 95% CI were calculated. All analyses were performed using Stata/SE 17.0 (Stata Corp, College Station, TX, USA), with a 2-sided p value < 0.05 considered as statistically significant.

3 | Results

3.1 | Characteristics of the Study Population

A total of 2245 participants were included in the final cohort, representing 21.01 million older adults. The baseline characteristics of the population are shown in Table 1. Most of the population were 70 years and older (62.22%), females (55.22%), White (85.38%), married or partnered (62.91%), and had some college degree or higher (66.65%). The average number of chronic conditions was 2.07 (SE = 0.03), and the average score of depression and anxiety was 5.20 (SE = 0.05).

3.2 | Trajectories of Frailty

The GBTM described 3 trajectories of physical frailty among the 3212 participants (see Figure 2). In the subset of 2245 participants, 74.00% had low-level frailty that remained low throughout follow-up (*low-stable group*), 21.14% had low-level frailty that rose gradually (*low-increasing group*), and 4.86% had high-level frailty that declined starting in 2019 (*high-level group*). The model fit indices indicated a good model fit (see Supporting Information S1: Tables S6–S8). We found differences in all the baseline characteristics among the trajectory groups. Compared with the low-stable group, older adults in the low-increasing and high-level groups were more likely to be older (proportion of 80 years older, Group 1: 10.08% vs. Group 2: 23.29% vs. Group 3: 31.33%), be female (51.80% vs. 63.25% vs. 72.38%), belong to minority groups (13.48% vs. 16.22% vs. 25.25%), be single (32.91% vs. 49.29% vs. 47.61%), have a lower education (college graduate and higher, 43.02% vs. 21.73% vs. 16.60%) and income (> 60,000$, 52.69% vs. 25.92% vs. 22.60%), present with more comorbidities (1.85 vs. 2.58 vs. 3.24), and have higher levels of anxiety and depression symptoms (4.93 vs. 5.72 vs. 7.03) (all $p < 0.001$).

3.3 | Predictors of Different Frailty Trajectories

The associations of socio-demographic and health-related factors with frailty trajectories were analyzed using the multinomial logistic regression, and the results are shown in Supporting Information S1: Table S9. Age, race/ethnicity, education, income, number of comorbidities, and anxiety and depression were associated with frailty trajectories, while sex and marital status were not. Specifically, taking the low-increasing group as the reference, older adults who were younger, were well-educated, had a higher income, presented with fewer comorbidities, and had lower levels of anxiety and depression symptoms were more likely to be in the low-stable group ($p < 0.05$); older adults who were older, were Hispanic, presented with more comorbidities, and had higher levels of anxiety and depression symptoms were more likely to be in the high-level group ($p < 0.05$).

TABLE 1 | Baseline characteristics of study population, stratified by frailty trajectories.

Characteristics	Total $n = 2245$	Group 1 (Low-stable) $n = 1544$	Group 2 (low-increasing) $n = 561$	Group 3 (high) $n = 140$	Statistics[a]
National estimates, million (%)	21.01	15.55 (74.00)	4.44 (21.14)	1.02 (4.86)	
Age, %					< 0.001
65–69	37.78	41.44	29.06	19.93	
70–74	30.36	30.75	29.92	26.40	
75–79	17.96	17.73	17.74	22.33	
80–84	9.24	7.16	14.38	18.52	
85–89	3.62	2.49	6.39	8.71	
90-	1.05	0.43	2.52	4.10	
Sex, %					< 0.001
Male	44.78	48.20	36.75	27.62	
Female	55.22	51.80	63.25	72.38	
Race/ethnicity, %					< 0.001
White	85.38	86.53	83.78	74.76	
Black	6.27	5.29	9.37	7.73	
Hispanic	5.75	5.20	5.28	16.15	
Other	2.61	2.99	1.57	1.37	
Marital status, %					< 0.001
Single	37.09	32.91	49.29	47.61	
Married or partnered	62.91	67.09	50.71	52.39	
Education level, %					< 0.001
Less than high school	9.44	7.04	16.10	17.09	
High school graduate	23.91	20.99	29.70	43.09	
Some college	29.41	28.94	32.47	23.22	
College graduate or higher	37.24	43.02	21.73	16.60	
Annual income ($), %					< 0.001
< 15,000	9.32	6.18	17.83	19.95	
15,000–29,999	15.85	13.05	22.44	29.79	
30,000–44,999	16.29	14.80	21.50	16.41	
45,000–60,000	12.98	13.28	12.31	11.25	
> 60,000	45.57	52.69	25.92	22.60	
No. of comorbidities, mean (SE)	2.07 (0.03)	1.85 (0.04)	2.58 (0.07)	3.24 (0.16)	< 0.001; 1 < 2 < 3[b]
Anxiety and depression symptoms, mean (SE)	5.20 (0.05)	4.93 (0.05)	5.72 (0.11)	7.03 (0.28)	< 0.001; 1 < 2 < 3[b]

Note: National estimates accounted for complex survey design.
Abbreviation: SE, standard error.
[a]*p* values compare older adults in different trajectory groups using Rao-Scott Chi-square or design-based F-tests.
[b]Multiple comparisons were conducted between trajectory groups.

3.4 | Trajectories of Frailty and Dementia Status

Out of 2245 participants with no dementia at baseline in 2015, 144 (6.41%) and 179 (7.97%) developed possible and probable dementia by 2021, respectively. The cases (proportion) of probable dementia in the low-stable, low-increasing, and high-level groups were 82 (5.31%), 71 (12.66%), and 26 (18.57%), respectively (see Supporting Information S1: Figure S1). The associations between frailty trajectories and dementia status are shown in Table 2 and Supporting Information S1: Table S10; the baseline socio-demographic (e.g., age, gender, and education) and health-related (e.g., comorbidities, mental health measures) factors were adjusted. The "no dementia" outcome was set as the reference category in the design-based multinomial logistic regression. Compared with the low-stable group, older adults in the low-increasing group had a higher risk of possible dementia (RRR:2.37, 95% CI: 1.41–3.97, $p < 0.001$) and probable dementia (RRR: 1.71, 95% CI: 1.08–2.73, $p = 0.02$) after controlling for

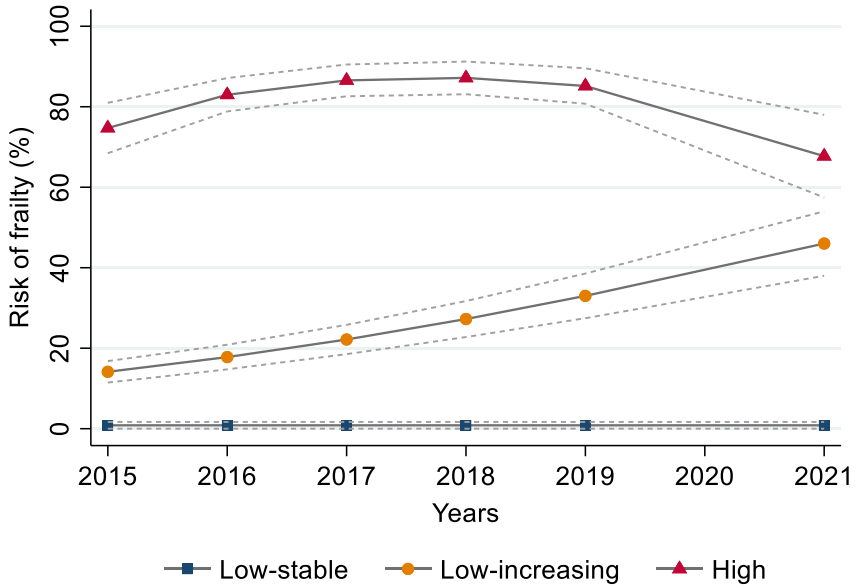

FIGURE 2 | Trajectories of physical frailty.

socio-demographic and health-related covariates; similarly, older adults in the high-level group had higher risks of possible dementia (RRR: 4.24, 95% CI: 1.74–10.36, $p < 0.001$) and probable dementia (RRR: 2.99, 95% CI: 1.32–6.76, $p = 0.01$) (Table 2). No significant differences were found in the risk of dementia between older adults in the high-level frailty group and those in the low-increasing frailty group ($p > 0.05$) (see Supporting Information S1: Table S10).

4 | Discussion

This longitudinal analysis of a national cohort identified 3 distinct patterns of change (namely, low-stable, low-increasing, and high-level) in frailty in older adults over a 6-year period. Both the low-increasing and high-level groups had a higher risk of developing dementia than the low-stable group. Interestingly, the dementia risk was not significantly different between the low-increasing and high-level frailty groups. The low-increasing frailty group comprised a larger population and contributed to a higher proportion of dementia cases than did the high-level group. It is worth noting that this group with a deteriorating trajectory was not readily identifiable at baseline, highlighting the importance of regular monitoring rather than single-time measures. Furthermore, this study identified that several socio-demographic and health-related characteristics could distinguish different frailty trajectories. Given the potential reversibility of frailty and its longitudinal association with future dementia status, public health initiatives designed for early identification and frailty amelioration could play a vital role in reducing the risk of dementia.

4.1 | Trajectories of Frailty

Monitoring the progression of frailty over time, rather than through static measurements, has emerged as a crucial factor in understanding its impact on the risk of dementia. Although previous research has identified frailty trajectories using longitudinal data, their primary focus was on the overlap between frailty and cognition using joint trajectory modeling [19]. This study advances this field by specifically examining the longitudinal association between different frailty trajectories in individuals without dementia at baseline and their subsequent dementia risk. Analytical approaches to trajectories presuppose the presence of diversity within a sample, which comprises undetected subpopulations that are homogeneous [33]. The trajectories of the high-level frailty group, which comprised 4.86% of the participants, are consistent with the literature that suggests that frailty tends to increase over time [34]. The unexpected reduction in the risk of dementia in the high-level frailty group starting from 2019 may be attributable to survivorship bias influenced by the COVID-19 pandemic, which may have led to higher mortality among the most vulnerable in this group [35]. This resulted in a post-pandemic follow-up cohort that disproportionately represented the healthier survivors, skewing the perceived risk downward. Such survival bias may underestimate the true dementia risk among high-frailty groups, leading to inaccurate assessments of disease burden and resource needs. This highlights the importance of accounting for external shocks, like the pandemic, in longitudinal studies to ensure robust and generalizable findings. The high-level frailty group represents a population at substantial risk for both adverse health outcomes and dementia. Trajectory analysis allows healthcare providers to monitor these individuals over time and allocate resources for intensive management, such as fall prevention programs, multimorbidity management, or advanced care planning [36]. As for the low-increasing and low-stable groups, their frailty level may not have reached the threshold of frailty severity that significantly elevated their mortality risk during the pandemic. The identification of a low-increasing group (21.14%) further supports that frailty is progressive, highlighting a critical window for intervention. This trajectory represents individuals whose frailty is progressing but has not yet reached severe levels. Personalized interventions, such as tailored exercise programs, nutritional

TABLE 2 | Association of frailty trajectories with dementia status.

	Possible dementia		Probable dementia	
	RRR (95% CI)	***p* value**	**RRR (95% CI)**	***p* value**
Frailty trajectories				
Group 1: low-stable	Reference		Reference	
Group 2: low-increasing	2.37 (1.41, 3.97)	< 0.001	1.71 (1.08, 2.73)	0.02
Group 3: high-level	4.24 (1.74, 10.36)	< 0.001	2.99 (1.32, 6.76)	0.01
Age				
65–69	Reference		Reference	
70–74	0.93 (0.45, 1.93)	0.85	2.12 (1.00, 4.49)	0.05
75–79	1.85 (0.91, 3.74)	0.09	2.71 (1.08, 6.78)	0.03
80–84	3.65 (1.89, 7.04)	< 0.001	5.48 (2.10, 14.28)	< 0.001
85–89	5.43 (2.53, 11.63)	< 0.001	9.44 (3.93, 22.68)	< 0.001
90-	5.81 (2.52, 13.40)	< 0.001	16.06 (6.25, 41.27)	< 0.001
Sex				
Male	Reference		Reference	
Female	0.88 (0.54, 1.45)	0.62	1.40 (0.82, 2.39)	0.21
Race/ethnicity				
White	Reference		Reference	
Black	1.30 (0.74, 2.26)	0.35	1.09 (0.57, 2.07)	0.80
Hispanic	1.47 (0.57, 3.75)	0.42	2.17 (0.70, 6.68)	0.18
Other	0.80 (0.22, 2.87)	0.73	1.39 (0.55, 3.47)	0.48
Marital status				
Single	Reference		Reference	
Married or partnered	0.95 (0.53, 1.68)	0.85	1.23 (0.73, 2.08)	0.43
Education level				
Less than high school	Reference		Reference	
High school graduate	1.08 (0.48, 2.43)	0.85	0.77 (0.40, 1.45)	0.41
Some college	0.89 (0.36, 2.19)	0.80	0.74 (0.40, 1.36)	0.33
College graduate or higher	0.70 (0.30, 1.62)	0.40	1.17 (0.55, 2.48)	0.68
Annual income ($)				
< 15,000	Reference		Reference	
15,000–29,999	0.54 (0.27, 1.10)	0.09	1.04 (0.53, 2.05)	0.91
30,000–44,999	0.56 (0.23, 1.35)	0.19	0.57 (0.27, 1.23)	0.15
45,000–60,000	0.37 (0.14, 1.03)	0.06	0.75 (0.26, 2.15)	0.59
> 60,000	0.29 (0.11, 0.79)	0.02	0.52 (0.17, 1.60)	0.25
No. of comorbidities	0.90 (0.74, 1.11)	0.32	1.10 (0.91, 1.32)	0.32
Anxiety and depression symptoms	1.11 (0.96, 1.27)	0.16	1.05 (0.94, 1.16)	0.39

Note: Multinomial logistic regression adjusting for complex survey design and weights. No dementia was set as the base outcome.
Abbreviations: CI, confidence interval; RRR, relative risk ratio.

support, and social engagement strategies, could be implemented to slow or even reverse frailty progression in this group [37, 38]. For the majority of participants (74%) who remained in the low-stable frailty group, trajectory analysis provides evidence for successful aging strategies. Public health efforts should focus on identifying and reinforcing the protective factors that enable individuals to maintain their health and prevent frailty progression. This could include encouraging healthy lifestyles, such as regular physical activity, a balanced diet, and preventive healthcare visits [39].

4.2 | Factors Associated With Frailty Trajectories

A previous review highlighted age as a leading factor in the acceleration of frailty, reinforcing this study's focus on older

populations [34]. Age-related physiological changes, such as reduced muscle mass, decreased bone density, and impaired immune function, contribute to increased vulnerability to frailty [40]. Additionally, older adults often experience a cumulative burden of chronic diseases and comorbidities, which can exacerbate frailty progression. The identified socio-demographic and health-related factors may help to capture older adults with a high-level or low-increasing trajectory. Specifically, older adults of advanced age and lower socio-economic status, with more comorbidities and worse mental health, may experience these concerning trajectories. The identified factors might increase the risk of higher frailty levels, potentially due to physiological aging, healthcare disparities, and the impact of comorbidities and mental health issues on overall health status [41]. It is imperative to identify population subgroups susceptible to frailty to target interventions across the lifespan appropriately. These findings emphasize the complexity of frailty and a holistic approach to managing it, underlining its multidimensional nature encompassing physical health, mental health, and socio-economic conditions. Addressing these factors is crucial. Interventions targeting at-risk subgroups across the lifespan can potentially mitigate frailty progression. These include improving access to healthcare, promoting healthy lifestyles, and implementing community-based programs to support older adults [42]. Public health policies should focus on reducing healthcare disparities and enhancing social support systems to improve outcomes for vulnerable populations. Evidence from a systematic review of 21 randomized controlled trials substantiated the modifiability of frailty, yet it also pointed out that not all interventions were effective in delaying frailty progression [42]. Further research into the mechanisms linking these factors with frailty trajectories is essential. This deeper understanding could pave the way for more effective interventions, potentially contributing to dementia prevention.

4.3 | Frailty and Dementia

The findings of this study are congruent with previous studies linking frailty with an increased risk of dementia [15, 43–46]. Specific changes, such as alterations in hippocampal synaptic function, neuronal membrane properties, and axonal pathways observed in people with frailty, could contribute to the development of dementia [47]. Frailty may also exacerbate these pathological processes through systemic inflammation, oxidative stress, and hormonal dysregulation, thereby increasing the vulnerability of the brain to neurodegeneration [48]. Previous studies relied on single measurements of frailty [15, 43–45], while our study expanded this knowledge by determining the associations between frailty trajectories over time and later dementia status. These findings emphasize the value of early detection and intervention strategies that may alter or modify this deteriorating trajectory and, subsequently, dementia risk. In line with another study, this study also confirmed that a higher level of frailty was independently associated with an increased risk of dementia [15]. Notably, the low-increasing group aligned with the high-level frailty group regarding the dementia risk. This suggests the importance of monitoring not just the frailty level but the pace of change in frailty, as a rapid increase could indicate a high dementia risk. The lack of significant differences in dementia risk between the high-level and the low-increasing frailty groups may be attributed to common biological mechanisms and shared risk factors (e.g., smoking and physical activity) that contribute to the progression of both frailty and dementia [49]. Additionally, the high-level frailty group may exhibit a potential "ceiling effect," where frailty risk reaches a physiological limit, leading to a plateau in its influence on dementia risk. This study challenges the conventional notion that a uniform progression of frailty is linked to an increased risk of dementia, emphasizing the necessity of considering the complex and varying trajectories of frailty. Public health initiatives should focus on raising awareness about the link between frailty and dementia and promoting lifestyle changes that can mitigate these risks.

4.4 | Implications

This study contributes to the understanding of frailty trajectories and dementia risk in older adults. The key finding is that it is not just the initial levels of frailty but the progression over time that matters. Specifically, both the low-increasing and high-level frailty groups were found to have a higher risk of subsequent dementia. This highlights the importance of continuously monitoring frailty levels over time rather than focusing only on the initial frailty status. Healthcare professionals should incorporate regular and systematic frailty assessments into routine care for older adults. These findings also suggest that interventions should be designed to slow or reverse frailty progression. Healthcare professionals (e.g., nurses) can lead educational programs and develop individualized care plans to increase awareness of frailty and dementia and advocate for early interventions. In addition, the identified socio-demographic and health-related factors could help to identify older adults at a higher risk of concerning trajectories. This study sought to shed light on the potential of a public health-oriented, preventative approach that focuses on modulating different physical frailty trajectories as a non-invasive intervention to mitigate dementia risk.

4.5 | Strengths and Limitations

Utilizing the NHATS data, this study captured diverse facets of frailty, incorporating objective measurements such as exhaustion, low physical activity, unintentional weight loss, slow gait, and weakness [12]. The analysis of frailty over 6 years provided a more comprehensive understanding of the relationships between frailty trajectories and dementia, challenging the conventional approach that relies on a one-time frailty assessment and fails to adequately account for the heterogeneity and dynamic nature of frailty over time. By recognizing the heterogeneity in frailty progression, trajectory analysis offers a framework for personalized and population-level interventions. It also contributes to the development of predictive models that can better allocate healthcare resources and improve outcomes for older adults at different stages of frailty. The diverse demographic representation enabled a broad and generalizable understanding of frailty and dementia risk.

However, this study has limitations. First, the analysis is based on the definition of physical frailty, which may not fully capture the multidimensional nature (e.g., biopsychosocial frailty) of frailty [20]. For instance, psychological and social factors (e.g., depression and isolation) could independently or interactively contribute to dementia risk, potentially altering the study's conclusions [50]. Future research incorporating multidimensional frailty frameworks may provide a more comprehensive understanding of these associations. Second, participants with missing data were excluded and the imputation for missing data was not used. The study may not fully represent the older adult population without dementia, as it excluded participants who either died during the follow-up or were unable to complete the frailty assessment for various reasons, such as safety concerns (e.g., risk of injury during walking speed tests). The high-risk frailty group had a lower survival and this survival bias may result in an underestimation of dementia risk in this group, which may impact the generalizability of our findings. However, in our analysis, we controlled for the complex sample design and weights, which were designed to improve the representativeness of the study population and address potential biases. Third, the lack of confirmed medical diagnoses for dementia is a limitation, as it requires reliance on proxy indicators; dementia status was determined using the validated classification widely used in NHATS-based studies that minimizes education-related bias, however, future studies could explore alternative tests or adjusted thresholds since age- and education-adjusted cutoffs were not applied. Further research, particularly randomized controlled trials, is needed to validate these findings and explore interventions to modify frailty trajectories for reducing the risk of dementia.

5 | Conclusion

This nationwide, population-based longitudinal study provides insights into the dynamic relationships between frailty trajectories and dementia status in older adults. The findings highlight the need for regular frailty assessments and early intervention, even for older adults with low-level frailty. The impacts of socio-demographic and health-related factors (e.g., mental health) on the development of different frailty trajectories point to the need for policies addressing health disparities and comprehensive prevention strategies.

Author Contributions

Fen Ye: conceptualization, methodology, project administration, validation, investigation, resources, writing – original draft, writing – review & editing, visualization. **Weijiao Zhou:** conceptualization, methodology, software, formal analysis, investigation, resources, data curation, writing – original draft, writing – review & editing. **Junlan Pu:** software, formal analysis, resources. **Haobo Chen:** validation, writing – review & editing; **Xiurong Wang:** writing – review & editing. **Jung Jae Lee:** conceptualization, writing – review & editing, visualization, supervision.

Conflicts of Interest

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

Data Availability Statement

Data for this study was derived from the National Health and Aging Trends Study (NHATS), and the data analysis code is available from the corresponding author upon reasonable request.

References

1. World Health Organization 2023. Dementia-Key Facts, https://www.who.int/news-room/fact-sheets/detail/dementia. Accessed, March 10, 2024.

2. N. Chowdhary, C. Barbui, K. J. Anstey, et al., "Reducing the Risk of Cognitive Decline and Dementia: WHO Recommendations," *Frontiers in Neurology* 12 (2022): 765584, https://doi.org/10.3389/fneur.2021.765584.

3. J. J. Manly, R. N. Jones, K. M. Langa, et al., "Estimating the Prevalence of Dementia and Mild Cognitive Impairment in the US: The 2016 Health and Retirement Study Harmonized Cognitive Assessment Protocol Project," *JAMA Neurology* 79, no. 12 (2022): 1242–1249, https://doi.org/10.1001/jamaneurol.2022.3543.

4. The World Bank 2022. GDP (Current US$) in 2019, https://data.worldbank.org/indicator/NY.GDP.MKTP.CD. Accessed, March 10, 2024.

5. G. Livingston, J. Huntley, A. Sommerlad, et al., "Dementia Prevention, Intervention, and Care: 2020 Report of the Lancet Commission," *Lancet* 396, no. 10248 (2020): 413–446, https://doi.org/10.1016/s0140-6736(20)30367-6.

6. P.-O. Lang, J.-P. Michel, and D. Zekry, "Frailty Syndrome: A Transitional State in a Dynamic Process," *Gerontology* 55, no. 5 (2009): 539–549, https://doi.org/10.1159/000211949.

7. M. Lozupone and F. Panza, "A Multidimensional Frailty Approach in Predicting and Preventing Dementia," *Lancet Healthy Longevity* 1, no. 2 (2020): e49–e50, https://doi.org/10.1016/s2666-7568(20)30009-x.

8. L. P. Fried, C. M. Tangen, J. Walston, et al., "Frailty in Older Adults: Evidence for a Phenotype," *Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 56, no. 3 (2001): M146–M157, https://doi.org/10.1093/gerona/56.3.m146.

9. F. Panza, M. Lozupone, V. Solfrizzi, et al., "Different Cognitive Frailty Models and Health-And Cognitive-Related Outcomes in Older Age: From Epidemiology to Prevention," *Journal of Alzheimer's Disease* 62, no. 3 (2018): 993–1012, https://doi.org/10.3233/jad-170963.

10. G. Kojima, Y. Taniguchi, S. Iliffe, and K. Walters, "Frailty as a Predictor of Alzheimer Disease, Vascular Dementia, and All Dementia Among Community-Dwelling Older People: A Systematic Review and Meta-Analysis," *Journal of the American Medical Directors Association* 17, no. 10 (2016): 881–888, https://doi.org/10.1016/j.jamda.2016.05.013.

11. J. Walston, E. C. Hadley, L. Ferrucci, et al., "Research Agenda for Frailty in Older Adults: Toward a Better Understanding of Physiology and Etiology: Summary From the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults," *Journal of the American Geriatrics Society* 54, no. 6 (2006): 991–1001, https://doi.org/10.1111/j.1532-5415.2006.00745.x.

12. N. M. Chu, K. Bandeen-Roche, J. Tian, et al., "Hierarchical Development of Frailty and Cognitive Impairment: Clues Into Etiological Pathways," *Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 74, no. 11 (2019): 1761–1770, https://doi.org/10.1093/gerona/glz134.

13. R. M. Collard, H. Boter, R. A. Schoevers, and R. C. Oude Voshaar, "Prevalence of Frailty in Community-Dwelling Older Persons: A Systematic Review," *Journal of the American Geriatrics Society* 60, no. 8 (2012): 1487–1492, https://doi.org/10.1111/j.1532-5415.2012.04054.x.

14. G. Kojima, "Prevalence of Frailty in Nursing Homes: A Systematic Review and Meta-Analysis," *Journal of the American Medical Directors Association* 16, no. 11 (2015): 940–945, https://doi.org/10.1016/j.jamda.2015.06.025.

15. N. T. Rogers, A. Steptoe, and D. Cadar, "Frailty Is an Independent Predictor of Incident Dementia: Evidence From the English Longitudinal Study of Ageing," *Scientific Reports* 7, no. 1 (2017): 15746, https://doi.org/10.1038/s41598-017-16104-y.

16. A. Vahedi, M. Eriksdotter, H. Ihle-Hansen, T. B. Wyller, A. R. Oksengard, and B. Fure, "Cognitive Impairment in People With Physical Frailty Using the Phenotype Model: A Systematic Review and Meta Analysis," *International Journal of Geriatric Psychiatry* 37, no. 11 (2022), https://doi.org/10.1002/gps.5822.

17. G. Grande, M. L. Haaksma, D. Rizzuto, et al., "Co-Occurrence of Cognitive Impairment and Physical Frailty, and Incidence of Dementia: Systematic Review and Meta-Analysis," *Neuroscience & Biobehavioral Reviews* 107 (2019): 96–103, https://doi.org/10.1016/j.neubiorev.2019.09.001.

18. F. Petermann-Rocha, D. M. Lyall, S. R. Gray, et al., "Associations Between Physical Frailty and Dementia Incidence: A Prospective Study From UK Biobank," *Lancet Healthy Longevity* 1, no. 2 (2020): e58–e68, https://doi.org/10.1016/s2666-7568(20)30007-6.

19. B. T. Howrey, S. Al Snih, J. A. Middleton, and K. J. Ottenbacher, "Trajectories of Frailty and Cognitive Decline Among Older Mexican Americans," *Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 75, no. 8 (2020): 1551–1557, https://doi.org/10.1093/gerona/glz295.

20. C. Y. Guo, Z. Sun, C. C. Tan, L. Tan, and W. Xu, "Multi-Concept Frailty Predicts the Late-Life Occurrence of Cognitive Decline or Dementia: An Updated Systematic Review and Meta-Analysis of Longitudinal Studies," *Frontiers in Aging Neuroscience* 14 (2022): 855553, https://doi.org/10.3389/fnagi.2022.855553.

21. A. Clegg, J. Young, S. Iliffe, M. O. Rikkert, and K. Rockwood, "Frailty in Elderly People," *Lancet* 381, no. 9868 (2013): 752–762, https://doi.org/10.1016/s0140-6736(12)62167-9.

22. J. D. Kasper and V. A. Freedman, *National Health and Aging Trends Study User Guide: Rounds 1–9 Beta Release* (Baltimore: Johns Hopkins University School of Public Health, 2020).

23. K. Bandeen-Roche, C. L. Seplaki, J. Huang, et al., "Frailty in Older Adults: A Nationally Representative Profile in the United States," *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences* 70, no. 11 (2015): 1427–1434, https://doi.org/10.1093/gerona/glv133.

24. J. D. Kasper, V. A. Freedman, and B. C. Spillman, Classification of Persons by Dementia Status in the National Health and Aging Trends Study. Technical paper 5, (Baltimore: Johns Hopkins University School of Public Health, 2013), 1–4. https://www.NHATS.org.

25. C. Buigues, C. Padilla-Sanchez, J. F. Garrido, R. Navarro-Martinez, V. Ruiz-Ros, and O. Cauli, "The Relationship Between Depression and Frailty Syndrome: A Systematic Review," *Aging & Mental Health* 19, no. 9 (2015): 762–772, https://doi.org/10.1080/13607863.2014.967174.

26. D. D. Ward, J. M. Ranson, L. M. K. Wallace, D. J. Llewellyn, and K. Rockwood, "Frailty, Lifestyle, Genetics and Dementia Risk," *Journal of Neurology Neurosurgery and Psychiatry* 93, no. 4 (2022): 343–350, https://doi.org/10.1136/jnnp-2021-327396.

27. K. Kroenke, R. L. Spitzer, and J. B. W. Williams, "The Patient Health Questionnaire-2: Validity of a Two-Item Depression Screener," *Medical Care* 41, no. 11 (2003): 1284–1292, https://doi.org/10.1097/01.mlr.0000093487.78664.3c.

28. J. G. Seo and S. P. Park, "Validation of the Generalized Anxiety Disorder-7 (GAD-7) and GAD-2 in Patients With Migraine," *Journal of Headache and Pain* 16, no. 1 (2015): 97, https://doi.org/10.1186/s10194-015-0583-8.

29. D. S. Nagin and C. L. Odgers, "Group-Based Trajectory Modeling in Clinical Research," *Annual Review of Clinical Psychology* 6, no. 1 (2010): 109–138, https://doi.org/10.1146/annurev.clinpsy.121208.131413.

30. H. L. Nguena Nguefack, M. G. Page, J. Katz, et al., "Trajectory Modelling Techniques Useful to Epidemiological Research: A Comparative Narrative Review of Approaches," *Clinical Epidemiology* 12 (2020): 1205–1222, https://doi.org/10.2147/clep.s265287.

31. B. L. Jones, D. S. Nagin, and K. Roeder, "A SAS Procedure Based on Mixture Models for Estimating Developmental Trajectories," *Sociological Methods & Research* 29, no. 3 (2001): 374–393, https://doi.org/10.1177/0049124101029003005.

32. C. Niyonkuru, A. K. Wagner, H. Ozawa, K. Amin, A. Goyal, and A. Fabio, "Group-Based Trajectory Analysis Applications for Prognostic Biomarker Model Development in Severe TBI: A Practical Example," *Journal of Neurotrauma* 30, no. 11 (2013): 938–945, https://doi.org/10.1089/neu.2012.2578.

33. D. Nagin, "Analyzing Developmental Trajectories: A Semi-parametric, Group-Based Approach," *Psychological Methods* 4, no. 2 (1999): 139–157, https://doi.org/10.1037//1082-989x.4.2.139.

34. D. Kaskirbayeva, R. West, H. Jaafari, et al., "Progression of Frailty as Measured by a Cumulative Deficit Index: A Systematic Review," *Ageing Research Reviews* 84 (2023): 101789, https://doi.org/10.1016/j.arr.2022.101789.

35. X. M. Zhang, J. Jiao, J. Cao, et al., "Frailty as a Predictor of Mortality Among Patients With COVID-19: A Systematic Review and Meta-Analysis," *BMC Geriatrics* 21, no. 1 (2021): 186, https://doi.org/10.1186/s12877-021-02138-5.

36. E. Dent, J. Morley, A. Cruz-Jentoft, et al., "Physical Frailty: ICFSR International Clinical Practice Guidelines for Identification and Management," *Journal of Nutrition, Health & Aging* 23, no. 9 (2019): 771–787, https://doi.org/10.1007/s12603-019-1273-z.

37. M. Giné-Garriga, M. Roqué-Fíguls, L. Coll-Planas, M. Sitjà-Rabert, and A. Salvà, "Physical Exercise Interventions for Improving Performance-Based Measures of Physical Function in Community-Dwelling, Frail Older Adults: A Systematic Review and Meta-Analysis," *Archives of Physical Medicine and Rehabilitation* 95, no. 4 (2014): 753–769.e753, https://doi.org/10.1016/j.apmr.2013.11.007.

38. L. Lorenzo-López, A. Maseda, C. de Labra, L. Regueiro-Folgueira, J. L. Rodríguez-Villamil, and J. C. Millán-Calenti, "Nutritional Determinants of Frailty in Older Adults: A Systematic Review," *BMC Geriatrics* 17 (2017): 1–13, https://doi.org/10.1186/s12877-017-0496-2.

39. M. T. E. Puts, S. Toubasi, M. K. Andrew, et al., "Interventions to Prevent or Reduce the Level of Frailty in Community-Dwelling Older Adults: A Scoping Review of the Literature and International Policies," *Age and Ageing* 46, no. 3 (2017): 383–392, https://doi.org/10.1093/ageing/afw247.

40. T. Fulop, A. Larbi, J. M. Witkowski, et al., "Aging, Frailty and Age-Related Diseases," *Biogerontology* 11, no. 5 (2010): 547–563, https://doi.org/10.1007/s10522-010-9287-2.

41. K. J. Ottenbacher, J. E. Graham, S. Al Snih, et al., "Mexican Americans and Frailty: Findings From the Hispanic Established Populations Epidemiologic Studies of the Elderly," *American Journal of Public Health* 99, no. 4 (2009): 673–679, https://doi.org/10.2105/ajph.2008.143958.

42. J. Apóstolo, R. Cooke, E. Bobrowicz-Campos, et al., "Effectiveness of Interventions to Prevent Pre-Frailty and Frailty Progression in Older Adults: A Systematic Review," *JBI Evidence Synthesis* 16, no. 1 (2018): 140–232, https://doi.org/10.11124/jbisrir-2017-003382.

43. P. A. Boyle, A. S. Buchman, R. S. Wilson, S. E. Leurgans, and D. A. Bennett, "Physical Frailty Is Associated With Incident Mild Cognitive Impairment in Community-Based Older Persons," *Journal of the American Geriatrics Society* 58, no. 2 (2010): 248–255, https://doi.org/10.1111/j.1532-5415.2009.02671.x.

44. A. S. Buchman, P. A. Boyle, R. S. Wilson, Y. Tang, and D. A. Bennett, "Frailty Is Associated With Incident Alzheimer's Disease and

Cognitive Decline in the Elderly," *Psychosomatic Medicine* 69, no. 5 (2007): 483–489, https://doi.org/10.1097/psy.0b013e318068de1d.

45. X. Song, A. Mitnitski, and K. Rockwood, "Nontraditional Risk Factors Combine to Predict Alzheimer Disease and Dementia," *Neurology* 77, no. 3 (2011): 227–234, https://doi.org/10.1212/wnl.0b013e318225c6bc.

46. L. M. K. Wallace, O. Theou, J. Godin, M. K. Andrew, D. A. Bennett, and K. Rockwood, "Investigation of Frailty as a Moderator of the Relationship Between Neuropathology and Dementia in Alzheimer's Disease: A Cross-Sectional Analysis of Data From the Rush Memory and Aging Project," *Lancet Neurology* 18, no. 2 (2019): 177–184, https://doi.org/10.1016/s1474-4422(18)30371-5.

47. N. A. Bishop, T. Lu, and B. A. Yankner, "Neural Mechanisms of Aging and Cognitive Decline," *Nature* 464, no. 7288 (2010): 529–535, https://doi.org/10.1038/nature08983.

48. D. M. Fabricio, M. H. N. Chagas, and B. S. Diniz, "Frailty and Cognitive Decline," *Translational Research* 221 (2020): 58–64, https://doi.org/10.1016/j.trsl.2020.01.002.

49. G. Bai, Y. Wang, R. Kuja-Halkola, et al., "Frailty and the Risk of Dementia: Is the Association Explained by Shared Environmental and Genetic Factors?," *BMC Medicine* 19, no. 1 (2021): 248, https://doi.org/10.1186/s12916-021-02104-3.

50. V. Solfrizzi, E. Scafato, M. Lozupone, et al., "Biopsychosocial Frailty and the Risk of Incident Dementia: The Italian Longitudinal Study on Aging," *Alzheimer's and Dementia* 15, no. 8 (2019): 1019–1028, https://doi.org/10.1016/j.jalz.2019.04.013.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.