Received: 7 February 2024 | Revised: 23 May 2024 | Accepted: 13 June 2024

DOI: 10.1002/alz.14109

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Sustained frailty remission and dementia risk in older adults: A longitudinal study

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Funding information
Key R&D Program Project of Hunan Province, Grant/Award Number: 2023SK2009

Abstract

INTRODUCTION: Physical frailty is reversible, but little is known about the sustainability of frailty remission and its impact on dementia.

METHODS: Data were derived from the National Health and Aging Trends Study (NHATS) (2011 to 2021). Physical frailty was assessed using the Fried frailty phenotype, and frailty transition patterns across three waves were defined. The relationship of sustained frailty remission with incident dementia was examined using Cox proportional regression, stratified by age and gender.

RESULTS: Among 1931 participants, 348 (18.0%) were capable of sustained frailty remission. During the 8-year follow-up, 279 participants developed dementia. In a fully adjusted model, sustained remission was associated with a lower risk of dementia (hazard ratio = 0.66, 95% confidence interval = 0.47 to 0.93). The association was more pronounced among younger-old and male participants but not observed among their counterparts.

DISCUSSION: Sustained frailty remission was associated with a reduced risk of developing dementia. Physical frailty could be an essential forewarning of dementia and a target for interventions.

KEYWORDS
dementia, frailty remission, incidence, older adults, transition patterns

Highlights

- We provided new insights into the natural progression of frailty and its impact on dementia risk using a nationally representative sample
- Sustained frailty remission reduced risk of incident dementia.
- Age and gender played a role in the frailty-dementia link, and thus individualized dementia risk screening is necessary.
- Physical frailty could be an essential forewarning of cognitive decline and an ideal target for interventions to prevent dementia.

1 | BACKGROUND

Physical frailty is a common geriatric syndrome related to the accelerated vulnerability and decreased ability to maintain or recover physical function following a stressor, considered a surrogate of physical capacity.[1] Physical frailty is highly prevalent among older adults and associated with multiple adverse outcomes, such as falls, cognitive impairment, hospitalization, and mortality.[2] Ample literature shows that physical frailty is a dynamic process capable of improvement as well as natural progression,[3–7] which means the physical capacity of older adults may return to its original status. A meta-analysis with community-dwelling older adults showed that the proportion of transition from pre-frailty to robust was 23.3% and transition from frailty to pre-frailty or robust was 35.2%, with a median follow-up time of 3 years.[8] As frailty improvement has been shown to be possible, promoting the remission of frailty among pre-frail and frail individuals may avert adverse related consequences.

Physical frailty and dementia share some common pathological pathways, such as oxidative stress, genetic factors, and inflammation.[9,10] In addition, frailty seems to play an essential role in the continuum of cognitive decline, from subjective memory complaints[11] and mild cognitive impairment[12] to dementia or Alzheimer's disease (AD).[13] Frail individuals have an increased risk of cognitive decline and are more likely to develop dementia.[14] Given the dynamic reversible nature of frailty, it is of great importance to examine the impact of frailty transition on the development of dementia in older adults. According to the theoretical framework, cognitive reserve,[15] dynamic cognitive processes, and underlying functional brain processes cope with brain changes or damage. Physical frailty is an important proxy of cognitive reserve, and frailty improvements might protect older adults against brain abnormality pathology and moderate disease pathology to dementia.[16]

Prior studies focused on the predictors of frailty transition, whereas its influences on health outcomes remain understudied.[17–20] No study to date has investigated how frailty transition contributes to dementia development. To the best of our knowledge, only one prospective study examined the association between frailty transition and cognitive function, finding that individuals who remained frail had the highest rate of cognitive decline, while the change from non-frail to frail status was significantly associated with the lowest cognitive function value over a 2-year span.[21] However, this study assessed frailty transition at two given waves without considering transition trends of frailty. Frailty improvements could have been overestimated due to measurement error or be just transient.[22] Compared with those who fluctuate between different frailty statuses, individuals with sustained frailty remission would have experienced genuine improvement.[22] Therefore, frailty transition patterns were extracted from three consecutive waves from a nationally representative database, the National Health and Aging Trends Study (NHATS), to reduce measurement error. We aimed to examine whether frailty remission could be sustained and whether sustained frailty remission could reduce the risk of developing dementia during an 8-year follow-up.

In addition, age-specific and gender-specific factors in the frailty–dementia link have attracted significant attention. Age represents a common risk factor for frailty and dementia. The age-specific impact of frailty on dementia was inconsistent in previous studies. Some studies supported the idea that the risk of dementia conferred by increased frailty was similar in magnitude from 65 years old into very old age (ie, aged ≥ 80 years old),[23,24] while others suggested that this association might diminish as individuals age, with a cut-point of near 70 years old.[25] Moreover, gender moderated the association between frailty and cognitive performance, as the negative effects of frailty on specific domains were stronger in females.[26] Thus, we hypothesized that older-old adults (defined as aged ≥ 80 years old in our study) could still benefit from reversing frailty to prevent dementia and that female older adults would be more responsive to improvements in frailty. A better understanding of the age-specific and gender-specific factors associated with developing dementia in older adults with sustained frailty remission might help professionals develop individualized and appropriate interventions to the vulnerable in the geriatric population.

RESEARCH IN CONTEXT

1. **Systematic review**: Physical frailty is increasingly recognized as a risk factor for dementia. Given the dynamic reversible nature of frailty, previous study assessed frailty transition at only two given waves. Whether frailty improvements could be sustained remains unclear. In addition, to our best, no study has investigated how frailty transition patterns contribute to dementia development.
2. **Interpretation**: We showed that sustained frailty remission reduced risk of dementia in cognitively intact older adults. Moreover, this reduction is more pronounced among younger-old and male participants, and no longer the case in female and older-old adults.
3. **Future directions**: These findings have important clinical implications, as they suggest that monitoring transition trend of frailty among older adults may help to prevent cognitive decline towards dementia. Future studies need to discuss how physical frailty and cognitive wellbeing interact and impact each other across the lifespan. Individualized interventions should be developed on the frail older adults at risk of dementia according to age and gender differences.

2 | METHODS

2.1 | Study population

This longitudinal study used data from NHATS, a population-based, prospective longitudinal cohort with Medicare beneficiaries ages 65 or older in the United States. Annual in-person interviews were conducted to collect relevant physical and cognitive indicators, except for the telephone interview in 2020 on account of the COVID-19

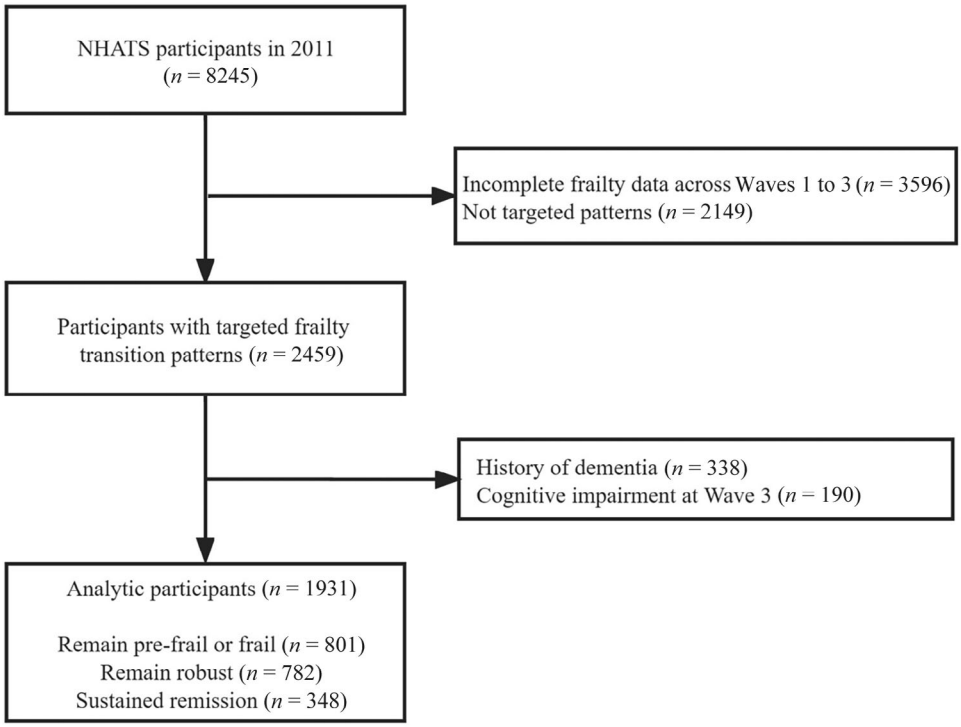

FIGURE 1 Flowchart of eligible participants and selection process.

pandemic. Evidence indicated no significant differences in cognitive scores between in-person and telephone test administration.[27]

The first round began in 2011 (Wave 1), with 8245 participants recruited, and the most recent data were collected in 2021 (Wave 11). Our initial sample was restricted to respondents who attended the first three waves and had complete data for frailty assessment ($n = 4649$). We identified individuals with three specified frailty transition patterns (remaining frail or pre-frail, remaining robust, and sustained remission on the basis of their measured frailty status from Wave 1 to Wave 3) ($n = 2459$) (Table S1). Wave 3 was defined as the baseline. To avoid overestimate of incident dementia risk, participants with a history of dementia (probable dementia, $n = 338$) from Wave 1 to Wave 3 or baseline cognitive impairment (possible dementia, $n = 190$) were excluded, leaving an analytic sample of 1931. The flowchart of eligible participants and selection process is shown in detail in Figure 1.

All respondents provided informed consent for their participation. The NHATS was approved by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline was followed in our study.[28]

2.2 | Frailty transition

Frailty status was annually assessed by the Fried frailty phenotype[1]: (1) exhaustion: defined as having low energy or being easily exhausted to the point of limiting activities in the last month; (2) low physical activity: defined as never walking for exercise or engaged in vigorous activities in the last month; (3) shrinking: defined as body mass index (BMI) < 18.5 kg/m^2, based on self-reported weight and height, or unintentional weight loss ≥ 4.54 kg in the last year; (4) weakness: measured by the best of two dominant handgrip strength measurements. Participants with handgrip strength $\leq$20th percentile of the population distribution stratified by sex and BMI groups were defined as having weakness; and (5) slowness: measured by gait speed from the first of two 3-m walking trails, with gait speed $\leq$20th percentile of the population distribution stratified by sex and height (Table S2). Individuals with none are considered "robust"; those meeting one or two criteria are considered "pre-frail"; and those with three, four, or five criteria are defined as "frail."[29]

In the main analysis, we focused on three frailty transition patterns[30]: (1) remaining frail or pre-frail from Wave 1 to Wave 3, indicating that older adults remained unhealthy; (2) remaining robust from Wave 1 to Wave 3, indicating that older adults remained healthy; (3) sustained remission, which includes older adults whose frailty status get improved from Wave 1 to Wave 2 (frail to pre-frail, pre-frail to robust, frail to robust) and then maintained or improved further into Wave 3. In the sensitivity analysis, another transition pattern was additionally analyzed: those with frailty remission from Wave 1 to Wave 2 but who deteriorate from Wave 2 to Wave 3 (Table S2).

2.3 | Dementia

For dementia status, NHATS participants were classified into three groups – probable dementia, possible dementia, and no dementia.[31]

Probable dementia was determined by meeting at least one of three criteria: (1) self- or proxy report of doctor's diagnosis of dementia or AD; (2) score of 2 or higher on the AD8 Dementia Screening Interview,[32] which was administered to proxy respondents; and (3) a cut-point of <1.5 SDs below the mean in at least two cognitive domains (memory, orientation, and executive function). Possible dementia was determined by <1.5 SDs below mean in one domain. Memory was assessed by immediate and delayed 10-word recall; orientation was assessed by asking the date, month, year, day of week, and names of present president and vice president; and executive function was assessed with clock drawing test. The interested outcome was incident dementia within 8 years of follow-up (Wave 4 to Wave 11), indicated by a classification of "probable dementia." Survival time was calculated the months from baseline (Wave 3) until dementia diagnosis, death, or the last interview.

2.4 | Covariates

To account for potential confounding factors on the relationship between frailty transition and dementia, we included sociodemographic and health-related covariates according to previous literature on dementia risk factors.[33] Sociodemographic covariates were collected on chronological age, gender (female /male), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, all others), education (less than high school, high school graduate, some college or vocational school, bachelor or higher), living arrangement (alone, with spouse/partner only, with others only, with spouse/partner, and with others).

Health-related covariates were as follows: (1) history of smoking was categorized as a binary variable (never, current/former smoker); (2) limited activities of daily living (ADL) were determined if the participants had difficulty in performing any daily and necessary tasks (eating, dressing, bathing, and toileting); (3) chronic diseases were assessed by the number of chronic diseases diagnosed by a doctor (heart attack, heart disease, stroke, diabetes, high blood pressure, arthritis, osteoporosis, lung disease, and cancer); (4) BMI was categorized into two groups (normal with BMI < 30 kg/m^2, and obesity with BMI ≥30 kg/m^2); (5) depressive symptoms were measured by the Patient Health Questionnaire (PHQ-2) scale[34]; (6) social participation was assessed by the number of social activities and categorized as a continuous variable.[35]

2.5 | Statistical analysis

Mean and standard deviations for continuous variables and frequency and percentage for categorical variables were used to characterize participants. Baseline characteristics between three frailty transition patterns were compared with chi-squared for categorical variables and ANOVA for continuous variables.

Nelson–Aalen cumulative risk curves were used to indicate the differences in the risk of developing dementia among three frailty transition patterns. Log-rank test was used to compare between groups and Bonferroni test was used for pairwise comparison. Cox proportional hazard regression model was used to examine the hazard ratio (HR) of incident dementia according to frailty transition patterns. Schoenfeld residuals were used to test the proportional hazard (HP) assumption.

To assess the roles of age and gender in the association between frailty transition patterns and incident dementia, Cox regression was reanalyzed after stratifying by baseline age group (younger-old [< 80 years; n = 1215] vs older-old [≥80 years; n = 716]) and by gender (female [n = 1088] vs male [n = 843]). Three models were created for all analyses in our study: Model 1 is an unadjusted crude model; Model 2 was adjusted for sociodemographic variables (age, gender, education, race/ethnicity, living arrangement); Model 3 was further adjusted for health-related variables (smoking, ADL impairment, chronic diseases, BMI, depression, social participation.). With the mcartest command in STATA,[36] missing values on covariates met Little's missing completely at random (MCAR) assumption, where missing data do not depend on observed or unobserved data. Considering that missing values on covariate variables were less than 2%, all analyses were conducted using complete case analysis.

In sensitivity analysis, we (1) analyzed another pattern of frailty transition; (2) accounted for the competing risk of death using Fine–Gray proportional subhazards model (ie, people could die before incident dementia was observed, which led to the biased estimation of dementia incidence rate); (3) accounted for the possibility of reverse causality after excluding those who developed "probable dementia" within a year of the baseline (ie, early undiagnosed dementia might lead to frailty rather than frailty leading to dementia); (4) assessed the impact of participation attrition after excluding participants who dropped out of the study; (5) stratified by white and black non-Hispanic to assess whether associations remained the same by race, but other underrepresented races were not examined due to insufficient power (more information is available in supplementary files). Two-tailed p values < .05 were considered to be statistically significant, and all data analyses were performed with STATA 16.0.

3 | RESULTS

3.1 | Baseline characteristics

Our initial sample contained 4649 participants who completed frailty assessment for the first three waves. Our final analytic sample consisted of 1931 participants within three specific patterns. Excluded participants were more likely to be older women, less educated, engaged in fewer social activities, and have depressive symptoms.

Among 1931 analytic participants, the mean age was 77.4 (6.9%), and 843 (43.7%) were male. About 76.8% were non-Hispanic White, 41.5% lived only with a spouse or partner, and 82.5% graduated at least from high school. Among 1931 participants, 801 (41.5%) remained frail or pre-frail and 782 (40.5%) maintained a robust status across three waves, while 348 (18.0%) improved frailty status from Wave 1 to Wave 2 and sustained or improved further in Wave 3. Compared to those

TABLE 1 Baseline characteristics of study population by frailty transition patterns ($N = 1931$).

	Total	Remain frail or pre-frail ($n = 801$)	Remain robust ($n = 782$)	Sustained remission ($n = 348$)	*p*-value
Age, M (SD)	77.4 (6.9)	78.8 (7.2)	75.8 (6.4)	77.5 (6.9)	<0.001
Male, *n* (%)	843 (43.7)	318 (39.7)	378 (48.3)	147 (42.2)	0.002
Race and ethnicity, *n* (%)					<0.001
White, non-Hispanic	1,483 (76.8)	593 (74.0)	642 (82.1)	248 (71.3)	
Black, non-Hispanic	336 (17.4)	163 (20.3)	102 (13.0)	71 (20.4)	
Hispanic	71 (3.7)	33 (4.1)	19 (2.4)	19 (5.5)	
Other[a]	41 (2.1)	12 (1.5)	19 (2.4)	10 (2.9)	
Education, *n* (%)					<0.001
Less than high school	337 (17.5)	202 (25.2)	73 (9.3)	62 (17.8)	
High school graduates	490 (25.4)	233 (29.1)	168 (21.5)	89 (25.6)	
Some college or vocational school	530 (27.5)	219 (27.4)	215 (27.5)	96 (27.6)	
Bachelor or higher	572 (29.6)	146 (18.2)	325 (41.6)	101 (29.0)	
Living arrangement, *n* (%)					<0.001
Alone	668 (34.6)	311 (38.8)	261 (33.4)	96 (27.6)	
With spouse/partner only	802 (41.5)	257 (32.1)	400 (51.2)	145 (41.7)	
With others only	270 (4.0)	139 (17.4)	67 (8.6)	64 (18.4)	
With spouse/partner and with others	191 (9.9)	94 (11.7)	54 (6.9)	43 (12.4)	
Current/former smoker, *n* (%)	979 (50.7)	422 (52.8)	379 (48.5)	178 (51.1)	0.231
ADL impaired, *n* (%)	1860 (96.3)	756 (94.4)	766 (98.0)	338 (97.1)	<0.001
No. chronic diseases, *n* (%)					<0.001
0	179 (9.3)	24 (3.0)	130 (16.6)	25 (7.2)	
1 to 3	1413 (73.2)	560 (69.9)	606 (77.5)	247 (71.0)	
≥4	339 (17.5)	217 (27.1)	46 (5.9)	76 (21.8)	
BMI ≥ 30 kg/m^2, *n* (%)	510 (26.4)	270 (34.1)	144 (18.6)	96 (27.8)	<0.001
Depressive symptoms, *n* (%)	172 (8.9)	120 (15.1)	24 (3.1)	28 (8.1)	<0.001
No. social activities, M (SD)	2.8 (1.0)	2.5 (1.0)	3.1 (0.9)	2.8 (0.9)	<0.001

Note: Missing variables: two were missing data on education, one on smoking, 22 on BMI, and eight on depression.
Abbreviations: ADL, activities of daily living; BMI, body mass index; M, mean; SD, standard deviation.
[a]Including non-Hispanic American Indian/Asian/Native Hawaiian/Pacific Islander/other specify, Hispanic, multiracial, unknown, or refused.

remaining frail or pre-frail, participants who sustained frailty remission were prone to be younger men, suffer from fewer chronic diseases, report less depression, and participate in more social activities. As shown in Table 1, all baseline characteristics by frailty transition status, except for history of smoking, were significantly different across groups ($p < 0.05$ for all comparisons).

3.2 | Association between frailty transition patterns and risk of incident dementia

The mean follow-up time was 70.0 months, with a maximum duration of 101 months. During the follow-up, 279 participants developed dementia, among whom 159 (57.0%) remained frail or pre-frail, 76 (27.2%) remained robust, and 44 (15.3%) sustained frailty remission across three waves. The Nelson–Aalen hazard curves for developing dementia in three patterns of frailty transition during Waves 1 to 3 are shown in Figure 2. Log-rank test was statically significant ($p < 0.001$). Further, pairwise comparison showed significant differences between "remain frail or pre-frail" and "remain robust," as well as between "remain frail or pre-frail" and "sustained remission." However, no significant difference was observed between "remain robust" and "sustained remission" (Table S3).

In the unadjusted model (Model 1), sustained remission was associated with a lower risk of dementia (HR = 0.54, 95% CI = 0.39 to 0.76, $p < 0.05$) (Table 2). The association was attenuated but still significant after adjusting for sociodemographic covariates (Model 2) and further adjusted for health-related covariates (Model 3). As expected, the risk of incident dementia was lowest in older adults remaining robust across three waves. The unadjusted HR was 0.36 (95% CI = 0.27

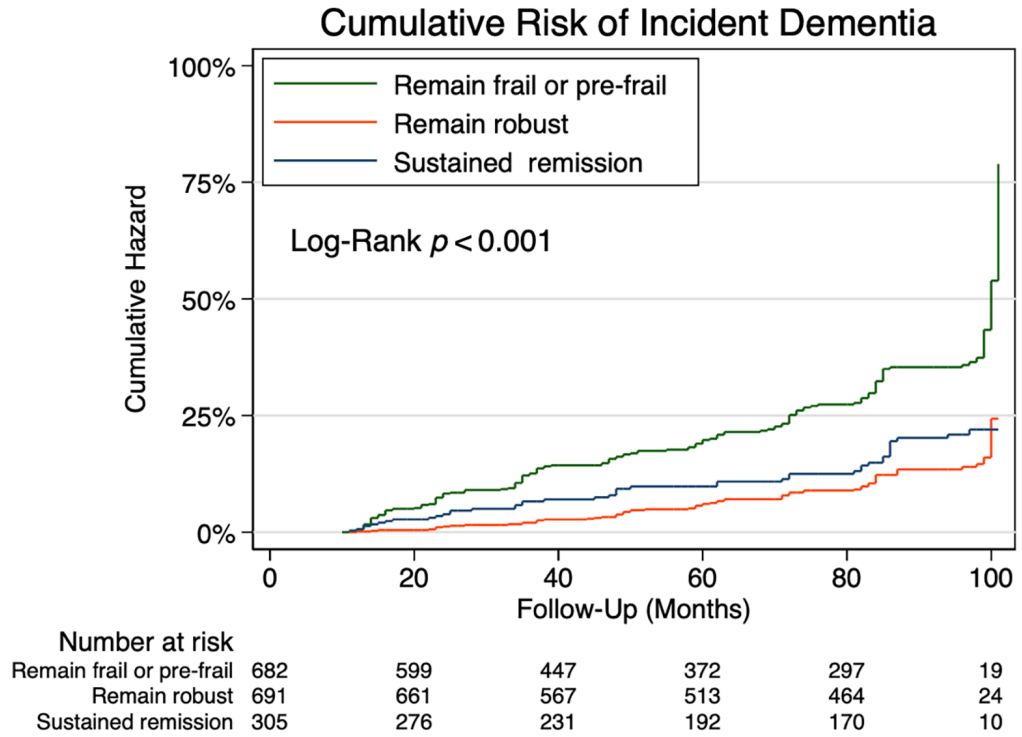

FIGURE 2 Nelson–Aalen cumulative hazard estimates of dementia risk by frailty transition patterns.

TABLE 2 Hazard ratios (HRs) with 95% CI of incident dementia by frailty transition patterns.

Frailty transition patterns	*n*	Model 1 HR (95% CI)	Model 2 aHR (95% CI)	Model 3 aHR (95% CI)
Remain frail or pre-frail	801	Reference	Reference	Reference
Remain robust	782	**0.36 (0.27, 0.47)**	**0.54 (0.40, 0.72)**	**0.63 (0.46, 0.87)**
Sustained remission	348	**0.54 (0.39, 0.76)**	**0.63 (0.45, 0.87)**	**0.66 (0.47, 0.93)**

Note: Model 1 unadjusted; Model 2 adjusted for age, gender, race and ethnicity, education, and living arrangement; Model 3 adjusted for Model 2, smoking, activities of daily living impairment, chronic diseases, body mass index, depression, and social participation.
Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio. Boldface indicates statistical significance ($p < 0.05$).

to 0.47) and fully adjusted HR was 0.63 (95% CI = 0.46 to 0.87) in Model 3.

We conducted a sensitivity analysis to compare the aforementioned three patterns with another pattern at baseline (Table S4). Compared to consistently frail or pre-frail participants, the lower risk of dementia among people with sustained remission across Wave 1 to Wave 3 remained significant (aHR = 0.66, 95% CI = 0.47 to 0.93), but not among those with frailty remission from Wave 1 to Wave 2 but who deteriorate from Wave 2 to Wave 3.

3.3 | Role of age in association between frailty transition patterns and incident dementia

In the further analysis stratified by age group (Table 3), younger-old participants remaining robust had a 47% decreased risk of incident dementia (aHR = 0.53, 95% CI = 0.33 to 0.87), and this association remained significant among older-old participants (aHR = 0.54, 95% CI = 0.36 to 0.82). For people with sustained frailty remission, there was also a significant lower hazard risk for younger-old participants (aHR = 0.54, 95% CI = 0.31 to 0.93), but not for older-old participants.

3.4 | Role of gender in association between frailty transition patterns and incident dementia

Stratified by gender (Table 4), male participants who remained robust or sustained frailty remission had the same lower risk of incident dementia (aHR = 0.52, 95% CI = 0.33 to 0.85 and aHR = 0.52, 95% CI = 0.29 to 0.95, respectively). However, significant associations were not observed in female counterparts.

TABLE 3 Multi-adjusted hazard ratios (HRs) with 95% CI of incident dementia by frailty transition patterns, stratified by younger-old and older-old groups.

	Younger-old (<80 years)		Older-old (≥80 years)	
Frailty transition patterns	***n***	**aHR (95% CI)**	***n***	**aHR (95% CI)**
Remain frail or pre-frail	438	Reference	363	Reference
Remain robust	556	**0.53 (0.33, 0.87)**	226	**0.54 (0.36, 0.82)**
Sustained remission	221	**0.54 (0.31, 0.93)**	127	0.72 (0.46, 1.13)

Note: Multi-adjusted for baseline age, gender, race and ethnicity, education, living arrangement, smoking, activities of daily living impairment, chronic diseases, body mass index, depression, and social participation.
Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval. Boldface indicates statistical significance ($p < 0.05$).

TABLE 4 Multi-adjusted hazard ratios (HRs) with 95% CI of incident dementia by frailty transition patterns, stratified by gender.

	Female		Male	
Frailty transition patterns	***n***	**aHR (95% CI)**	***n***	**aHR (95% CI)**
Remain frail or pre-frail	483	Reference	318	Reference
Remain robust	404	0.70 (0.46, 1.08)	378	**0.53 (0.33, 0.85)**
Sustained remission	201	0.76 (0.50, 1.18)	147	**0.53 (0.29, 0.95)**

Note: Multi-adjusted for baseline age, gender, race and ethnicity, education, living arrangement, smoking, activities of daily living impairment, chronic diseases, body mass index, depression, and social participation.
Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval. Boldface indicates statistical significance ($p < 0.05$).

4 | DISCUSSION

With a nationally representative survey in the United States, this prospective study found that frailty was capable of significant improvement over time and could be sustained for a period in older adults. Among our final analytic sample, 348 (18.0%) participants improved from Wave 1 to Wave 2 and experienced sustained frailty remission in the next follow-up. This proportion was slightly higher than that reported by Davies et al., who defined frailty across waves using the frailty index.[30] The rate of frailty improvements reported in prior studies ranged from 13.7% to 23.3%.[3,7,8] One study showed that the transition toward greater frailty status was more likely (22.9%) than transition toward lower frailty status (19.9%), while the majority (57.2%) remained unchanged.[3] However, it is rather difficult to make comparisons due to the differing operationalization of frailty transition, sample population, and assessment tools.

To our knowledge, this is the first longitudinal study to investigate the relationship between sustained frailty remission across three waves and onset of dementia. Specifically, older adults who sustained frailty remission had a lower risk of incident dementia than those who persistently remained frail or pre-frail. This finding partially agrees with the longitudinal study by Li and colleagues showing that frail people had a higher risk of incident dementia than non-frail ones (HR = 1.56, 95% CI: 1.07 to 2.26).[25] However, prior studies did not assess the impact of frailty transition as we did in the current study.[25,37] As expected, older adults with stable physical capacity (ie, remaining robust) had a diminished risk of dementia. However, it is worth noting that there was no significant difference in dementia risk between participants with sustained remission and those remaining robust. A recent prospective study showed that people who experienced sustained improvement in frailty status had the lowest fall risk compared with those who remained persistently frail, but pairwise comparisons were not reported in the study.[30] Since dementia might be preventable at an early stage, our finding highlights the sustainability of frailty improvements and its potential benefits, supporting frailty as a target to prevent dementia.

The frailty–dementia link can be explained by several underlying mechanisms, including hormonal and inflammatory processes, nutritional, vascular, neuropathological, and metabolic influences.[38] Frailty acts as a marker of dementia vulnerability, and frail individuals have an increased risk of reducing cognitive reserve, accelerating disease pathology and expression of dementia-related genes.[39,40] In contrast, people who can stay physically healthy may endure a better degree of neuropathological burden without cognitive decline. Therefore, older adults with sustained frailty remission may build up cognitive reserve via the integration of heathy lifestyles, self-management on risk factors, and social activities.

Although improved transitions observed in our study might be spontaneous, it indicates that intervention on physical capacity could be beneficial to prevent dementia in older adults. Sánchez and colleagues found that multicomponent physical exercise (Vivifrail) could promote components of intrinsic capacity among frail cognitively impaired older adults, especially in terms of locomotion, cognition, and vitality domains.[41] Another 2-year multidomain lifestyle intervention (SINGER) in Singapore that included dietary advice, exercise, cognitive training, and vascular risk factors management induced significant effects in delaying cognitive decline in older adults at risk of dementia.[42] In 2020, *The Lancet* updated and constructed a life-course

model of dementia prevention, including 12 risk factors, among which keeping physically active in later life was strongly recommended.[43] Future studies need to discuss how physical frailty and cognitive well-being interact and impact each other across the lifespan. In addition, researchers should develop and validate a multicomponent intervention program, especially an effective exercise program oriented toward maintaining one's physical and cognitive function.

In subgroup analysis, our study demonstrates that the association of sustained frailty remission with dementia might be more pronounced in the younger (<80 years), as opposed to later (≥80 years) old age. This finding is consistent with Nari's demonstration of a positive impact of frailty improvements on cognitive function only in earlier old age.[21] Thus, early interventions should be developed on the frail or pre-frail older adults at risk of dementia. However, older-old participants were underrepresented in our study due to a relatively smaller sample size, which limits the statistical power to detect an effect. Moreover, elective survival could have impacted the association between frailty remission and dementia among older-old adults because very old people may die before dementia is diagnosed. Unexpectedly, prediction of sustained frailty improvements on incident dementia varies in males and females. A popular explanation is the "male-female health survival paradox," according to which females have a longer life expectancy and can tolerate frailty better.[44] Males may experience a wider cognitive deficit from a persistent high level of frailty and be more sensitive to sustained improvements. Our finding suggests that frailty-targeted intervention for dementia prevention should be distinguished by gender differences.

Though not yet routine in clinical practice, screening and monitoring for frailty is being increasingly recognized as essential to identifying vulnerable older populations.[45,46] Our study shows that capturing frailty transitions can not only reflect a person's physical capacity but yield good predictions for cognitive condition as well. Since it seems promising to slow down cognitive decline maintaining one's physical health, keeping a close eye on transition trends of frailty will allow for early dementia intervention.

There are some limitations in our study. First, the frailty model in NHATS is based on only five physical phenotypes, whereas another common model, cumulative deficit model, represents the occurrence of clinical syndromes, chronic diseases, and other health lifestyles.[47] But prior studies show that both models are equally predictive of cognitive performance.[48] Moreover, recent studies reported risks of cognitive decline and dementia from diverse frailty dimensions, such as social frailty[49] and biopsychosocial phenotype.[50] Future studies are needed to integrate and refine these frailty dimensions for better risk assessment of dementia. Second, though we defined frailty sustained remission using three consecutive waves, measurement error could only be reduced, not eliminated. Moreover, due to the lack of frailty data before Wave 1, the duration of exposure to frailty or pre-frailty status remains unknown in our study, which might influence the probability and sustainability of remission. Third, dementia refers to a mixed concept here, including all-cause dementia. The correlation between frailty and subtypes of dementia varied,[51] but evidence shows that with advancing age, mixed dementia proves to be the predominant subtype.[52] More research is warranted to explore whether frailty transition patterns differently contribute to subtypes of dementia. In addition, the relationship between frailty remission and incident dementia might be influenced by death or potential reverse causality of prodromal dementia. The given associations were still significant in Models 1 and 2, not in Model 3 (Tables S5 and S6). Finally, attrition in NHATS due to follow-up limited the sample size. But our results were not significantly altered after excluding participants who dropped out of the study (Table S7). However, the dominance of white non-Hispanics introduced a potential risk of selection bias, and the associations between sustained frailty remission and incident dementia were no longer statistically significant when stratified by race (Table S8).

In conclusion, we investigated the relationship between frailty remission trend and onset of dementia. We found that older adults who sustained frailty remission had a lower risk of developing dementia than those who persistently remained frail or pre-frail. In addition, age and gender may play a role in the frailty–dementia association. Future research should yield a better understanding of the progression of dementia within different transition patterns of frailty status, which will facilitate the development of targeted interventions to delay cognitive decline toward dementia.

AUTHOR CONTRIBUTIONS

Shuomin Wang and Minhui Liu contributed to the conception and design of the study. Shuomin Wang conducted the data analyses and drafted the manuscript. All authors interpreted the data, reviewed and provided critical revisions, and approved the final version for publication. Minhui Liu is the guarantor of this work, having full access to all the data in the study, and takes responsibility for the accuracy or integrity of all aspects of the work.

ACKNOWLEDGMENTS

The data and samples used for this research were obtained from the NHATS. We thank the workers, researchers, and participants involved in the NHATS. The publication of this manuscript was supported by the Key R&D Program Project of Hunan Province Grant from (2023SK2009).

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose. Author disclosures are available in the Supporting information.

CONSENT STATEMENT

Informed consent was obtained from all participants or their proxies by the NHATS investigators. Our analysis of publicly available, deidentified data was exempt from the need for Institutional Review Board approval.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Wang S, Li Q, Wang S, et al. Sustained frailty remission and dementia risk in older adults: A longitudinal study. *Alzheimer's Dement*. 2024;20:6268–6277. https://doi.org/10.1002/alz.14109