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Original Research

Frailty Trajectories and Its Associated Factors in Japanese Older Adults

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Abstract

BACKGROUND: Associated factors for frailty development according to age group remain unclear.

OBJECTIVES: To identify frailty score trajectories among community-dwelling older Japanese individuals and examine their associated factors.

DESIGN: 13-year longitudinal study.

SETTING: Kusatsu Town in Gunma Prefecture, Japan.

PARTICIPANTS: 1706 older adults aged ≥ 65 years who completed an annual frailty assessment at least once between 2007 and 2019.

MEASUREMENTS: Frailty status was determined using an index based on the Fried frailty phenotype criteria. Potential associated factors for frailty trajectory included physical, biological, lifestyle-related, and psychological factors, as well as comorbidities.

RESULTS: We identified five trajectory patterns in the frailty score from age of 65 to 90 years —individuals who were robust (Group 1, 10.5%) as well as individuals with late-onset frailty (Group 2, 16.1%), middle-onset frailty (Group 3, 25.6% and Group 4, 35.2%), and early-onset frailty (Group 5, 12.7%). Compared with the other groups, the early-onset group showed a higher prevalence of cerebrovascular diseases, bone and joint diseases, poor nutrition, sarcopenia, hospitalization, low cognitive function, and smoking at the end of follow-up. Associated factors in the middle-onset group largely overlapped with those of the early-onset group. The late-onset frailty group tended to have a higher association with heart disease and bone and joint diseases compared with the robust group.

CONCLUSION: Our findings from a 13-year longitudinal study identified five frailty trajectory patterns and seven associated factors for frailty trajectory. Proposed effective population-based frailty prevention strategies in each age group may contribute to effective strategies to extend healthy life expectancy in aging, aged, and super-aged communities.

Key words: Associated factor, frailty prevention, population-based strategy.

Introduction

Frailty is characterized by multisystem dysregulation of homeostatic mechanisms, including reduced physiological reserves and increased vulnerability due to age-related deficits (1). Frailty is an important risk factor for adverse health outcomes, including dementia (2), long-term care, and mortality (3-7). It is a reversible condition, with a previous study reporting that 13.7% and 56.5% of community-dwelling older adults improved and maintained their frailty status, respectively, within a mean follow-up period of 3.9 years (8). Moreover, frailty status can be improved by nutritional (9, 10), physical (9, 11), cognitive (9), and combined interventions (9, 10, 12, 13).

A previous study (14) described protective and risk factors for frailty in community-dwelling older adults. Specifically, several sociodemographic factors (education level and income), physical and biological factors (sex, obesity, albumin level, white cell count, and monocytes), lifestyle factors (dietary patterns, smoking, and alcohol consumption), and psychological factors (depression and cognitive function) were identified. Moreover, a recent review of frailty trajectories reported that the gradient of frailty progression was influenced by several factors, i.e., socioeconomic factors, social support, physical activity, diabetes, and brain pathologies (15) . Although previous studies have revealed risk factors that affect the onset or progression of frailty over time, associated factors in frailty progression according to age at frailty onset remain unclear. Identifying modifiable associated factors for early- and middle-onset frailty would contribute to effective frailty prevention strategies to extend healthy life expectancy in aging, aged, and super-aged communities.

The present prospective study of community-dwelling older adults used repeated measures data on frailty status from a 13-year longitudinal study of rural Kusatsu Town, Japan. The present study had two objectives: to identify aging trajectories in frailty status from age 65–90 years among community-dwelling older Japanese; and to identify factors associated with this trajectory among these people.

Materials and Methods

Participants

In 2001, a longitudinal study was initiated in collaboration with the government of Kusatsu Town in Gunma Prefecture, Japan. This municipality had the census population of 6694, among whom 37% are older people aged 65 years or older. The main industry is hot spas and resorts (16). Annual preventive health check-ups were offered to all residents aged ≥40 years.

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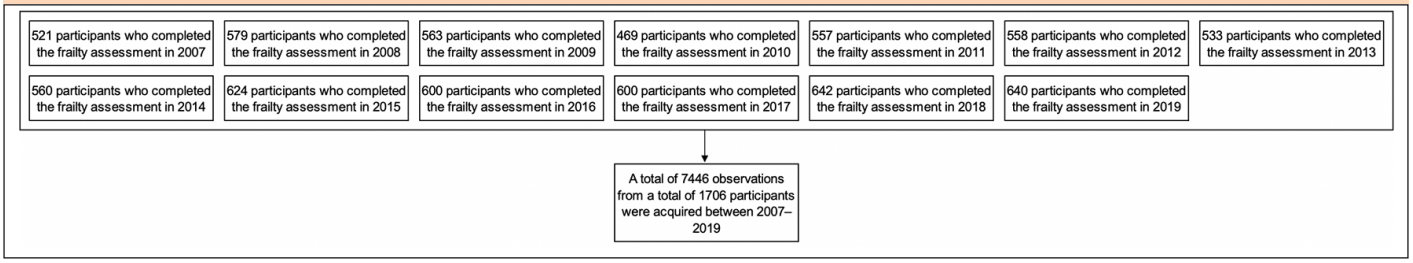
Figure 1. Study flow



In addition, participants aged ≥65 years underwent geriatric assessments. All older residents were invited to participate in annual geriatric assessments, which were all carried out in the same manner. The details of the Kusatsu study have been described previously (3, 6, 16-18). We reported the associations of frailty trajectories with mortality and medical and long-term care costs in Kusatsu town using the close methodology to the current study (18). The present study included those participants who underwent geriatric assessment and provided written informed consent under the conditions approved by the Ethics Committee of the Tokyo Metropolitan Institute of Gerontology.

We included only individuals with complete data regarding the frailty score index obtained at least once between 2007 and 2019. Finally, we included 1706 adults aged ≥ 65 years. Average and total number of follow-up assessments were 4.4 and 7446, respectively (Figure 1).

Frailty assessment

Frailty status was determined based on the Fried frailty phenotype criteria (18, 19), which included slowness (usual gait speed <1.0 m/s) (6, 18, 20, 21); weakness (grip strength < 26 kg for men and < 18 kg for women) (6, 18, 20, 21); exhaustion ("no" response to the question, "Do you feel full of energy?" and a score of ≥5/15 on the Geriatric Depression Scale, short version) (18, 22); low physical activity (response of "less than once a day" to the question, "How often do you usually go outdoors?" (6, 18, 20)), and weight loss (responses of "yes" to the question, "Have you lost 2–3 kg or more in the past 6 months? (from 2007–2015)" and "Have you lost ≥ 3 kg in the past 6 months? (from 2016–2019)") (6, 18, 20). Gait speed was measured over a straight 11 m walkway marked with tape at 3 m and 8 m. Using a stopwatch, well-trained examiners assessed the time required to walk 5 m at a natural speed and calculated the usual gait speed. Handgrip strength was measured twice in the dominant hand: the participant squeezed a Smedley-type handgrip dynamometer (Yagami Co., Tokyo, Japan) as hard as possible, and the higher of the two measured values was included in the analysis. The frailty score ranged from 0–5 (0 = robust, 1 or 2 = prefrail, and 3–5 = frail).

Demographic and health characteristics

We assessed the following potential associated factors for frailty trajectories concurrently at the end of follow-up for frailty assessment. For example, for individuals who underwent frailty assessment 2 times during the follow-up period, the potential associated factors data collected at second time were used. Variables were sex (14), age (14), smoking status (23), alcohol drinking status (24), dietary variety score (25), chronic diseases (26) (hypertension, diabetes mellitus, cerebrovascular disease, heart disease, and bone and joint disease), body mass index (BMI) (14), obesity (BMI ≥ 25 kg/m2) (14), limb skeletal muscle mass (27), sarcopenia (27), hospitalization during the past year (28), albumin levels (14), hemoglobin levels (29), and Mini-Mental State Examination (MMSE) score (14). The dietary variety score comprises 10 food-based components, including meat, fish/shellfish, eggs, milk, soybean products, green/yellow vegetables, potatoes, fruit, seaweed, and fats/oils (30), which constitute a large proportion of daily-life main and side dishes in Japanese people. Regarding chronic diseases, cerebrovascular diseases included cerebral infarction, cerebral hemorrhage, and subarachnoid hemorrhage. Heart diseases included angina, myocardial infarction, and arrhythmia. Bone and joint diseases included arthritis of the knee and hip joints. For each of these conditions, participants were asked if they had received a physician's diagnosis or medical treatment (yes or no). Limb skeletal muscle mass was measured in the arms and legs through direct segmental multifrequency bioelectrical impedance analysis (InBody 720 analyzer; InBody Co., Ltd., Seoul, Korea (31)) and divided by the height squared (m2). Sarcopenia was assessed based on the Asian Working Group for Sarcopenia (AWGS) 2019 criteria (32), with cutoff values for appendicular lean mass of <7.0 kg/m2 for men and <5.7 kg/m2 for women. Non-fasting blood samples were collected using standard procedures, followed by analysis of albumin and hemoglobin levels at Sanaikai Clinic, which is regularly monitored by several domestic authorities (33). The MMSE assesses orientation, memory, concentration, language, and praxis based on 11 items scored from 0–30, with lower scores indicating poorer global cognitive ability (34). The MMSE was administered by well-trained investigators (35).

Statistical analysis

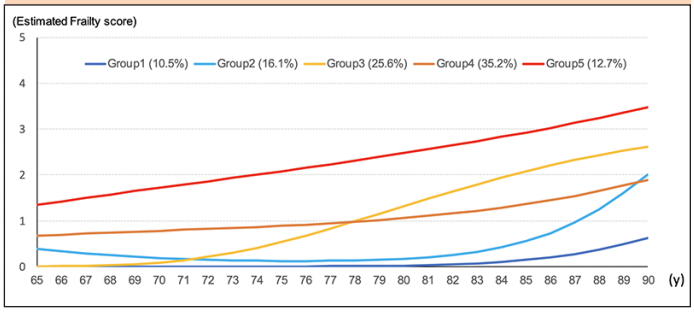
First, we identified trajectory patterns in frailty scores calculated between the ages of 65 and 90 years using latent class trajectory models in PROC TRAJ (SAS Institute, Inc.) (36, 37), with each latent class comprising individuals who follow an approximately homogeneous growth trajectory and individual trajectory can be estimated despite prospective missing values. Cubic trajectory models were fitted to a fixed number of latent classes. Moreover, the posterior probabilities for class assignment were calculated for each individual. Model

selection for the number of trajectory groups and functional form was based on the following criteria: Bayesian information criterion for the models, precision of group proportion, interpretability of the clinical trajectory, and average posterior probability of group assignment (37-38). Subsequently, we performed among-group comparisons of demographic and health characteristics at the end of follow-up using the $\chi 2$ test or analysis of variance, with the results presented as proportions, mean values, and standard deviations. Finally, multinomial logistic regression analysis was used to examine the association between health characteristics and frailty trajectory. The dependent variable was the frailty trajectory group and the independent variables were health characteristics at the end of follow-up, with the lowest trajectory pattern used as reference group. All multinomial logistic regression analyses were performed after adjusting for age and sex. Statistical analyses were performed using SPSS (version 25.0; IBM Corp., Armonk, NY, USA) and SAS (version 9.4; SAS Institute Inc., Cary, NC, USA).

Results

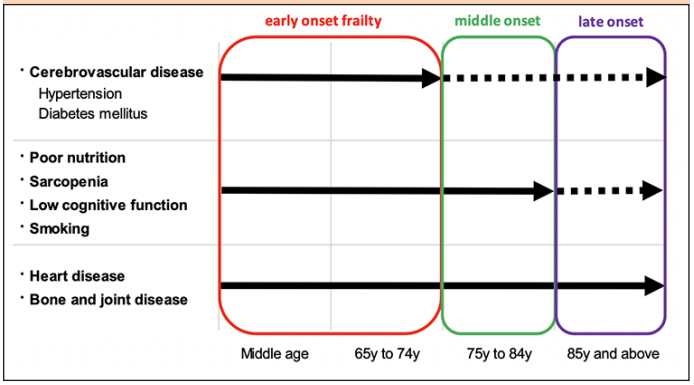
The mean (standard deviation) age of participants was 71.1 (6.2) years, and 44.5% were women. Among participants, 17.6% and 25.3% were current and past smokers, respectively, while 40.5% and 19.3% were current and past alcohol consumers, respectively. The mean dietary variety score was 3.8 (2.5). Among participants, 38.6% had hypertension, 11.1% had diabetes mellitus, 4.9% had cerebrovascular disease, 10.1% had heart disease, 10.2% had bone and joint diseases, and 8.7% had been hospitalized within the past year. Average BMI, limb skeletal muscle mass, albumin level, hemoglobin level, and MMSE score was 23.1 (3.2) kg/m^2, 16.4 (4.0) kg/m^2, 4.20 (0.25) g/dL, 14.01 (1.36) g/dL, and 27.5 (2.5), respectively.

Figure 2. Frailty trajectories by Fried phenotype: Group-based semiparametric mixture model



We identified five trajectory patterns: robust (Group 1, 10.5%), late-onset frailty (Group 2, 16.1%), middle-onset frailty (Group 3, 25.6% and Group 4, 35.2%), and early-onset frailty (Group 5, 12.7%) (Figure 2). Cubic trajectory models with 5 groups showed small BIC value, appropriate SE, the posterior probability, and interpretability of the clinical trajectory (Supplemental Table 1). The robust group (Group 1) was consistently robust until the age of 90 years. The late-onset frailty group (Group 2) comprised individuals who became prefrail after the age of 80 years. The middle-onset frailty group (Groups 3 and 4) became pre-frail after the late 70s, but not frailty even at age of 90. Although Group 3 had lower frailty scores at age 65 than Group 4, they showed rapid progression of frailty after the age of 70 years. Group 3 had higher score than Group 4 after the late 70 years old. The early-onset frailty group (Group 5) comprised individuals who were already pre-frail at the age of 65 years, and their frailty score gradually progressed to frail status around the age of 85 years.

Figure 3. Population-based preventive strategies considering the associated factors of early, middle, and late onset of frailty



The solid lines indicate population-based strategies and the dotted lines show sub-targets.

Table 1 shows the proportions and mean values of demographic and health characteristics at the end of follow-up. Participants in the early-onset frailty group (Group 5) were more likely to be current smokers and/or past alcohol consumers as well as to have cerebrovascular disease, bone and joint disease, sarcopenia, and hospitalization during the past year compared with those in other groups. Additionally, participants in the early-onset frailty group (Group 5) were less likely to be women and current alcohol consumers, and also less likely to have favorable dietary variety scores, limb skeletal muscle mass, albumin levels, hemoglobin levels, and MMSE scores. Compared with participants in the robust group (Group 1), those in middle-onset frailty group (Groups 3 and 4) were more likely to have current smoking habits, heart disease, bone and joint disease, hospitalization during the past year, lower dietary variety scores, and lower MMSE scores. Further, compared with Group 1, Group 2 tended to have higher proportions of participants with diabetes mellitus, heart disease, and bone and joint diseases.

Table 2 shows the age- and sex-adjusted odds ratios of health characteristics for each frailty trajectory compared with the robust group (Group 1). The early-onset frailty group (Group 5) showed significantly higher odds ratios for current smoking, sarcopenia, and hospitalization during the past year, as well as non-significantly higher odds ratios for cerebrovascular disease and bone and joint diseases. In contrast, they showed significantly lower odds ratios for current alcohol consumption, dietary variety score, limb skeletal muscle mass, albumin levels, hemoglobin levels, and MMSE score. Results of multinomial logistic regression analysis for the middle-onset frailty group (Group 3 and Group 4) largely overlapped those in early-onset frailty group, although ORs for poor dietary variety and

Table 1. Demographic and health characteristics of the frailty trajectory groups at the end of follow-up

	Group 1 (n = 179)	Group 2 (n = 274)	Group 3 (n = 436)	Group 4 (n = 600)	Group 5 (n = 217)	P-value
Sex (women, %)	48.6	46.4	47.7	44.3	33.2	< 0.01
Age (year)	78.8 (6.1)	77.8 (5.6)	72.5 (7.2)	75.8 (6.9)	75.1 (6.6)	< 0.01
Smoking status (%)						< 0.01
Current	5.8	7.7	17.7	17.6	20.8	
Past	32.2	26.2	28.6	30.3	21.3	
Never	62.0	66.2	53.8	52.1	57.9	
Alcohol consumption status (%)						< 0.01
Current	38.0	33.7	39.5	36.4	23.3	
Past	28.7	29.1	31.7	26.8	32.7	
Never	33.3	37.2	28.8	36.8	44.1	
Dietary Variety Score	4.5 (2.4)	4.7 (2.6)	4.0 (2.5)	3.7 (2.4)	3.3 (2.4)	< 0.01
History of chronic disease (yes, %)						
Hypertension	43.9	46.0	43.4	49.8	48.3	0.31
Diabetes mellitus	9.9	14.6	13.1	11.4	11.9	0.59
Cerebrovascular disease	6.4	4.6	4.1	6.3	10.4	0.03
Heart disease	9.9	16.1	12.4	14.6	12.9	0.36
Bone and joint disease	9.4	15.8	15.8	17.1	17.5	0.16
Body Mass Index (kg/m^2)	23.1 (3.2)	22.8 (2.9)	23.1 (3.3)	23.1 (3.3)	22.9 (3.8)	0.84
Obesity (BMI ≥25 kg/m^2, %)	25.7	21.9	27.1	25.0	27.6	0.55
Limb skeletal muscle mass (kg /m^2)	15.9 (3.7)	15.5 (3.5)	16.4 (4.2)	15.5 (3.9)	14.2 (4.2)	< 0.01
Sarcopenia based on AWGS 2019 (%)	38.4	42.5	35.2	47.0	57.0	< 0.01
Hospitalized during the past year (%)	7.2	8.5	10.6	11.0	15.3	0.09
Albumin (g/dL)	4.22 (0.30)	4.20 (0.28)	4.23 (0.28)	4.18 (0.27)	4.15 (0.29)	< 0.01
Hemoglobin (g/dL)	13.97 (1.43)	13.89 (1.43)	14.13 (1.52)	13.91 (1.54)	13.50 (1.44)	< 0.01
Mini-Mental State Examination Score	28.0 (2.2)	27.9 (2.4)	27.6 (2.7)	27.2 (3.0)	26.6 (3.2)	< 0.01

Values are percentages or mean (standard deviation). P-values are calculated by the $\chi 2$ test or analysis of variance.

sarcopenia were not significant in Group 3. Of interest, the late-onset frailty group (Group 2) showed high odds ratios for heart disease and bone and joint diseases.

Discussion

This study identified various factors associated with frailty trajectories (early-, middle-, and late-onset frailty), including cerebrovascular disease, poor nutrition, sarcopenia, low cognitive function, smoking, heart disease, bone and joint disease, and recent hospitalization. Seven associated factors for early-onset frailty were identified, namely cerebrovascular disease, heart disease, bone and joint disease, poor nutrition, sarcopenia, low cognitive function, and smoking. This evidence is consistent with the findings of the Whitehall II study, which indicated that risk factors at age 50 years for subsequent frailty included hypertension, cardiovascular disease, current smoking, and poor nutrition (39). Further, we revealed that associated factors largely overlapped between middle-onset and early-onset frailty groups, and included poor nutrition, sarcopenia, low cognitive function, smoking, heart disease, and bone and joint diseases. Among middle-onset frailty groups, it seems that poor nutrition and sarcopenia accelerate the onset of frailty progression. In contrast, the only associated factors for late-onset frailty were heart disease and bone and joint diseases.

The Women's Health Initiative Observational Study reported that coronary heart disease, stroke, diabetes mellitus, and arthritis were significantly related to incident frailty among women aged 65–79 years (40). The Whitehall II study reported that the cardiovascular disease risk score was associated with the risk of future frailty occurrence among patients aged 45–69 years (41). Additionally, frailty trajectories have been reported to be associated with several risk and protective factors, including Alzheimer's disease, diabetes, injury, osteoporotic fractures, increased physical activity, and social support (42). Other risk factors for frailty development include poor nutrition, sarcopenia, low cognitive function, and smoking (14, 15, 23, 25, 27, 43). However, the association of these factors with frailty progression by age at frailty onset remains unclear. To our knowledge, this is the first study to identify associated factors for early-, middle-, and late-onset frailty.

Table 2. Age- and sex-adjusted odds ratios of potential associated factors for the frailty trajectory groups

Independent variable	Group 2 vs Group 1	Group 3 vs Group 1	Group 4 vs Group 1	Group 5 vs Group 1
Smoking status (vs. Never)				
Current	1.19 (0.52–2.75)	3.21* (1.53–6.72)	4.61** (2.24–9.49)	5.95** (2.72–13.04)
Past	0.76 (0.46–1.25)	1.07 (0.68–1.70)	1.46 (0.94–2.27)	1.17 (0.67–2.02)
Alcohol consumption status (vs. Never)				
Current	0.77 (0.46–1.27)	0.99 (0.62–1.58)	0.91 (0.59–1.42)	0.54* (0.31–0.93)
Past	0.88 (0.54–1.45)	1.09 (0.68–1.74)	0.86 (0.55–1.35)	0.91 (0.54–1.51)
Dietary Variety Score (per 1-point increase)	1.03 (0.95–1.11)	0.95+ (0.85–1.06)	0.88** (0.82–0.95)	0.81** (0.73–0.88)
History of chronic disease (vs. Never)				
Hypertension	1.11 (0.75–1.63)	1.09 (0.76–1.57)	1.27 (0.90–1.80)	1.21 (0.80–1.83)
Diabetes mellitus	1.56 (0.85–2.87)	1.35 (0.75–2.43)	1.19 (0.68–2.10)	1.32 (0.68–2.56)
Cerebrovascular disease	0.72 (0.31–1.68)	0.68 (0.31–1.51)	1.01 (0.50–2.02)	1.87 (0.87–4.01)
Heart disease	1.80+ (0.99–3.30)	1.53 (0.85–2.76)	1.57 (0.90–2.74)	1.44 (0.75–2.77)
Bone and joint disease	1.81+ (0.98–3.37)	1.97* (1.09–3.55)	1.97* (1.12–3.47)	1.87+ (0.99–3.54)
Body Mass Index (per 1kg/m^2 increase)	0.98 (0.94–1.03)	0.99 (0.95–1.03)	1.00 (0.97–1.03)	1.01 (0.98–1.04)
Obesity (vs. BMI<25kg/m^2)	0.80 (0.51–1.25)	1.00 (0.67–1.49)	0.97 (0.66–1.43)	1.13 (0.72–1.78)
Limb skeletal muscle mass (per 1kg/m^2 increase)	0.95 (0.88–1.03)	1.02 (0.95–1.10)	0.95 (0.89–1.02)	0.84** (0.77–0.92)
Sarcopenia based on AWGS 2019 (vs no)	1.31 (0.86–1.97)	1.19 (0.81–1.76)	1.53* (1.06–2.21)	2.32** (1.49–3.60)
Hospitalized during the past year (vs no)	1.22 (0.59–2.54)	1.68 (0.86–3.29)	1.59 (0.84–3.04)	2.42* (1.19–4.90)
Albumin (per 1 g/dL increase)	0.72 (0.35–1.48)	0.67 (0.34–1.30)	0.59 (0.31–1.11)	0.34** (0.16–0.72)
Hemoglobin (per 1 g/dL increase)	0.95 (0.82–1.10)	0.99 (0.87–1.14)	0.99 (0.87–1.13)	0.84* (0.73–0.98)
Mini-Mental State Examination Score (per 1 point increase)	0.96 (0.87–1.05)	0.85** (0.78–0.93)	0.87** (0.80–0.94)	0.80** (0.73–0.88)

+ P<0.1, *P<0.05, **P<0.01; Multinomial logistic regression analysis shows odds ratio and (95% confidence Interval) adjusted for age and sex.

Based on the present evidence, we propose effective population-based frailty prevention strategies in each age group in Figure 3. First, population-based interventions from middle age to youngest-old for lifestyle-related diseases, including stroke and its risk factors such as hypertension, diabetes mellitus, smoking, heart disease, bone and joint disease, poor nutrition, sarcopenia, and low cognitive function, are important to prevent early-onset frailty. Second, population-based strategies from middle age to middle-old targeting poor nutrition, sarcopenia, low cognitive function, smoking, heart disease, and bone and joint diseases are necessary to protect against middle-onset frailty. Third, population-based approaches from middle age to oldest-old targeting heart, bone, and joint diseases should be conducted to prevent late-onset frailty. Future community-based intervention studies are needed to verify the effectiveness of these population-based frailty prevention strategies.

This study has several strengths. First, we obtained longitudinal and repeated-measures data of community-dwelling older adults, which allowed the use of a group-based semiparametric mixture model to yield potential trajectories in frailty score for up to 13-time points. Second, we included a wide range of variables, which allowed a comprehensive examination of the potential risk factors for frailty trajectories. However, this study also has several limitations. First, we did not include some variables due to limited data, including education level, household income, neighborhood, living arrangements, and immune-endocrine biomarkers (44). Second, given the small size of each trajectory group, the odds ratio of cerebrovascular disease in Group 5, as well as the odd ratios of heart disease and bone and joint disease in Group 2, might not have reached statistical significance. Third, we only included individuals who underwent health checkups in a rural Japanese town. The rate of participation in health check-ups in this town was 50–60% of the census population. In Japan, most patients who receive treatment for chronic diseases from their primary care physician do not undergo community-based health checkups. Therefore, the proportions of each trajectory group might not represent the general population, with potential underestimation and overestimation of early-onset and late-onset frailty. Fourth, as for frailty criteria for the exhaustion, unfortunately, we did not have commonly used indexes, e.g. by using the Center for Epidemiologic Studies depression scale (19). Thus, exhaustion was defined by using the Geriatric Depression Scale-15 including self-reported exhaustion. Finally, we assessed the following potential associated factors for frailty trajectories at the end of follow-up by using multinomial logistic regression analysis. Further study is needed to consider potential changes in wide range of health characteristics during the follow-up period and to determine the clinical impact and utility of distinguishing between trajectory groups.

In conclusion, this 13-years longitudinal study among community-dwelling older Japanese identified five trajectory patterns of frailty and seven associated factors for frailty trajectory, including cerebrovascular disease, heart disease,

bone and joint disease, poor nutrition, sarcopenia, low cognitive function, and smoking. We propose effective population-based frailty prevention strategies in each age group: specifically, population-based interventions for lifestyle-related diseases should be covered from middle age to youngest-old; strategies targeting poor nutrition, sarcopenia, low cognitive function, smoking, heart disease, and bone and joint diseases are important for middle age to middle-old; and approaches targeting heart, bone, and joint diseases should be conducted from middle age to oldest-old. As Japan has one of the longest life expectancies in the world, the present findings may contribute to effective frailty prevention strategies to extend healthy life expectancy in aging, aged, and super-aged communities.

Author Contributions: AK and YT: study concept and design, data analysis and interpretation, and drafting of the manuscript. TH, KF, TA, YN, SS, YY, and YF: Data acquisition and critical revision of the manuscript for important intellectual content. SS: Study concept and coordination, data acquisition, and data interpretation. All the authors approved the final version of the manuscript.

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Conflicts of Interest: The authors have no potential conflicts of interest related to this research.

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Ethical standards: The present study was approved by the Ethics Committee of the Tokyo Metropolitan Institute of Gerontology.

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