Polypharmacy and lack of joy predict physical frailty among northern Japanese community-dwellers from the ORANGE cohort study

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Abstract

Background: A gradually increasing prevalence of frailty is recognized in the super-aging society that Japan faces, and early detection and intervention of frailty in community-dwellers are critical issues to prevent frailty. Although previous studies have well documented the characteristics of physical disability, there is limited information on frail state differences among older adults in Japanese rural areas. The aim of this study was to clarify the association and predictors of frail status in northen Japan community-dwellers aged 65 or more.

Methods: The investigation was conducted from 2018 to 2020. After obtaining informed consent from each participant, assessments and outcomes were evaluated according to the ORANGE protocol. Participants were recruited from Akita community-dwellers in northern Japan. We applied the frailty index of Gerontology - the Study of Geriatric Syndromes (NCGG-SGS) to classify frailty status, collecting data of demographics and psycho-social status using the Kihon checklist and cognitive domains including the National Center for Geriatrics and Gerontology Functional Assessment Tool (NCGG-FAT).

Results: Our subjects included 313 older adults divided into 138 robust, 163 prefrail and 12 frail. For statistical analysis, physical frailty and cognitive decline were related, and polypharmacy and a lack of joy in daily life were the main predictors of frail status.

Conclusions: Reducing medications and finding fun in your life are important to prevent frailty.

Background

Frailty, a reversible intermediate state of aging process with increased risk for negative health-related events, includes physical, cognitive and psycho-social phenotypes. Especially, physical frailty reduces physiologic functions, which diminishes muscle strength and endurance. The proportion of the population over the age of 65 is growing the most rapidly, and Japan has experienced the largest super-aged society the world.[1] Of issues currently facing a northern rural region in Japan with the most super-aging society (e.g., the number of individuals over aged 75 in Akita is estimated to reach 205,000 people by 2025[1]), countermeasures against physical frailty need to be addressed urgently. Physical frailty is globally recognized, and has an impact on adverse health outcomes such as comorbidity and disability.[2–4] Recently, some studies have well documented the effects of interventions including in exercise[5–7], nutritional[8] and multifactorial (e.g. physical activity plus nutrition)[9,10] programs, with improved physical functions. However, the etiology of physical frailty remains poorly understood. Therefore, clarification of the characteristics of physical frailty in a super-aging society is important in order to prevent a physical bedridden state and dementia in older adults.

Here, we present an epidemiological report of Akita's cohort in a nationwide clinical registry called the Organized Registration for the Assessment of dementia on Nationwide General consortium toward

Effective treatment (ORANGE) in Japan.[11] In this study, we investigated which factors were related to a physical frail status as compared to non- or prefrail older adults. To clarify the characteristics of individuals with physical frailty, we focused on three points as follows. First, we mainly compared medical history, polypharmacy, physical performance, cognitive functions and psycho-social activities in frail individuals with those in robust or prefrail individuals. Second, we examined correlations between physical performance, cognitive and mental functions in each group. Finally, a logistic regression model was estimated to determine predictive factors for physical frailty.

Methods

Participants

This survey was performed from 2018 to 2020. The participants were recruited in Akita prefecture, which had a super-aged rate of 37.9% in 2020. The inclusion criteria were age 65 years and over, ability to walk, and living at home. The exclusion criteria were dementia, severe hearing or visual impairment, intellectual disability, need for support or care as certified by public long-term care insurance system due to disability, and inability to complete cognitive tests. According to sample size calculations using the G*Power for one-way analysis of variance (one-way ANOVA)[12], we estimated a sample size of 159 participants was needed to detect a clinically significant effect with $\alpha = 0.05$, power = 80% and effect size = 0.25.

Our assessments and outcomes were evaluated according to the ORANGE protocol as follows; age, gender, education, health variables including height [cm], weight [kg], body mass index (BMI) [kg/m^2] and medical history, such as hypertension, stroke, cardiac disease, diabetes, hyperlipidemia, osteoporosis, respiratory disease, osteoarthrosis (OA), bone fracture history, neoplasm, Parkinson's disease (PD), Alzheimer's disease (AD), depression and rheumatoid arthritis (RA).

Criteria of frailty status

Frailty status was defined based on five dimensions of the Fried frailty index[13], including shrinking, exhaustion, low level of activity, weakness and slowness, 0 for robust, 1–2 for prefrail, and 3–5 for frail, and the frailty index of Gerontology-the Study of Geriatric Syndromes (NCGG-SGS)[14] was applied for the Japanese version, which includes (i) unintentional weight loss (e.g., a decrease of 2–3 kg in six months), (ii) self-reported exhaustion (e.g., presence of fatigue for two weeks), (iii) low physical activity (e.g., no exercise habit for a week), (iv) weakness (e.g., grip strength (GS) is less than 26/18 kg for male/female) and (v) slow walking speed (WS) (e.g., less than 1.0 m/s in five meter walking test).

Definition of polypharmacy

A systematic review reported that, globally, there is large heterogeneity in the definition of polypharmacy ranging from numerical counts only, numerical counts for a given therapeutic setting or duration.[15] A cross-sectional study has investigated the prevalence of polypharmacy in Sweden, divided into two strata of no use to use of four medications (i.e. no-polypharmacy) and use of five or more medications (i.e.

polypharmacy).[16] In Japan, the “Guidelines for Medical Treatment and its Safety in the Elderly 2015” reported that an increase in occurrence of adverse drug events (ADE) is associated with the number of medications, such as six or more kinds of medication.[17] Considering the current information on polypharmacy domestically and overseas, we recorded the follow definition; (i) polypharmacy of international classification based on use of five or more medications (polypharmacy-IC) and (ii) polypharmacy of Japanese classification based on use of six or more medications (polypharmacy-JC), as reported by Kojima et al.[17] For this study, we analyzed the presence of polypharmacy in different strata of frailty.

Domains of Comprehensive Geriatric Assessment (CGA)

Dependence in daily activities and social activities was assessed using the Kihon checklist (KCL)[18] including Q1-25 items (Supplementary Table 1). Difficulty in response to any question was counted as a score in KCL, and a higher score of the checklist indicated higher risk of requiring support in each domain. Participants were then required to answer Qi-viii items regarding social activities (Supplementary Table 1). In addition, trained staffs conducted the Geriatric Depression Scale short-form (GDS-15).[19]

Evaluation of cognitive function

To evaluate cognitive function in the participants, we applied the National Center for Geriatrics and Gerontology Functional Assessment Tool (NCGG-FAT).[20]

1. Tablet version of word-recognition (WR)

WR test consists of two computerized tasks of immediate recognition and delayed recall. At the start of the immediate recognition task, 10 target words were individually displayed for 2 s. After presenting all the target words, participants were then required to correctly touch the target words in a total of 30 words including 10 target and 20 non-target words and completed the trial three times. The average number of correct answers was scored as a score ranging from 0 to 10. In another delayed recall task, participants were instructed to correctly recall the 10 target words after 20 min.

2. Tablet version of trail making test version A (TMT-A) and version B (TMT-B)

In TMT-A, target numbers from 1 to 15 were randomly presented on the display. Participants were required to touch the target number in order as rapidly as possible. In TMT-B, participants were instructed to touch target numbers from 1 to 15 and letters in turn. The required time (seconds) to complete each task was scored, with a maximum time of 90 s.

3. Tablet version of Symbol Digit Substitution Task (SDST)

In this task, nine pairs of numbers and symbols were presented in the upper part of the tablet display. When a target symbol was shown in the center of the tablet panel, participants were instructed to select the target number out of selectable numbers displayed at the bottom as quickly as possible.

Analyses

According to results of the normalization test (Kolmogorov–Smirnov test), one-way analysis of variance (one-way ANOVA) was applied for age, height, weight, and BMI. Kruskal Wallis test for 2 × 3 contingency (e.g. each nominal scale [Yes/No] × robust/prefrail/frail) was carried out for gender (% female), medical history (%Yes), polypharmacy classification, and frailty index. Education, total KCL score, GS, WS, and cognitive measurements of NCGG-FAT and GDS-15 were analyzed by the Kruskal Wallis test (Table 1).

After confirming no normalization examined by Kolmogorov–Smirnov test, Spearman correlation analysis was performed to examine the correlation of age, BMI, education, total KCL score, GS, WS, subtests of NCGG-FAT, and total GDS-15 score (Table 2). Additionally, Cramér's coefficient of association for 2 × 3 contingency was calculated to clarify the correlation between frailty status and nominal scales including gender, medical history and domains of CGA (Table 3). The above bivariate analysis including Spearman correlation analysis and Cramér's coefficient of association was carried out to select independent variables for the following logistic regression analysis in advance. Finally, ordered logistic regression analysis was performed to clarify predictors of frail status (Table 4). A reference value of $p < 0.20$ was set up to input into independent variables of the ordered logistic regression model. The regression model was set up with frailty classification as the dependent variable and predictors (i.e. independent variables) depending on the procedure (Supplementary Table 2). Before interpreting the results of regression analysis, the confirmation of parallel slope assumption between two linear regression equations estimated in this study needed to be established ($p > 0.05$). After fulfilment of the parallel slope assumption, we confirmed the main effect of the predictors. SPSS Version 26.0 for Windows (SPSS Inc., Chicago. IL, USA) was used for analysis, and the level of significance was set at $p = 0.05$.

Results

The 313 participants consisted of 138 robust, 163 prefrail and 12 frail persons. As shown in Table 1, we compared age, gender, height, weight, BMI, education, KCL score, frailty, cognitive, mental status, medical history, polypharmacy-IC, -JC, and some domains of CGA among the robust, prefrail and frail groups. We found that height, education, presence of RA, polypharmacy-IC, -JC, some domains of KCL, social activities, TMT-A, SDST and GDS-15 showed significant differences among the robust, prefrail and frail groups ($p < 0.05$). Polypharmacy-IC and -JC showed significant differences among the groups ($p < 0.01$). Of the KCL items, 13 items (Q3, 6, 7, 8, 9, 10, 11, 18, 20, 21, 22, 23, 25) were significantly different among the groups ($p < 0.05$), as well as social activities of Qvii ($p = 0.02$).

Second, we analyzed the correlations between physical performance, cognitive and mental functions (Table 2). According to the results of Spearman correlation analysis, WS showed a correlation with GS, WR, TMT-A&B, and SDST in the robust group ($|r| > 0.20$, $p < 0.01$), TMT-A&B and SDST in the prefrail group ($0.15 < |r| < 0.35$, $p < 0.05$), and TMT-B in the frail group ($|r| > 0.60$, $p < 0.05$), as well as correlations between age, education and cognitive subtests.

Third, we analyzed the associations between frailty classification, gender, each item of KCL and social activities in each group (Table 3). As a result of Cramér's coefficient of association between frailty classification and these nominal scales, frail status was significantly associated with the presence of OA, RA, polypharmacy-IC, -JC, and 14 items of CGA (Q3, 6–11, 18, 20–23,25, Qvii) ($p < 0.05$).

Finally, to make an ordered logistic regression model, 31 items were selected as independent variables by the above bivariate analysis, including age, education, hypertension, osteoporosis, RA, polypharmacy-IC, -JC, items of CGA (Q1, 3, 6–10, 13–15, 17, 18, 20–24, Qvi, vii), WR, TMT-A&B, SDST and GDS-15. We conducted regression models to determine predictive factors for frail status with reference to the robust group (Table 4). We made three regression models (Model I-III) according to the procedure to make each model (Supplementary Table 2). As the final regression model (Model III), we extracted six predictors including age (coefficient, 0.03; 95% confidence interval [95% CI], -0.01, 0.07; $p = 0.17$), education (coefficient, -0.15; 95%CI, -0.27, -0.03; $p = 0.01$), polypharmacy-JC (coefficient, 1.08; 95% CI, 0.42, 1.75; $p = 0.001$), Q8 (coefficient, 0.85; 95% CI, 0.19, 1.50; $p = 0.01$), Q9 (coefficient, 0.85; 95% CI, 0.21, 1.49; $p = 0.01$), and Q22 (coefficient, 2.82; 95%CI, 1.66, 3.98; $p < 0.0001$), with significant adaptation of the model ($p < 0.0001$) and establishment of the parallel slope assumption ($p = 0.07$).

Discussion

To summarize our study, we observed the prevalence of physical frailty (3.8%) and significant differences in polypharmacy-IC, -JC, some domains of CGA, education, cognitive function and mental status among the groups (Table 1). Next, we observed the correlations between physical performance and cognitive function within each group (Table 2). Finally, to determine predictive factors of frailty, we analyzed the associations between frail status and nominal scales (gender, each item of CGA) (Table 3). Interestingly, Model III indicated that the presence of polypharmacy-JC ($\beta = 1.08$, 95% CI = 0.42–1.75, $p = 0.001$) and item Q22 ($\beta = 2.82$, 95% CI = 1.66–3.98, $p < 0.0001$) were extracted as strong predictive variables (Table 4).

Initially, we expected that the prevalence would be higher than that regions of southern because our participants living in an area of heavy snowfall in the north would have experienced a negative impact on gait performance[21] due to fewer opportunities to go out and join in social activities. However, our result was similar to that in community-dwellers aged 65 or more estimated at approximately 3.5 to 7.4%.[22–24]

Recent studies have reported that physical frailty is associated with cognitive as well as physical functions.[25] There are also reports that individuals with physical frailty are prone to dementia.[26] In our study, RA and OA, musculoskeletal diseases, showed a significant increase in the frail group, but no difference was observed in diseases that affect cognitive function such as AD, PD and depression (Tables 1 and 3). On the other hand, regarding measurements of cognitive and mental function, the frail group showed worse scores in TMT-A, SDST and GDS-15 than the other groups (robust/prefrail). TMT and SDST reflect executive and information-processing functions, respectively.[27] These results suggest that the frail group may experience a decline of these functions before a decline in memory function

(WR). More interestingly, when we estimated the correlations within each group, we found a stronger correlation between motor function WS and TMT-B in the frail group ($|r| > 0.60$, $p < 0.05$) than in the other groups (robust/prefrail) ($0.15 < |r| < 0.35$, $p < 0.05$), although there was an opposite relationship regarding GDS-15 (Table 2).

KCL is a simple tool for checking any decline in physical and mental functions for early identification of older adults. Some studies showed that the KCL score reflects the state of physical frailty.[18,28] According to them, physical frailty could be diagnosed when 8 or more out of 25 items were applied. In our study, the KCL score tended to be significantly higher in the frail group than in the other groups (median 9.0 vs 3.0–4.0) (Table 1). Considering each item of KCL, it was shown that not only the items of physical (Q6-11) and exhaustion (Q25) but also the items of motivation (Q21-23) in addition to cognitive function (Q3, 18, 20, Qvi, vii) were lower in the frail group than in the other groups (Table 1). On the other hand, there was no difference between the groups regarding each item of oral functions (Q13-15) and social activities (Q1, 2, 4, 5, Qi-v, viii) (Tables 1 and 3). These results indicate that physical frailty and cognitive function are most likely related, and KCL could be useful for screening for physical frailty.

As shown in Table 4, the final model adjusted by age and educational duration suggested that a frail status was associated with the presence of polypharmacy-JC and three items (Q8, 9, 22). According to the coefficient (β) of predictors (Model III), the polypharmacy-JC (β = 1.08, 95% CI = 0.42–1.75, p = 0.001) and motivation in Q22 (β = 2.82, 95% CI = 1.66–3.98, p < 0.0001) were most strongly associated with a frail status. Although there is little material available to compare with our result in the Japanese population, frailty and polypharmacy are common, and their relationship has been widely studied in older adults. Because different measurements or definitions of frailty and polypharmacy have been used, the association of frailty and polypharmacy may be complex and bidirectional.[29] However, several studies showed that the mean drug consumption by frail patients is higher than that of robust ones, and the association was found only with physical frailty domain and not with psychological or social domain.[30,31] Similar to our study, in a sample of community-dwelling men aged 70 years or older in Australia, Gnjidic et al established that the best discriminating number of concomitant medications associated with the presence of frailty was 6.5.[32] Moulis et al also reported a similar analysis with men and women aged 65 years or older in France, reporting a cut-off score of at least 6 drugs.[33] Moreover, there is evidence that the HR for polypharmacy on mortality was high among frailer individuals in a cohort study sampling 1,154 cognitively impaired participants aged 65 years or older.[34] These results indicate polypharmacy may be a contributor to the development of frailty, and it should be noted that patients taking multiple drugs (6 or more) are at risk of frailty. In the future, it is necessary to clarify which is the cause, and the mechanism of the association of frailty and polypharmacy.

Several limitations of the present study should be mentioned. First, sampling in this study satisfied the condition estimated by the G*Power for one-way ANOVA[12], but our cohort consisted of a localized group in one rural area. Second, although not examined this time, it is necessary to take into consideration the number of comorbidities and the types of drugs taken, in order to properly examine the relationship

between polypharmacy and frailty. Finally, our regression models might have selection bias due to small sample size. In fact, since the prevalence of frailty in this study agree with those reported by nationwide studies[23,24], we believe this cross-sectional study may provide novel information about physical frailty. Understanding of the association among frail status, polypharmacy and psycho-social activities needs to be established in a follow-up longitudinal survey.

Conclusions

In the present study, we concluded that physical frailty and cognitive decline are related, and that polypharmacy and diminished motivation in daily life may be a risk for frailty in older adults. We propose that reducing the number of medications and finding fun in daily life may contribute to prevention of frailty.

Abbreviations

Alzheimer's disease
AD, Body mass index:BMI, Comprehensive Geriatric Assessment:CGA, Frailty index of Gerontology - the Study of Geriatric Syndromes:NCGG-SGS, Geriatric Depression Scale short-form (GDS-15), Grip strength:GS, Kihon checklist:KCL, National Center for Geriatrics and Gerontology Functional Assessment Tool:NCGG-FAT, Organized Registration for the Assessment of dementia on Nationwide General consortium toward Effective treatment:ORANGE, Osteoarthrosis:OA, Parkinson's disease:PD, Polypharmacy of international classification:polypharmacy-IC, Polypharmacy of Japanese classification:polypharmacy-JC, Rheumatoid arthritis:RA, Symbol Digit Substitution Task:SDST, Trail Making Test version A:TMT-A, Trail Making Test version B:TMT-B, Walking speed:WS

Declarations

Ethics approval and consent to participate:

The present study was approved by the ethics committee of the Faculty of Medicine, Akita University (approval No. 1649) and was performed in accordance with the Declaration of Helsinki II. Informed consent was obtained from all participants.

Consent for publication:

Consent for publication was obtained from all participants in this study.

Availability of data and materials:

The datasets generated and analyzed during the current study are not publicly available due to no decided rules but will be available from the corresponding author on reasonable request in the future.

Competing interests:

All authors declare that they have no competing interests.

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Author's contributions:

Conceived the trial and participated in the study design: H Shimada, H Makizako, S Lee, and H Ota. Recruited and collected data: T Takahashi, Y Itakura, T Ono, and H Ota. Analyzed data: Y Kume and H Ota. All authors participated in the interpretation of results. Y Kume and H Ota drafted the manuscript, and all authors contributed to the critical review and revision of the manuscript. H Ota takes responsibility for the manuscript as a whole.

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Tables

Table 1. Characteristics of participants according to frailty status

	Robust N = 138		Prefrail N = 163		Frail N = 12		
Basic information	Mean	SD	Mean	SD	Mean	SD	p value
Age (years)	73.7	5.4	74.7	5.9	77.3	6.2	0.08
Gender (% female)	66.7%		71.2%		58.3%		0.52
Height (cm)	155.4	8.8	152.3	7.9	154.6	8.2	0.005 **
Weight (kg)	58.1	10.6	56.1	10.0	58.7	7.7	0.20
BMI (kg/m^2)	24.0	3.2	24.1	3.7	24.6	2.9	0.78
	Median	IQR	Median	IQR	Median	IQR	p value
Education (years)	12.0	2.0	12.0	2.0	9.0	2.0	p < 0.001 †††
Kihon Checklist Total score (score)	3.0	3.0	4.0	4.0	9.0	5.0	p < 0.001 †††
Frailty status	%Yes	%Missing	%Yes	%Missing	%Yes	%Missing	p value
Weight loss in past six months (%)	0	0.0	15.3	0.0	50.0	0.0	p < 0.001 †††
Exhaustion (%)	0	0.0	30.7	0.0	58.3	0.0	p < 0.001 †††
Low level of activity (%)	0	0.0	27.6	0.0	58.3	0.0	p < 0.001 †††
Weakness (%)	0	0.0	29.4	0.0	75.0	0.0	p < 0.001 †††
Slowness (%)	0	0.0	29.4	0.0	91.7	0.0	p < 0.001 †††
	Median	IQR	Median	IQR	Median	IQR	p value
Walking speed (m/s)	1.3	0.3	1.2	0.4	0.9	0.2	< 0.001 †††
Grip strength (kg)	25.5	10.0	23.2	7.4	20.7	10.0	< 0.001 †††
Cognitive function & mental status	Median	IQR	Median	IQR	Median	IQR	p value
Word recognition (score)	11.7	5.3	11.3	5.7	10.0	5.1	0.29
Tablet version of TMT-A (s)	20.0	8.0	22.0	11.0	25.0	5.0	0.03 †
Tablet version of TMT-B (s)	35.5	19.0	40.0	23.0	36.5	14.0	0.07
Tablet version of SDST (score)	41.0	14.0	39.0	13.0	34.5	18.0	0.007 ††
GDS-15 total score (score)	2.0	3.0	3.0	4.0	6.0	8.0	< 0.001 †††
Medical history	%Yes	%Missing	%Yes	%Missing	%Yes	%Missing	p value
Hypertension (%)	46.4	2.9	53.4	0.0	75.0	0.0	0.16
Stroke (%)	3.6	0.0	1.8	0.0	8.3	0.0	0.34
Cardiac disease (%)	20.3	0.0	28.2	0.0	16.7	0.0	0.23
Diabetes (%)	15.2	0.0	16.6	0.0	16.7	0.0	0.95
Hyperlipidemia (%)	36.2	0.0	32.5	0.6	16.7	0.0	0.36
Osteoarosis (%)	26.1	0.0	27	0.6	41.7	0.0	0.51
Respiratory disease (%)	10.1	2.9	6.1	0.0	16.7	0.0	0.25

Table 2. Correlations for robust, prefrail and frail groups

	Robust group (N = 138)						Prefrail group (N = 163)						F	
	WS	GS	WR	TMT-A	TMT-B	SDST	WS	GS	WR	TMT-A	TMT-B	SDST	WS	GS
Age (years)	-.33 **	-.12	-.36 **	.41 **	.52 **	-.54 **	-.28 **	-.19 *	-.46 **	.51 **	.42 **	-.50 **	-.30	.33
BMI (kg/m^2)	-.11	.16	-.01	.23 **	.07	-.13	-.12	.07	-.03	.05	.11	.01	-.21	-.38
Education (years)	.22 *	.03	.12	-.29 **	-.29 **	.24 **	.05	.05	.22 **	-.25 **	-.34 **	.29 **	.07	-.34
KCL (score)	.01	.00	-.08	.02	.06	-.05	.01	-.10	-.02	.12	.01	-.14	.22	.37
GS (kg)	.24 **	1.00	-.12	.01	-.07	.08	.05	1.00	.13	-.13	-.18 *	.27 **	.56	1.00
WS (m/s)	1.00	.24 **	.24 **	-.24 **	-.23 **	.24 **	1.00	.05	.14	-.34 **	-.19 *	.21 **	1.00	.56
GDS-15 (score)	-.01	-.04	-.11	-.06	-.03	-.04	.00	-.04	.00	.01	-.06	-.01	.24	.31

* p < 0.05, ** p < 0.01, Statistics represent Spearman r correlations for each parameter.

The number of subjects who completed KCL was n = 136 for robust group, n = 155 for prefrail group, and n = 11 for frail group, excluding subjects with r

BMI, body mass index; GDS-15, Geriatric Depression Scale-15; KCL, Kihon Checklist; WS, walking speed; GS, Grip strength; WR, word recognition; TI

TMT-B, Trail Making Test B version; SDST, Symbol Digit Substitution Task.

Table 3. Cramér's coefficient of association between frail classification and nomial scales

Reference variable			
Frail classification = dummy variable	robust = 1, prefrail = 2, frail = 3		
Variables (dummy variable)	n	Cramér's value	p value
Background information & medical history			
Gender (female = 0, male = 1)	313	0.065	0.515
Hypertension (Yes = 1, No = 0)	309	0.108	0.163 ‡
Stroke (Yes = 1, No = 0)	313	0.083	0.336
Cardiac disease (Yes = 1, No = 0)	313	0.097	0.229
Diabetes (Yes = 1, No = 0)	313	0.018	0.949
Hyperlipidemia (Yes = 1, No = 0)	312	0.081	0.363
Osteoporosis (Yes = 1, No = 0)	312	0.066	0.508
Respiratory disease (Yes = 1, No = 0)	312	0.094	0.252
Osteoarthrosis (Yes = 1, No = 0)	312	0.121	0.104 ‡
Bone fracture history after age 60 (Yes = 1, No = 0)	311	0.101	0.202
Neoplasm (Yes = 1, No = 0)	313	0.027	0.890
Parkinson's disease (Yes = 1, No = 0)	313	no statistical value	
Alzheimer's disease (Yes = 1, No = 0)	313	no statistical value	
Depression (Yes = 1, No = 0)	313	0.054	0.630
Rheumatoid arthritis (Yes = 1, No = 0)	312	0.144	0.040 *
Polypharmacy-IC (Yes = 1, No = 0)	313	0.189	0.004 **
Polypharmacy-JC (Yes = 1, No = 0)	313	0.218	0.001 **
Kihon checklist			
Q1 (Yes = 0, No = 1)	311	0.110	0.150 ‡
Q2 (Yes = 0, No = 1)	312	0.043	0.749
Q3 (Yes = 0, No = 1)	312	0.152	0.027 *
Q4 (Yes = 0, No = 1)	313	0.027	0.895
Q5 (Yes = 0, No = 1)	313	0.057	0.605
Q6 (Yes = 0, No = 1)	313	0.202	0.002 **
Q7 (Yes = 0, No = 1)	313	0.203	0.002 **
Q8 (Yes = 0, No = 1)	311	0.175	0.008 **
Q9 (Yes = 1, No = 0)	313	0.211	0.001 **
Q10 (Yes = 1, No = 0)	312	0.165	0.015 *
Q11 (Yes = 1, No = 0)	313	0.367	0.000 ***
Q12 (Yes = 1, No = 0)	313	0.065	0.518
Q13 (Yes = 1, No = 0)	313	0.117	0.118 ‡
Q14 (Yes = 1, No = 0)	313	0.135	0.058 ‡
Q15 (Yes = 1, No = 0)	312	0.100	0.181 ‡
Q16 (Yes = 0, No = 1)	313	0.062	0.545
Q17 (Yes = 1, No = 0)	313	0.131	0.068 ‡
Q18 (Yes = 1, No = 0)	313	0.173	0.009 **
Q19 (Yes = 0, No = 1)	313	0.035	0.824
Q20 (Yes = 1, No = 0)	313	0.144	0.039 *
Q21 (Yes = 1, No = 0)	311	0.267	0.000 ***
Q22 (Yes = 1, No = 0)	312	0.339	0.000 ***
Q23 (Yes = 1, No = 0)	311	0.265	0.000 ***
Q24 (Yes = 1, No = 0)	313	0.135	0.058 ‡
Q25 (Yes = 1, No = 0)	313	0.440	0.000 ***
Social activities			
Qi (Yes = 1, No = 0)	312	0.087	0.323
Qii (Yes = 1, No = 0)	312	0.066	0.502
Qiii (Yes = 0, No = 1)	312	0.056	0.614
Qiv (Yes = 1, No = 0)	311	0.038	0.803
Qv (Yes = 1, No = 0)	311	0.043	0.753
Qvi (Yes = 1, No = 0)	311	0.139	0.050 ‡
Qvii (Yes = 1, No = 0)	312	0.163	0.016 *
Qviii (Yes = 1, No = 0)	312	0.093	0.247

* $p < 0.05$,** $p < 0.01$,*** $p < 0.001$, Cramér's coefficient of associatiom.

‡ $p < 0.2$, reference p value to select independent variables for logistic regression model.

Because two items, Q11 "Have you lost 2 kg or more in the past 6 months?" and Q25 "In the last 2 weeks have you felt tired without a reason?", correspond to (i) unintentional weight loss (e.g., a decrease of 2–3 kg in six months) and (ii) self-reported exhaustion (e.g., presence of fatigue for two weeks) of the frailty criteria, the items were excluded from independent variables for the logistic regression model.

Polypharmacy-IC, Polypharmacy based on international classification (i.e., number of medications is 5 or more); Polypharmacy-JC, Polypharmacy based on Japanese classification (i.e., number of medications is 6 or more).

Table 4. Comparison of models according to ordered logistic regression analysis.

		β	SE	Wald	95% CI		p value
Model I	Threshold						
	Frailty classification = 1	2.58	2.77	0.87	-2.84	8.00	0.35
	Frailty classification = 2	7.30	2.81	6.74	1.79	12.80	0.01
	Dependent variables						
	Age (years)	0.02	0.03	0.71	-0.03	0.08	0.40
	Education (years)	-0.11	0.07	2.59	-0.24	0.02	0.11
	Hypertension (Yes = 1/No = 0)	0.22	0.27	0.69	-0.30	0.75	0.41
	Osteoporosis (Yes = 1/No = 0)	-0.06	0.35	0.03	-0.75	0.63	0.86
	Rheumatoid arthritis (Yes = 1/No = 0)	0.77	0.59	1.69	-0.39	1.94	0.19
	Polypharmacy-IC (Yes = 1/No = 0)	-0.01	0.48	0.00	-0.95	0.93	0.98
	Polypharmacy-JC (Yes = 1/No = 0)	0.98	0.56	3.09	-0.11	2.08	0.08
	Q1 (Yes = 0/No = 1)	0.03	0.39	0.01	-0.74	0.80	0.93
	Q3 Yes = 0/No = 1)	1.09	0.74	2.17	-0.36	2.53	0.14
	Q6 (Yes = 0/No = 1)	0.29	0.32	0.83	-0.34	0.92	0.36
	Q7 (Yes = 0/No = 1)	-0.31	0.47	0.43	-1.23	0.61	0.51
	Q8 (Yes = 0/No = 1)	0.82	0.37	4.81	0.09	1.55	0.03
	Q9 (Yes = 1/No = 0)	0.80	0.38	4.37	0.05	1.55	0.04
	Q10 (Yes = 1/No = 0)	0.03	0.30	0.01	-0.55	0.61	0.93
	Q13 (Yes = 1/No = 0)	-0.10	0.32	0.10	-0.74	0.53	0.75
	Q14 (Yes = 1/No = 0)	0.39	0.31	1.61	-0.21	1.00	0.21
	Q15 (Yes = 1/No = 0)	-0.16	0.19	0.73	-0.54	0.21	0.39
	Q17 (Yes = 1/No = 0)	0.02	0.40	0.00	-0.77	0.80	0.97
	Q18 (Yes = 1/No = 0)	-0.37	0.43	0.76	-1.21	0.47	0.39
	Q20 (Yes = 1/No = 0)	-0.53	0.32	2.64	-1.16	0.11	0.10
	Q21 (Yes = 1/No = 0)	0.12	0.49	0.06	-0.84	1.08	0.81
	Q22 (Yes = 1/No = 0)	2.29	0.77	8.96	0.79	3.80	0.00
	Q23 (Yes = 1/No = 0)	0.49	0.33	2.19	-0.16	1.14	0.14
	Q24 (Yes = 1/No = 0)	-0.29	0.48	0.36	-1.24	0.66	0.55
	Qvi (Yes = 1/No = 0)	0.37	0.29	1.60	-0.20	0.94	0.21
	Qvii(Yes = 1/No = 0)	0.23	0.29	0.61	-0.35	0.80	0.43
	WR (score)	0.06	0.05	1.64	-0.03	0.15	0.20
	TMT-A (s)	0.01	0.02	0.42	-0.02	0.05	0.52
	TMT-B (s)	0.01	0.01	0.68	-0.01	0.02	0.41
	SDST (score)	0.00	0.02	0.02	-0.04	0.03	0.88
	GDS-15 (score)	0.10	0.06	2.62	-0.02	0.23	0.11
Model II	Threshold						
	Frailty classification = 1	1.21	1.99	0.37	-2.70	5.11	0.55
	Frailty classification = 2	5.87	2.04	8.28	1.87	9.87	0.00
	Dependent variables						
	Age (years)	0.03	0.02	1.47	-0.02	0.07	0.23
	Education (years)	-0.13	0.06	4.36	-0.25	-0.01	0.04
	Rheumatoid arthritis (Yes = 1/No = 0)	0.68	0.53	1.65	-0.36	1.72	0.20
	Polypharmacy-JC (Yes = 1/No = 0)	0.97	0.36	7.46	0.28	1.67	0.006
	Q3 (Yes = 0/No = 1)	1.07	0.70	2.35	-0.30	2.44	0.13
	Q8 (Yes = 0/No = 1)	0.87	0.34	6.54	0.20	1.54	0.011
	Q9 (Yes = 1/No = 0)	0.81	0.34	5.78	0.15	1.47	0.02
	Q20 (Yes = 1/No = 0)	-0.39	0.29	1.79	-0.95	0.18	0.18
	Q22 (Yes = 1/No = 0)	2.19	0.68	10.44	0.86	3.52	0.001
	Q23 (Yes = 1/No = 0)	0.60	0.31	3.81	0.00	1.20	0.05
	GDS-15 (score)	0.10	0.05	3.43	-0.01	0.21	0.06
Model III	Threshold						
	Frailty classification = 1	0.75	1.90	0.16	-2.97	4.47	0.69
	Frailty classification = 2	5.09	1.95	6.83	1.27	8.90	0.009
	Dependent variables						
	Age (years)	0.03	0.02	1.89	-0.01	0.07	0.17
	Education (years)	-0.15	0.06	6.28	-0.27	-0.03	0.01
	Polypharmacy-JC (Yes = 1/No = 0)	1.08	0.34	10.15	0.42	1.75	0.001
	Q8 (Yes = 0/No = 1)	0.85	0.33	6.47	0.19	1.50	0.01
	Q9 (Yes = 1/No = 0)	0.85	0.33	6.71	0.21	1.49	0.01
	Q22 (Yes = 1/No = 0)	2.82	0.59	22.75	1.66	3.98	$p < 0.0001$

The reference group for analysis was the non-frail group (i.e., robust group = 1; prefrail group = 2; frail group = 3 for each category of independent variables).

Model I. Number of cases for statistical analysis: robust, n = 130; prefrail, n = 154; frail, n = 11. Model χ^2 test, $p < 0.0001$; Parallel slope assumption test, $p < 0.0001$.

Model I. Number of cases for statistical analysis: robust, n = 136; prefrail, n = 159; frail, n = 11. Model χ^2 test, $p < 0.0001$; Parallel slope assumption test, $p = 0.114$.

Model III. Number of cases for statistical analysis: robust, n = 138; prefrail, n = 160; frail, n = 12. Model χ^2 test, $p < 0.0001$; Parallel slope assumption test, $p = 0.070$.

β, coefficient; SE, standard error; Wald, Wald test; CI, confidence interval; Polypharmacy-IC, Polypharmacy based on international classification (i.e., number of medications is 5 or more); Polypharmacy-JC, Polypharmacy based on Japanese classification (i.e., number of medications is 6 or more); WR, word recognition; TMT-A, Trail Making Test A version; TMT-B, Trail Making Test B version; SDST, Symbol Digit Substitution Task; GDS, Geriatric Depression Scale-15.

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