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Research Article

Natural History Trajectories of Frailty in Community-Dwelling Older Japanese Adults

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Abstract

Background: The gap between the average life expectancy and healthy life expectancy remains wide. Understanding the natural history of frailty development is necessary to prevent and treat frailty to overcome this gap. This study elucidated the trajectories of 5 frailty assessment components using group-based multitrajectory modeling.

Methods: Overall, 845 community-dwelling older adults (aged 65–91 years; 433 males and 412 females) who underwent longitudinal frailty assessments at least 3 times were included in the analysis. The mean follow-up period (±*SD*, range) was 7.1 (±2.3, 3.8–11.3) years. In each wave, the physical frailty was assessed for the following 5 partially modified components of the Cardiovascular Health Study criteria: *shrinking*, *weakness*, *exhaustion*, *slowness*, and *low activity*. Using group-based multitrajectory modeling, we identified subgroups that followed distinctive trajectories regarding the 5 frailty components.

Results: Five frailty trajectory groups were identified: *weakness*-focused frail progression group (Group 1 [G1]; 10.9%), robust maintenance group (Group 2 [G2]; 43.7%), *exhaustion*-focused prefrail group (Group 3 [G3]; 24.3%), frail progression group (Group 4 [G4]; 6.7%), and *low activity*–focused prefrail group (Group 5 [G5]; 14.4%). The Cox proportional hazards model analysis showed that G1, G4, and G5 had significantly higher mortality risks after adjusting for sex and age (G2 was the reference group).

Conclusion: Based on the natural history of frailty, the 5 distinctive trajectory groups showed that some individuals remained robust, while others remained predominantly prefrail or progressed primarily owing to physical mobility decline. Therefore, identifying individuals belonging to these progressive frailty groups and providing interventions according to the characteristics of each group may be beneficial.

Keywords: Five frailty assessment components, Group-based multitrajectory modeling, Longitudinal data, Trajectory groups

The average life expectancy of the Japanese population is 81.1 years for males and 87.1 years for females and is one of the longest in the world (1). However, the gap between the average life expectancy and healthy life expectancy (8.5 years for males and 10.2 years for females) remains large. Therefore, effective strategies to extend healthy life expectancy, such as identifying the changes in the natural history of frailty over time before individuals become physically impaired, are urgently warranted.

Frailty lies between being in a robust and independent state and having a physical impairment that requires support and care from others. Frailty is an age-related condition where a decline in physiological reserve increases the vulnerability to stressors (2,3). Although frailty often progresses with aging, recovery from frailty and prefrailty (reversibility) has been reported (4–8). According to the Cardiovascular Health Study (CHS) criteria, the phenotype of frailty is defined based on 5 components: "*shrinking*," "*weakness*," "poor endurance and energy (*exhaustion*)," "*slowness*," and "*low physical activity level*" (9). To assess frailty, all 5 components are treated with equal weight. Individuals are classified as "frail" when 3 or more criteria are met, "prefrail" when 1 or 2 criteria are met, and "robust" when none of the criteria are met. However, various studies have reported that *slowness*, measured by gait speed, and *weakness*,

measured by grip strength, are more prevalent in individuals assessed as frail and are predictive of functional decline and death (10–12). The difference in subsequent outcomes according to the components of frailty might also suggest that the presence or absence of these 5 components does not occur synchronously. Moreover, at the onset of prefrailty and frailty state, *weakness*, *slowness*, and *low activity* are likely to be initial symptoms, and there are combinations of components that are likely to be applicable (13). However, these are only static findings often observed at specific points in time, and more than one pattern might exist in the direction, timing, and extent of change. Collard et al. suggested that basic research needs to consider not only the total frailty score but also the individual components (14). However, to the best of our knowledge, few longitudinal studies have examined changes in these 5 components in terms of their relationship to each other in frailty progression or improvement.

Knowing the natural history of frailty development is necessary for intervening to prevent and treat frailty (3,13). In recent years, there has been a growing interest in identifying the transition patterns of frailty (including the trajectory of frailty) (15); however, studies have essentially addressed the longitudinal transition of frailty status (16–19) and have paid little attention to the changes in the 5 components, which is the basis of this transition. A recent study that analyzed the changes in the 5 components in middle-aged and older robust individuals reported that several patterns may exist in the progression from robust to prefrail state (20) (see Author Note 2). Thus, this study aimed to identify the natural history trajectories of 5 frailty components using group-based multitrajectory modeling (21), identify the characteristics of each subgroup, and elucidate the role of each component in the natural history of frailty.

Method

Study Cohort

The data used in this study were collected as part of the National Institute for Longevity Sciences-Longitudinal Study of Aging (NILS-LSA) in Japan. NILS-LSA is a project started in November 1997 to systematically observe and describe the process of normal and successful aging over time and the onset of geriatric diseases. The details regarding NILS-LSA have already been reported in other studies (22).

The participants in NILS-LSA were randomly selected as sex- and age-decade-stratified noninstitutionalized individuals living in the National Center for Geriatrics and Gerontology (NCGG) neighboring areas of Obu City and Higashiura Town in Aichi Prefecture, central Japan (age range: 40–79 years at the time of their first participation).

The participants were examined at the NCGG examination center from the first to the seventh wave at intervals of approximately 2 years. From the second to the seventh wave, dropouts aged ≤79 years at the follow-up survey were replaced with additional participants of the same sex and age by decade. In addition, participants aged 40 years were included each year to prevent the study cohort from aging.

All NILS-LSA protocols were approved by the Committee of Ethics of Human Research of the NCGG (No. 899-6). Written informed consent was obtained from all participants.

Study Participants

We included participants with a sufficient number of observation time points to identify the distinctive frailty trajectories. We limited study participation to include 845 individuals (433 males, 412 females) aged ≥65 years who participated in any of the 7 study waves and had available data from at least 3 frailty assessments. As previously mentioned, NILS-LSA is a dynamic cohort in which new participants are added at each follow-up point. Our analysis was limited to those aged ≥65 years; thus, the first frailty assessment wave was different for each participant. In addition, *shrinking*, one of the components of frailty, was assessed based on the difference from the actual weight measurement of the previous wave; thus, frailty assessment was performed from the second to seventh waves (Figure 1, eTable 1 in the Supplement). The number of participants per wave of their first frailty assessment was 407 (48.2%), 180 (21.3%), 144 (17.0%), and 114 (13.5%) for the second, third, fourth, and fifth study waves, respectively. The mean (±*SD*, range) age was 69.7 (±4.5, 65–82) years at the participants' first assessment. The participants underwent frailty assessments 4.4 times (±1.1; n = 247 (29.2%), 218 (25.8%), 190 (22.5%), 190 (22.5%), in order from 3 to 6 times), and the NILS-LSA follow-up period was 7.1 years (±2.3, 3.8–11.3). Table 1 shows the characteristics of the participants at the first frailty assessment (eText 1 in the Supplement).

Measurements

Physical frailty assessment

Physical frailty was assessed in terms of 5 partially modified components (23) according to the CHS criteria (9) in each wave (eText 2 in the Supplement). The following components were evaluated as applicable (1) or not applicable (0).

Shrinking was defined as ≥5% weight loss in the previous 2 years, as NILS-LSA performed biennial examinations. The weight loss rate was calculated from the weight (measured using a digital scale) of the previous wave and the relevant wave. *Weakness* was defined as a maximum grip strength <26 kg in males and <18 kg in females, which was measured using a handgrip dynamometer. *Exhaustion* was defined by responses other than "rarely or none of the time (<1 day)" during the past week to the 2 items for "depressed affect" of the Center for Epidemiologic Studies Depression Scale (24,25) used in the CHS criteria. *Slowness* was defined as a comfortable gait speed < 1.0 m/s or gait disturbance. *Low activity* was defined as the lowest 20% of leisure-time physical activity among each NILS-LSA wave participants (limited to age ≥65 years) by sex.

The frailty status was determined based on the number of the components present (frailty scores): robust (0 components), prefrail (1–2 components), or frail (3–5 components).

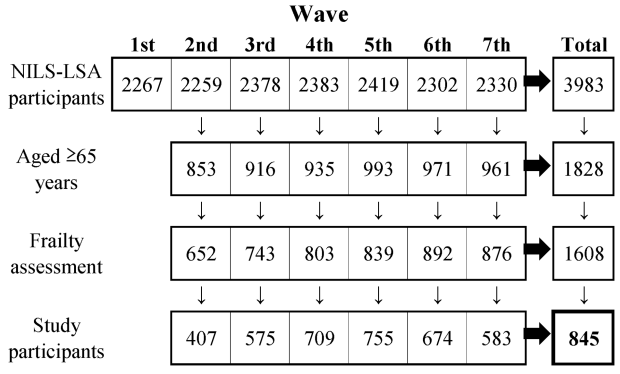

Figure 1. Flow chart of the study participants: The study participants were limited to those aged ≥65 y with at least 3 frailty assessments.

Table 1. Characteristics of the Participants in Total and According to the Frailty Trajectory Group at Their First Frailty Assessment

	All (N = 845)		G1 (n = 92)		G2 (n = 369)		G3 (n = 205)		G4 (n = 57)		G5 (n = 122)			
	Mean, *SD*/*n*, (%)		Mean, *SD*/*n*, (%)		Mean, *SD*/*n*, (%)		Mean, *SD*/*n*, (%)		Mean, *SD*/*n*, (%)		Mean, *SD*/*n*, (%)		*F*/χ^2	*p*
Age*, y	69.7	4.5	72.4	4.6	68.6	3.9	69.6	4.3	74.7	4.2	68.7	4.2	39.87	<.001
NILS-LSA follow-up period†, y	7.1	2.3	7.4	2.2	6.9	2.3	7.3	2.3	7.0	2.3	7.1	2.4	1.64	.163
Sex: males	433	(51.2)	24▼	(26.1)	229△	(62.1)	109	(53.2)	18▼	(31.6)	53	(43.4)	52.68	<.001
Education‡, y	11.1	2.7	10.3	2.2	11.6	2.8	11.0	2.5	10.5	2.7	10.9	2.4	6.09	<.001
MMSE score (0–30)	28.1	1.7	27.8	1.8	28.2	1.7	27.9	1.8	28.0	2.0	28.0	1.7	2.11	.078
Current smoking: yes	117	(13.9)	8	(8.7)	42	(11.4)	35	(17.1)	9	(15.8)	23	(18.9)	8.40	.078
Marital status: married	689	(81.5)	72	(78.3)	324△	(87.8)	159	(77.6)	37▼	(64.9)	97	(79.5)	23.24	<.001
Medical history: yes														
Hypertension	322	(38.3)	31	(34.1)	118▼	(32.1)	88	(42.9)	33△	(60.0)	52	(42.6)	20.53	<.001
Dyslipidemia	185	(22.0)	17	(18.7)	82	(22.3)	48	(23.4)	19	(34.6)	19	(15.6)	8.82	.066
Diabetes	73	(8.7)	7	(7.7)	31	(8.4)	21	(10.2)	2	(3.6)	12	(9.8)	2.84	.586
Cerebrovascular disease	44	(5.2)	5	(5.5)	15	(4.1)	15	(7.3)	7△	(12.7)	2	(1.6)	12.25	.016
Heart disease	145	(17.4)	22	(24.7)	56	(15.3)	32	(15.7)	15	(26.8)	20	(16.7)	8.29	.082
Number of frailty components§ (0–5)	0.8	0.9	1.3	1.0	0.3	0.5	1.0	0.6	1.9	1.1	1.3	0.8	118.15	<.001

Notes: MMSE = Mini-Mental State Examination; NILS-LSA = National Institute for Longevity Sciences-Longitudinal Study of Aging. Continuous variables were expressed as means and *SD*, and intergroup comparisons were made using the general linear model, with post hoc Tukey–Kramer multiple-comparison analysis. Categorical variables were expressed as numbers and percentages, and the χ^2 test was applied, with post hoc residual analysis: The black triangle (downwards) indicates significantly less frequent cases, and the white triangle (upwards) indicates significantly more frequent cases.

*Results of multiple comparisons for age: G2, G5, G3 < G1 < G4.

†Interval between the date of the first and last frailty assessments in the NILS-LSA.

‡Results of multiple comparisons for education: G1, G4 < G2.

§Results of multiple comparisons for the number of frailty components: G2 < G3 < G5, G1 < G4.

All-cause mortality

We used statistical data recorded by the Japan Ministry of Health, Labour and Welfare to obtain information regarding the death of participants at the end of December 2017. The follow-up period was calculated as the interval (in years), starting from the date of the first frailty assessment for each participant to the endpoint of the follow-up period defined as the time of death, moving out of the cohort area, or December 31, 2017. However, for those who moved out of the cohort area and participated in NILS-LSA even after they moved out, the endpoint was determined as the earlier of (a) the last participation date where the participant was confirmed to be alive and (b) December 31, 2017. Information on moving out was obtained from the local offices of the cohort areas.

Analysis

Extraction of trajectory subgroups for frailty assessment

We used group-based multitrajectory modeling (21), an extension of univariate group-based trajectory modeling and one of the latent class analyses, to identify subgroups that followed distinctive trajectories concerning the 5 components of frailty assessment. Although more than one longitudinal change pattern may exist in the direction, timing, and extent, a standard analysis was conducted to study the development and aging that estimates a single average trajectory. In addition, conventional statistical methods often had difficulty in fully utilizing the information obtained from multivariate longitudinal data on the interrelation of multiple indicators of change over time since the indicators of interest were often analyzed in sequence rather than jointly (21). Meanwhile, group-based multitrajectory modeling is a procedure that allows us to identify subgroups (clusters of individuals) that followed similar developmental trajectories within the population by considering multinomial heterogeneity in the changes in multiple indicators and simultaneously estimate the trajectory of each subgroup (21,26–31). Nagin stated that group-based multitrajectory modeling was designed "to link trajectories for 2 or more outcomes by defining a trajectory in terms of trajectories for all of the outcomes of interest" (27). Such analytical methods would provide a useful path to identify adverse trajectories that diverged early on as targets for intervention (32). We performed this analysis using SAS macro PROC TRAJ (https://www.andrew.cmu.edu/user/bjones/index.htm), which is based on a semiparametric mixture modeling strategy and uses the maximum-likelihood method for the estimation of the model parameters. This allows specifying polynomials of different orders for each trajectory subgroup (30). In this study, the logistic model was applied as each frailty component was evaluated as binary data. We entered the wave of the NILS-LSA as the time variable. The selection of the number of trajectories (2–8 trajectories were tested) and the order of the trajectory (intercept only, linear, quadratic, or cubic) of each component for each subgroup was based on the log Bayes factor of the Bayesian information criterion (2[ΔBIC] > 2 for a more complex model vs simpler model), group membership probability, average posterior probabilities of group membership, and odds of correct classification (OCC) (26–30).

Characteristics of frailty trajectory groups

Between the frailty trajectory groups, age at first assessment, years of NILS-LSA follow-up (ie, the interval between the date of the first frailty assessment and the date of the last frailty assessment in the NILS-LSA), years of education, Mini-Mental State Examination (MMSE) score, and frailty scores were analyzed using analysis of variance, and proportions of sex, smoking, marital status, and medical history were analyzed using the χ^2 test. In addition, Cox proportional hazards models were used to examine the differences in all-cause mortality risk between the groups. For the analysis, the unadjusted model and the model adjusted for sex and age at the first frailty assessment were examined.

Statistical analyses were performed using the Statistical Analysis System software version 9.3 (SAS Institute, Inc., Cary, NC).

Results

Frailty Trajectory Groups Based on the 5 Components of Frailty Assessment and Their Characteristics

Five distinct frailty trajectories were identified by analysis using group-based multitrajectory modeling (eTable 2 in the Supplement). The average posterior probabilities of group membership were 0.87–0.94 (threshold of acceptability (31): ≥0.7 for all groups), and the OCC was 19.8–165.0 (>5.0 for all groups), which can be interpreted as indicating a good fit of the model. The estimated trajectories of the 5 frailty components were plotted on a graph for each group to better understand the characteristics of each group (Figure 2).

Group 1: *Weakness*-Focused Frail Progression Group

Group 1 (G1; *n* = 92, 10.9%) was characterized by a longitudinal increase in the presence of *weakness* (probability: from 0.43 in the second wave to 0.93 in the seventh wave) and a low level of fluctuation of *shrinking* (0.03–0.25; 0.30 in the sixth wave). The other components were present at low to moderate levels: The probabilities of *low activity* were consistent at 0.26. The probabilities of *exhaustion* were unchanged at 0.46 and *slowness* ranged 0.00–0.39; however, neither of the estimated parameters was significant (see eTable 2 in the Supplement). The percentage of frail participants (participants meeting 3–5 criteria) increased markedly from 10.0% in the second wave to 41.7% in the seventh wave (eTable 3 in the Supplement).

Group 2: Robust Maintenance Group

Group 2 (G2; *n* = 369, 43.7%), which was the largest group, was characterized by the almost nonexistence of frailty components, where all but *exhaustion* had a probability less than 0.1; however, this group showed a slight but statistically significant increase in the presence of *weakness* (0.00–0.05) and *exhaustion* (0.08–0.15). The percentage of robust participants (participants meeting zero criteria) was consistently high (63.8%–76.4%), and there were almost no frail participants.

Group 3: *Exhaustion*-Focused Prefrail Group

Group 3 (G3; *n* = 205, 24.3%) appeared to have a higher presence of *exhaustion* only (0.66–0.83); almost no other components were present (less than 0.15). However, a slight but significant increase was observed in the presence of *weakness* (0.00–0.12). This group consistently comprised a high volume (74.5–84.7%) of prefrail participants (participants meeting 1 or 2 criteria) at all time points. The percentage of frail participants increased slightly; however, it reached a maximum of 8.0% in the seventh wave.

Group 4: Frail Progression Group

Group 4 (G4; *n* = 57, 6.7%) was characterized by a longitudinal increase in the presence of *slowness*, *exhaustion*, and *weakness* (0.47–0.98, 0.47–0.73, 0.18–0.65, respectively); *shrinking* showed

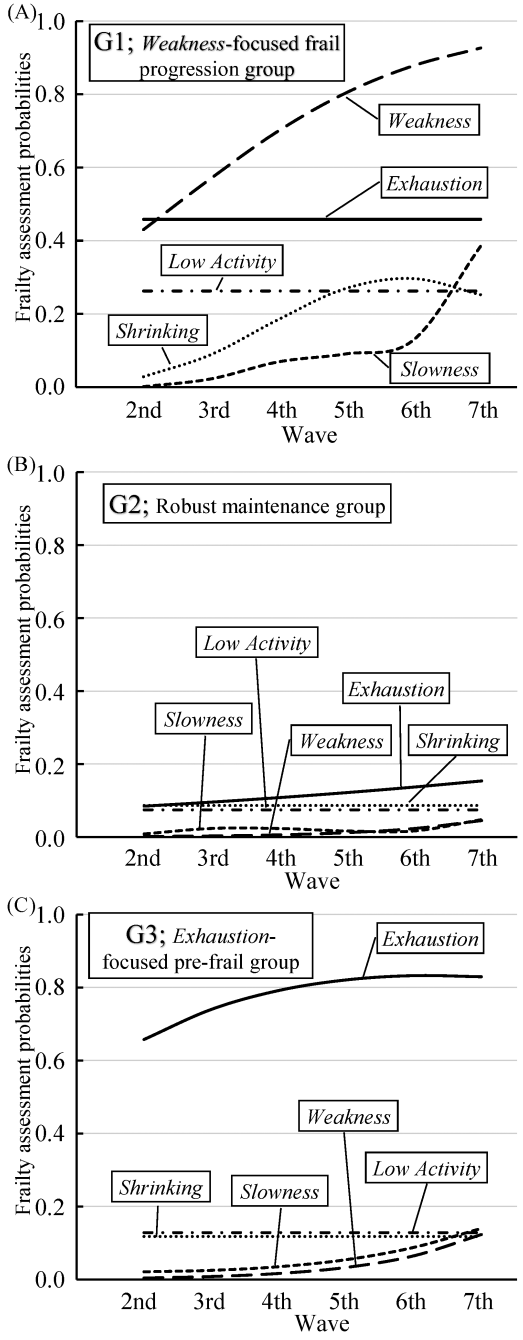

Figure 2. Trajectories of the 5 components of frailty by groups: (**A**) G1: *Weakness*-focused frail progression group, (**B**) G2: Robust maintenance group, (**C**) G3: *Exhaustion*-focused prefrail group, (**D**) G4: Frail progression group, and (**E**) G5: *Low activity*–focused prefrail group.

a fluctuation around the level of non-presence (0.17–0.12; however, it was lowest at 0.07 in the third wave and the highest at 0.33 in the sixth wave). Although 22.0% of G4 participants were assessed as frail at the second wave, the percentage increased markedly to 70.8% by the seventh wave.

Group 5: *Low Activity*–Focused Prefrail Group

Group 5 (G5; n = 122, 14.4%) was characterized by an inverse U-shaped change in the presence of *low activity* (0.71–0.58; 0.80 in

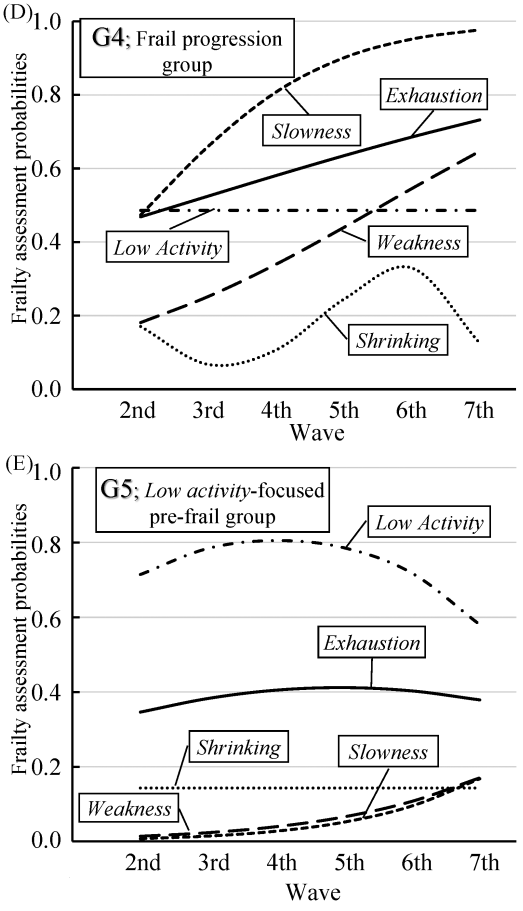

Figure 2. Continued.

the fourth wave). The estimated values of the other 4 components ranged from almost nonexistent to moderate presence; however, there was a slight but statistically significant increase in the presence of *weakness* and *slowness* (0.01–0.17 for both). The probabilities of *shrinking* were consistent at 0.14. The probabilities of the presence of *exhaustion* were approximately 0.4; however, the estimated parameters were not statistically significant. Prefrail participants comprised approximately 70%–80% of the G5 group in all waves.

Characteristics of Frailty Trajectory Groups

The analysis of variance (Table 1) between the trajectory groups showed a significant difference in age at the first frailty assessment (F = 39.87, p < .001; G2, G5, G3 < G1 < G4), years of education (F = 6.09, p < .001; G1, G4 < G2), and frailty scores (F = 118.15, p < .001; G2 < G3 < G5, G1 < G4), but not in the follow-up period and MMSE scores. The χ^2 test suggested that the trajectory group and the ratios of sex, marital status, and medical history of hypertension and cerebrovascular disease were significantly related (χ^2 = 52.68, p < .001; χ^2 = 23.24, p < .001; χ^2 = 20.53, p < .001; χ^2 = 12.25, p = .016), but not in smoking and medical history of dyslipidemia, diabetes, or heart disease. G4 participants were older, had a lower level of education, and had a significantly higher proportion of females and those without a spouse. They had significantly higher frailty scores and were significantly higher in the proportion of those with medical history of hypertension and cerebrovascular disease. In contrast, G2 had generally the opposite characteristics of

Table 2. Association Between All-Cause Mortality and Frailty Trajectory Group

		Unadjusted model						Adjusted model*					
		β	*SE*	χ^2	*p*	HR	95% CI	β	*SE*	χ^2	*p*	HR	95% CI
Frailty trajectory group†	G1	0.77	0.23	11.54	<.001	2.15	1.38–3.35	0.87	0.24	12.78	<.001	2.38	1.48–3.83
	G3	0.08	0.21	0.14	.712	1.08	0.71–1.65	0.08	0.21	0.14	.711	1.08	0.71–1.65
	G4	1.16	0.23	25.09	<.001	3.18	2.02–4.99	0.84	0.25	11.09	<.001	2.31	1.41–3.78
	G5	0.34	0.24	2.08	.149	1.41	0.88–2.25	0.55	0.24	5.18	.023	1.73	1.08–2.76
Sex†	Females							–1.20	0.17	49.27	<.001	0.30	0.22–0.42
Age‡, y								0.12	0.02	46.41	<.001	1.13	1.09–1.17

Notes: CI = confidence interval; HR = hazard ratio. Mean follow-up period (y) ± *SD*: G1, 13.5 ± 3.5; G2, 13.4 ± 2.7; G3, 14.0 ± 2.7; G4, 13.5 ± 3.5; G5, 13.4 ± 3.1. Number of deceased (%) as of December 31, 2017: G1, 31 (33.7); G2, 54 (14.6); G3, 37 (18.1); G4, 29 (50.9); G5, 26 (21.3).

*Adjusted for sex and age at first frailty assessment.

†Reference group: G2 for the frailty trajectory group; males for sex.

‡Age at first frailty assessment.

G4 concerning these characteristics. G1 had the second-oldest age group after G4 and a significantly higher proportion of females.

Furthermore, Cox proportional hazards models were used to examine the risk of all-cause mortality in each trajectory group (Table 2). In the unadjusted model with G2 as the reference, the risk of mortality was significantly higher in G1 and G4; it remained the same even after adjusting for sex and age (hazard ratio [95% confidence interval]: 2.38 [1.48–3.83], 2.31 [1.41–3.78], respectively). In the adjusted model, it was suggested that G5 participants also had a significantly higher risk of mortality (1.73 [1.08–2.76]). Supplementary analyses were performed for (a) the model excluding study participants whose deaths occurred between the second and seventh waves and (b) the model adjusting for the presence or absence (0/1) of the medical history of hypertension, dyslipidemia, diabetes, cerebrovascular disease, and heart disease (both adjusted for sex and age at first frailty assessment, reference = G2). The results for G1, G4, and G5 were (a) 2.12 [1.16–3.89], 2.10 [1.14–3.88], and 1.73 [0.95–3.17], respectively (G5 was marginally significant at $p = .075$) and (b) 2.45 [1.50–4.00], 1.92 [1.15–3.21], and 1.68 [1.04–2.70], respectively. Thus, the results were generally robust.

Discussion

Natural History Trajectories of Frailty

In this study, we identified 5 different trajectories in the natural history of frailty by analyzing longitudinal data on the 5 components of frailty assessment in community-dwelling older adults. Aging affects the progression of frailty. However, the frailty trajectory identified in this study shows that even if the trajectory of each group is shifted by the amount of the age difference between the groups (each wave is approximately 2 years apart), the differences in trajectories are clearly visible. These results suggested that multiple distinct patterns exist in the progression of frailty.

Among the extracted trajectory groups, G2 (robust maintenance group) was the largest group with >60% robust participants in all waves; almost all of the remaining participants were prefrail. G2 participants had a relatively low mortality rate (14.6%), suggesting that they generally maintained high functioning throughout the NILS-LSA follow-up period, and relatively good health even thereafter. They may be typical cases of the "rejuvenation" phenomenon supposed to be occurring in the new generation of Japanese older adults (33). Although the higher proportion of males in G2 may well explain the longer years of education and higher marital status (among Japanese older generations, the husband's age is generally higher than the wife's age (34)), it is also plausible that these factors may be linked to the lower incidence of physical frailty via health literacy and social support (15,35–38).

The participants of the second largest group, G3 (*exhaustion*-focused prefrail group), were approximately the same age as the G2 participants; G3 was the only group not significantly different from G2 in terms of mortality risk. As many participants in G3 met the *exhaustion* criterion, more than 70% of them were classified as prefrail in all waves. They generally maintained a high level of physical functioning and were considered to be distinguished from G2 only by their psychological/response tendencies.

In contrast, the G5 (*low activity*–focused prefrail group) participants, belonging to the third largest group, had more frailty components at first frailty assessment and a higher risk of mortality in the adjusted model despite being similar in age to the G2 and G3 participants. In this group, the presence of *weakness* and *slowness* increased slightly longitudinally, whereas the presence of *low activity* increased once and subsequently began to decrease. The awareness of inactivity and tiredness may have encouraged them to engage in physical activity, but the accumulated negative effects of their previous *low activity* may not have been resolved, resulting in an increased risk of mortality.

The fourth largest group, G1 (*weakness*-focused frail progression group), consistently contained approximately 60% prefrail participants throughout the follow-up period. However, the proportion of robust participants gradually decreased, and conversely, the proportion of frail participants increased over time, reaching approximately 40%. Such changes in frailty status can be regarded as the progression of the frailty cycle starting from the decline in muscle strength, with the addition of *slowness* and *shrinking* to the preceding presence of *weakness*, surfacing as changes in various physical aspects. Even the age-adjusted model suggested that this group had a higher risk of mortality; therefore, earlier intervention might be necessary to halt the progression to frail.

Furthermore, the smallest group, G4 (frail progression group) was the oldest and had the highest frailty scores at the first frailty assessment. It showed a decline in physical functions, such as *slowness* and *weakness,* as well as an increase in the subjective *exhaustion* over the follow-up period, with the proportion of frail participants increasing from approximately 20% to >70%. In addition, this group had a mortality rate >50%; therefore, much attention is required to stop the participants' progression to frailty and prevent them from deteriorating to a state requiring nursing care.

In this study, the frailty trajectories were extracted for those with 3 or more available frailty assessment data (n = 845); but to verify the effect of the analysis subject selection, we also conducted additional analyses of trajectory extraction for those with at least 1 (n = 1 608) and at least 5 (n = 380) available frailty assessment data. The analysis for those with at least 1 frailty assessment identified 5 subgroups with similar trajectories to those of this study (eFigure 1 in the Supplement). In contrast, the analysis of those with 5 or more frailty assessments extracted 2 groups with similar trajectories to G2 and G3, which had larger proportions in this study, and 2 groups with similar trajectories for core components as G1 and G5 in this study, but somewhat different trajectories for the other components (eFigure 2 in the Supplement). The group corresponding to G4, the smallest group in this study, was not extracted. Conducting group-based trajectory modeling analysis with small sample sizes may affect the power of the analysis, the number of trajectories that can be identified, and the robustness of the results (26,39,40). Therefore, it might be necessary to allow the inclusion of a given number of missing waves in the longitudinal measurements, and/or it may be important to use sufficient large data sets to make it possible to identify groups that are relatively small in number.

Further additional analysis to identify trajectories was performed using the frailty scores for the study participants (n = 845). The analysis extracted 3 groups: a robust maintenance group whose scores remained unchanged at nearly zero, a prefrail group whose scores increased slightly longitudinally within the prefrail range, and a frail progression group whose scores increased from prefrail to near frail (eFigure 3 in the Supplement). In previous studies (18,19,37,38) that examined the subgroups of the trajectory of frailty development based on a single variable, although there were differences that may have originated from the measures of frailty used, participants' characteristics, and the number of participants, generally 3 or 4 groups were extracted as described above. Thus, although using single variables such as frailty scores can generally identify distinctive frailty trajectories, they only provide information on the differences in the paces of development of frailty. Analyzing the 5 frail components separately may have more potential for use in interventions, as the characteristics of each component will be more clearly understood (15).

Frailty reversibility has been observed in previous studies (4,7,8,41). However, in the present study, although there were signs of changes in the direction of decrease in the presence of *shrinking* and *low activity* in some groups, no trajectory group clearly showed "recovery in frailty status" that could be extracted. The possible reasons for this are that the analysis using group-based multitrajectory modeling requires each group to include at least approximately 5% of the total participants as one of the criteria for determining the number of trajectory groups, or that shorter follow-up periods are more likely to capture reversibility. Other reasons may be that reversibility is not influenced by a specific component or occurs at a specific time; therefore, its existence is only revealed when it is captured as a total score. Thus, more studies are warranted.

Characteristics of the Frailty Components Suggested by Frailty Trajectory Groups

The trajectories of the frailty components in this study allowed us to infer several aspects of the characteristics of these components. First, as G1 and G4 have shown fluctuations of increase and decrease for *shrinking*, even if weight loss occurs at a certain point in time, it would not usually occur continuously in the range of healthy to typical frailty.

Stenholm et al. (42) reported that weight loss may not necessarily be useful for the early detection of risk groups for the development of frailty. In addition, Yuki et al. (11) found that although the presence of weight loss had a significant effect on the subsequent increased risk of mortality, this effect was not observed when deaths within 2 years of baseline were excluded. Therefore, weight loss may be a result of frailty rather than a causal factor (42). In contrast, in G1 and G4, which indicated the progression of frailty and higher risk of mortality, the presence of *weakness* and *slowness* increased, which is consistent with previous studies (10–12), suggesting that these components are predictors of physical decline and mortality.

Previous studies have reported that although the presence of *exhaustion* can be an early predictor of subsequent onset of frailty (13,42), it remained constant over the years, regardless of the onset of frailty (42). Furthermore, Demura et al. (43) stated that older Japanese individuals tend to overestimate mild depressive symptoms on multiple rating scales. In this study, the presence of *exhaustion* showed a longitudinal increase only in G4 (slightly in G2) and remained consistent at a moderate to high level in G1, G3, and G5. Similarly, there was no clear longitudinal change in the presence of *low activity* except in G5. Considering these points, it could be possible that the presence of *exhaustion* and/or *low activity* may reflect both the progression of frailty and individual characteristics or tendencies related to *exhaustion* and *low activity* that have been maintained over the years. Additional research is needed to elucidate the role of the 5 components in the natural history of frailty.

Summary and Limitations of This Study

Using group-based multitrajectory modeling to analyze the longitudinal data of the 5 components of frailty in community-dwelling older adults, 5 trajectory patterns were identified: The group that maintained robust status without almost any of the components (G2), groups that maintained the prefrail status by having fatigue and/or low physical activity (G3 and G5), and groups with progressive frailty mainly due to low grip strength and slow walking speed (G1 and G4). To the best of our knowledge, this is the first study to demonstrate the existence of multiple trajectories of change in the natural history of frailty based on the 5 frailty components.

This study had several limitations. First, because NILS-LSA was conducted at an examination center, it had the advantage of obtaining objective data based on actual measurements of grip strength, walking speed, weight, etc. However, the data may be biased toward high-functioning individuals whose physical and mental functions are maintained to the extent that they can visit the center and take the survey. To clarify the natural history of frailty, including more advanced status, it may be necessary to collect data via methods that do not require visiting examination center (eg, mail surveys, utilization of data of the Certification of long-term care need, etc.).

Second, differences in the criteria for assessing frailty and differences in the responding tendencies might have led to differences in the results. Although, a study which used the same criteria for assessing frailty for participants in 11 European countries also reported that there were differences in the progression and improvement of frailty between countries (36). Therefore, it may be necessary to accumulate studies on individuals from diverse countries and cultures.

Third, although we examined the differences in basic characteristics at the first frailty assessment among the frailty trajectory groups, it will be necessary to examine the associations of trajectories with

longitudinal changes in psychosocial variables and cognitive function in the future.

Author Notes

1. Part of this study was reported at the 61st Annual Meeting of the Japan Geriatrics Society (44).
2. NILS-LSA is an interdisciplinary, long-term longitudinal research project, and many studies have been published using data from the NILS-LSA cohort. The study by Huang et al. (20) is one such study that performed an analysis of the five frailty components using group-based multitrajectory modeling in Phase 1 of the study to confirm the existence of subtypes that are applicable to only specific frailty components, operationally defined in a previous study (45), by focusing on the timing of progression from the robust state to prefrailty. Thus, the analysis included only robust participants (no frailty component) at the wave before their index wave (which serves as the baseline) aged ≥50 years. Many middle-aged participants aged 50–64 years and only participants aged ≥65 years who were fairly healthy were included. Therefore, the study of Huang et al. is quite different from the present study, which aimed to elucidate the natural history trajectories of frailty in older adults.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

None declared.

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Author Contributions

Study concept and design: C.T. and R.O.; acquisition of data: C.T., Y.N., M.T., R.O., F.A., and H.S.; analysis and interpretation of data: C.T., Y.N., M.T., R.O., F.A., H.S., and H.A.; preparation of manuscript: C.T., Y.N., M.T., R.O., F.A., H.S., and H.A. All authors approved the final version of the manuscript.

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