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The impact of physical frailty on disability in community-dwelling older adults: a prospective cohort study

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Abstract

Objective To examine the relationship between physical frailty and risk of disability, and identify the component(s) of frailty with the most impact on disability in community-dwelling older adults.

Design Prospective cohort study.

Setting A Japanese community.

Participants 4341 older adults aged ≥65 living in the community participated in a baseline assessment from 2011 to 2012, and were followed for two years.

Main outcome measures Care-needs certification in the national long-term care insurance (LTCI) system of Japan, type of physical frailty (robust, pre-frail, frail), and sub-items (slowness, weakness, exhaustion, low activity, weight loss), adjusted for several potential confounders such as demographic characteristics; analysed with Kaplan-Meier survival curves for incidence of disability by frailty phenotype.

Results During the two-year follow-up period, 168 participants (3.9 %) began using the LTCI system for incidence of disability. Participants classified as frail (hazard ratio 4.65, 95% confidence interval: 2.63 to 8.22) or pre-frail (2.52, 1.56 to 4.07) at the baseline assessment had an increased risk of disability incidence compared with robust participants. Analyses for sub-items of frailty showed that slowness (2.32, 1.62 to 3.33), weakness (1.90, 1.35 to 2.68), and weight loss (1.61, 1.13 to 2.31) were related to increased risk of disability incidence. In stratified analyses, participants classified as frail and who had lower cognitive function had the highest percentage (30.3%) of disability incidence during the two years after baseline assessment.

Conclusion Physical frailty, even being pre-frail, had a strong impact on the risk of future disability. Some components of frailty, such as slowness, weakness, and weight loss, are strongly associated with incident disability in community-dwelling older adults.

Strengths and limitations of this study

- This study included a large-scale prospective sample of community-dwelling Japanese older adults and the application of a comprehensive measure of physical frailty including not only questionnaires but physical performance measurements.
- Physical frailty, even being pre-frail, strongly predicts increased risk of disability in the Japanese older population.
- Modified cutoff values for slowness (walking speed <1.0 m/s) and weakness (handgrip strength <26 kg for men and <18 kg for women) are appropriate criteria for physical frailty assessments in the Japanese older population.
- Slowness, weakness, and weight loss are particularly associated with incident disability.
- This study did not determine the causes of the incident of disability.

Introduction

Japan has a rapidly aging population, and assessing frailty earlier in this population could help identify those more at risk for disability earlier to implement a more effective intervention.

Disability is an adverse outcome of frailty.[1] Frailty is recognized as a biological syndrome associated with multisystem declines in physiologic reserve and increased vulnerability to stressors, resulting in an increased risk of adverse outcomes such as disability, hospitalization, and death.[2-4] Although there is a general consensus on the definition of frailty phenotype, which classifies it into robust, pre-fail, and frail,[2] many different ways to assess frailty have been reported.[5]

The well-known concept of physical frailty model includes slowness, weakness, exhaustion, low activity, and weight loss.[4] Moreover, these components could have an additive effect on adverse outcomes such as disability.[2 3] We hypothesized that these components have differential effects on the incidence of disability. Thus, the purpose of this prospective cohort analysis was to evaluate the association between physical frailty phenotype and incidence of disability, and to identify the component(s) of frailty that has the most impact on disability among older adults (≥65 years) in Japan.

Methods

This prospective cohort study sampled 4341 community-dwelling elderly adults (≥65 years) enrolled in the Obu Study of Health Promotion for the Elderly (OSHPE). OSHPE participants were recruited from Obu, a residential suburb of Nagoya, Japan. Inclusion criteria were age of ≥65 years at examination in 2011 or 2012, being a resident of Obu, participation in follow up assessments, and no previous participation in other studies. Exclusion criteria were the need for support or care certified by the Japanese public long-term care insurance system (LTCI; care level ≥ 3/5), disability in basic activities of daily living (e.g., history of Parkinson's disease and stroke), and inability to undergo performance-based assessments (e.g., Mini-Mental State Examination (MMSE) score <18.[6, 7] Participants who died or who moved to another city during the two-year follow-up period were also excluded. Between August 2011 and February 2012, 5104 community-dwelling elderly people participated in a baseline OSHPE assessment that included a face-to-face interview and measures of physical and cognitive function.

Participants were then followed monthly and monitored for inclusion into the LTCI system for the next two years. The mandatory social LTCI system was implemented in Japan on April 1, 2000.[8 9] Every Japanese person aged 65 and older is eligible for benefits (institutional and community-based services, but not cash) in cases of physical and/or mental disability. To assess eligibility for these benefits, the LTCI system conducts assessments on incident disability. Informed consent was obtained from all participants prior to their inclusion in the study, and the Ethics Committee of the National Center for Gerontology and Geriatrics approved the study protocol (#490).

Baseline assessments

Licensed nurses recorded demographic data, including age, sex, number of prescribed medications, and medical history in face-to-face interviews. Participants were asked about their history regarding the following diagnoses: stroke, Parkinson's disease, hypertension, heart disease, diabetes mellitus, and osteoporosis. We measured participants' height and weight and calculated their body mass index (BMI). Global cognitive function was assessed using the MMSE,[7] with a cut-off point of 23/24.[10] Depressive symptoms were measured using the 15-item Geriatric Depression Scale (GDS).[11] The cut-off score of ≥6 has a sensitivity of 82% and a specificity of 75% with a structured clinical interview for depression.[12]

Operationalization of the physical frailty phenotype

We considered the physical frailty phenotype to be characterized by limitations in three or more of the following five conditions based on those used in Fried's original studies[2]: slowness, weakness, exhaustion, low activity, and weight loss. Participants who had none of these components were considered to be robust; those with one or two components were considered to be pre-frail.

A majority of previous prospective cohort studies seem to agree with the use of walking speeds for health predictors in aging. [13] Walking speed was measured in seconds using a stopwatch. Participants were asked to walk on a flat and straight surface at a comfortable walking speed. Two markers were used to indicate the start and end of a 2.4-m walk path, with a 2-m section to be traversed before passing the start marker, such that participants were walking at a comfortable pace by the time they reached the timed path. Participants were asked to continue walking for an additional 2 m past the end of the path to ensure a consistent walking pace while on the timed path. Slowness

was established according to a pre-determined cutoff (<1.0 m/s).[6] Together with slowness, low handgrip strength is considered an important indicator of health outcome such as fractures,[14] disability,[15] and death.[16] Weakness was defined using maximum grip strength. Grip strength was measured in kilograms using a Smedley-type handheld dynamometer (GRIP-D; Takei Ltd., Niigata, Japan). In addition, weakness was established according to a sex-specific cutoff (<26 kg for men and <18 kg for women).[17] Exhaustion was considered present if the participant responded "yes" to the following questions, taken from the Kihon-Checklist, a self-reported comprehensive health checklist developed by the Japanese Ministry of Health, Labour and Welfare[18]: "In the last two weeks, have you felt tired for no reason?" We evaluated the role of physical activity by asking the following questions about time spent engaged in sports and exercise: (1) "Do you engage in moderate levels of physical exercise or sports aimed at health?" and (2) "Do you engage in low levels of physical exercise aimed at health?" Participants who answered "no" to both of these questions were classified as low activity.[6] Weight loss was assessed by a response of "yes" to the question, "Have you lost 2 kg or more in the past six months?"[18]

Outcomes

Participants were followed monthly for incident certification of need of care according to the LTCI system during the two years after the baseline assessment. We defined onset of disability as the point at which a participant was certified as needing care according to LTCI classification. The computer-aided standardized needs-assessment system used by the mandatory social LTCI system categorizes people into seven levels of needs.[9]

Statistical analyses

Student's t test and Pearson's chi-square test were used to test differences in baseline characteristics between participants with incidence of disability during the two years after baseline assessment and those without.

We calculated the cumulative incidence of disability during follow-up according to baseline frailty status (frail, pre-frail, and robust) and corresponding to each frailty component (slowness, weakness, exhaustion, low activity, and weight loss) with Kaplan-Meier curves. Intergroup differences were estimated by the log-rank test.

Cox proportional hazards regression models were used to analyse the associations between frailty phenotype and disability risk. The first model (Model 1) was adjusted

for age and sex. We then used a multiple adjustment model adjusted for age, sex, BMI, MMSE, number of prescribed medications, hypertension, heart disease, diabetes mellitus, osteoporosis, and GDS (Model 2). We estimated adjusted hazard ratios (HRs) for incidence of disability and their 95% confidence intervals (95% CIs).

Stratified analyses were performed to examine the relationship between frailty and disability risk in different subgroups defined by sex, age (74/75 years old), cognitive function (MMSE score 23/24), and depressive symptoms (GDS score 5/6).[12] Adjusted HRs for incidence of disability and their 95% confidence intervals were also estimated in the stratified analyses.

All analyses were conducted using IBM SPSS Statistics 19.0 (IBM Japan Tokyo). The level of statistical significance was set at $P < 0.05$.

Results

Of 5104 participants who completed a baseline assessment from Aug 2011 to Feb 2012, 763 had a history of Parkinson's disease (n = 23), stroke (n = 281), MMSE scores of <18 (n = 31), missing data for frailty phenotype (n = 294), were already using the LTCI system (n = 124) at baseline, or had missing follow-up data (n = 55), and were excluded from further analyses. The mean (SD) age of the 4341 participants included in the study was 71.8 (5.4); 2241 (51.6%) were women. The prevalence rates of each component for determining frailty phenotype including slowness, weakness, exhaustion, low activity, and weight loss were 14.8%, 16.4%, 13.2%, 28.6%, and 14.8%, respectively. During the two-year follow-up period, 168 participants (3.9 %) had incident disability and were certified as needing care or support according to LTCI criteria. Figure 1 shows the incident disability rates of frailty status and components.

Table 1 presents participants' baseline characteristics by incidence of disability during follow-up. Participants who developed disability during these two years were older, more often women, had more prescribed medications, and higher prevalence of hypertension, heart disease, and osteoporosis compared with those who remained independent. Those in transition to disability exhibited lower MMSE and higher GDS scores compared to those in the independent group at baseline. The prevalence of frailty in those who developed disability within these two years was 31.5% and approximately five-fold compare with in those who remained independent (5.9%).

Figure 2 and 3 shows the cumulative risk of disability based on frailty status and components. Survival analyses with the Kaplan-Meier log-rank test showed that the probability of incidence of disability was significantly higher in participants categorized as frail compared to those categorized as pre-frail or robust ($P < 0.001$). Furthermore, there was a significant difference in the incidence of disability between pre-frail and robust individuals ($P < 0.001$). Survival analysis performed for frailty components showed significant differences in the incident of disability, according to the presence of frailty sub-items at baseline ($P < 0.001$) (Figure 3).

Cox proportional hazards regression models were used to analyse associations between frail categories and disability risk (Table 2). In the first model (Model 1) that was adjusted for age and sex, participants classified as frail (HR 5.85, 95% CI 3.44 to 9.96) or pre-frail (HR 2.73, 95% CI 1.72 to 4.33) at the baseline assessment had an increased risk of incident disability compared with robust participants. All sub-items of frailty were significantly associated with increased risk of disability. The second model (Model 2) was adjusted for age, sex, BMI, MMSE, number of prescribed medications, hypertension, heart disease, diabetes mellitus, osteoporosis, and GDS. Both frail (HR 4.65, 95% CI 2.63 to 8.22) and pre-frail (HR 2.52, 95% CI 1.56 to 4.07) remained significantly associated with the incident of disability in Model 2. In Model 2, analyses for the sub-items of frailty showed that slowness (HR 2.32, 95% CI 1.62 to 3.33), weakness (HR 1.90, 95% CI 1.35 to 2.68), and weight loss (HR 1.61, 95% CI 1.13 to 2.31) were related to increased risk of incident disability. Exhaustion (HR 1.15, 95% CI 0.79 to 1.69) and low activity (HR 1.27, 95% CI 0.92 to 1.75) did not reach statistically significant levels in Model 2.

Figure 4 shows the results of the stratified analyses. Each status is defined by sex, age, cognitive function, and depressive symptoms. In all statuses, participants classified as frail had increased risk of incident disability across various strata defined by sex, age, cognitive function, and depressive symptoms, even after adjustment for age, sex, BMI, MMSE, number of prescribed medications, hypertension, heart disease, diabetes mellitus, osteoporosis, and GDS. Critically, participants with lower MMSE scores (<24 points) and who were classified as frail had the highest disability incidence rate (30/99, 30.3%) and those who were younger (<75 years) and classified as non-frail had the lowest disability incidence rate (12/1543, 0.8%) during the two years after baseline assessment.

Discussion

Clinical and policy implications

Many different ways to assess physical frailty were reported in previous studies from around the world,[5] with the majority of cohort studies conducted in Western countries.[19] Thus, it might be inappropriate to extend the results of these studies to Asian countries. Indeed, the European Working Group on Sarcopenia in Older People [20] and Asian Working Group for Sarcopenia (AWGS) [17] have different diagnostic cutoffs for the frailty phenotype. Thus, assessing frailty phenotype in an Asian population would develop a more comprehensive definition of the concept and lead to better-designed studies on its effect on the risk of disability among community-dwelling older adults in Asian countries. In this prospective cohort study of community-dwelling older adults, individuals with frail or pre-frail phenotype at baseline had an increased risk of disability incidence during the two years after baseline assessment. These results support findings from previous cohort studies with large samples.[2 3] Regarding the components of frailty, slowness, weakness, and weight loss were more strongly associated with incident disability than the other components. The associations between frailty and the incident of disability remained across various strata defined by sex, age, cognitive function, and depressive symptoms. Specifically, participants with both frail phenotype and lower cognitive function (MMSE scores <24) had the highest disability incidence rate (30.3%) during the two years after baseline assessment (Figure 3). Thus, physical frailty and lower cognitive function could have additive effects on the risk for disability incidence.

The results of this prospective study showed that participants with the slowness component (defined as having a walking speed slower than 1.0 m/s) had more than a two-fold higher risk of disability. However, there is no consensus regarding the cutoff point for walking speed as an indicator of slowness [21 22 23]. Although additional studies are necessary to determine the optimal cutoff values, slowness defined as a walking speed slower than 1.0 m/s could be useful as a component of frailty for predicting disability and preventing functional decline among community-dwelling older adults who are relatively well functioning. In this study, weakness was also determined using modified cutoff values of handgrip strength for Asian populations suggested in a consensus report from AWGS. The AWGS recommends using <26 kg for men and <18 kg for women as the cutoff values for handgrip strength among community-dwelling older adults in Asia.[17] Our findings indicated that low handgrip strength suggested by

AWGS was independently associated with incident of disability after adjustment for potential covariates; thus, these modified cutoff values would be appropriate for diagnosing frailty in Asian populations. Two components of frailty, exhaustion and weight loss, assessed using items in the Kihon Checklist, identified prevalence rates similar to those reported in a previous cohort study sampling more than 5000 community-dwelling older adults [2].

Taken together, our findings indicate that combining questionnaires and performance-based assessments could be an effective method to identify older adults with frailty phenotype as a way to predict risk for disability incidence. Indeed, slowness and weakness assessed by performance-based methods were strongly associated with incident disability in our study. Although assessments using questionnaires are feasible methods to obtain data from a large sample, using questionnaires alone might be insufficient to identify older individuals with higher risks for disability incidence. Furthermore, assessments of walking speed and handgrip strength are very simple and easy to implement in community settings, and are good predictors for health outcomes.[24] A notable point of our findings is that older adults with both physical frailty and lower cognitive function (MMSE scores <24) concurrently represented the highest percentage, more than 30%, of incident disability in stratified analyses. These findings suggest that physical frailty and lower cognitive function have additive effects on disability incidence.

Strengths and limitations

A major strength of this study is the application of a monthly follow-up of disability using a mandatory social LTCI in Japan. Because most frailty models were developed in white populations, different cutoffs for frailty should be considered when examining different populations.[4] Although few prospective cohort studies regarding frailty phenotype and disability have been reported in Asia, this study included a large scale prospective sample of community-dwelling Japanese older adults and the application of a comprehensive measure of physical frailty including not only questionnaires but physical performance measurements.

Nevertheless, several limitations should be considered. This study involved community-dwelling older people who were relatively well functioning and able to participate in the assessments at the community centre on their own. Therefore, this is likely to lead to an underestimation of the actual incidence of disability. In addition, our

follow-up period was shorter than that in previous studies.[2 3 25 26] Another limitation is that the causes of the incident of disability were not determined. The major causes of incident disability certification by the LTCI include post-stroke, dementia, and severe stage of frailty. Moreover, anybody aged 65 and older (and anyone aged 40 to 64 with an aging-related disability) is eligible for LTCI.[27] Thus, future studies examining causes of disability incidence and the longitudinal relationships between frailty and disability using longer follow-up data would be helpful for the development of preventive strategies for disability.

Conclusion

In summary, the results of this prospective cohort study show that physical frailty, even being pre-frail, has a strong impact on increased risk of disability. Among the components of physical frailty, slowness, weakness, and weight loss are more strongly associated with incident disability in community-dwelling Japanese older adults. These findings indicate that physical frailty assessments including simple performance measurement (slowness, weakness) and questionnaires (exhaustion, low activity, and weight loss) could be combined for a more effective prediction of disability incidence in the Japanese older population.

Contributors: HM and HS conceived and designed the study. HM performed the analyses and drafted the manuscript. HS, TD, KT, and TS revised the manuscript. TD and KT prepared the data. All authors participated in interpreting the results. All authors had full access to the data and are guarantors for the study.

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Competing interests: None declared.

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Data sharing: No additional data available.

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Figure legends

Figure 1 Incident disability rates during the two years after baseline assessment by frailty status and frailty components at baseline Frailty phenotype containing three or more of the following was defined as frail, one or two as pre-frail, and none as robust: slowness, weakness, exhaustion, low activity, and weight loss

Figure 2 Kaplan-Meier estimates of cumulative incidence of disability according to frailty status

Frailty phenotype containing three or more of the following was defined as frail, one or two as pre-frail, and none as robust: slowness, weakness, exhaustion, low activity, and weight loss

Figure 3 Kaplan-Meier estimates of cumulative incidence of disability according to components of frailty phenotype

Cutoffs for definition of slowness (walking speed) were <1.0 m/s and weakness (handgrip strength) were <26 kg for men and <18 kg for women

Figure 4 Hazard ratios estimate relative risk of incidence of disability in subgroups defined by sex, age, cognitive function, and depressive symptoms in stratified analyses

Hazard ratios estimate relative risk of disability incidence in those classified as pre-frail or frail compared with those classified as robust (reference group) in different subgroup defined by sex, age (74/75 years), cognitive function (MMSE score 23/24), and depressive symptoms (GDS score 5/6)

Table 1 Baseline characteristics of participants by incidence of disability during the two years after baseline assessment

Characteristics	Overall (n = 4341)	Missing	Independent (n = 4173)	Transition to disability (n = 168)	P value*
Mean (SD) age (years)	71.8 (5.4)	0	71.5 (5.2)	78.1 (6.3)	<0.001
Women	2241 (51.6)	0	2139 (51.3)	102 (60.7)	0.016
Mean (SD) BMI	23.2 (3.6)	2	23.2 (3.5)	23.0 (4.1)	0.485
Mean (SD) MMSE score	26.4 (2.6)	0	26.4 (2.5)	24.7 (2.9)	<0.001
Mean (SD) GDS score	2.7 (2.5)	12	2.7 (2.5)	3.8 (2.8)	<0.001
Mean (SD) prescribed medications	1.9 (2.0)	0	1.9 (2.0)	2.7 (2.3)	<0.001
Hypertension	1930 (44.5)	0	1841 (44.1)	89 (53.0)	0.023
Heart disease	689 (15.9)	0	652 (15.6)	37 (22.0)	0.026
Diabetes mellitus	561 (12.9)	0	535 (12.8)	26 (15.5)	0.314
Osteoporosis	457 (10.5)	2	426 (10.2)	31 (18.5)	0.001
Frail	301 (6.9)	0	248 (5.9)	53 (31.5)	<0.001

* χ^2 test for proportions and Student's t test for continuous measures.

Table 2 Hazard ratios for incident disability two years after baseline assessment according to frailty status and sub-items (n = 4341)

	Model 1			Model 2		
	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*
Frailty status						
Robust	1			1		
Pre-frail	**2.73**	**1.72–4.33**	**<0.001**	**2.52**	**1.56–4.07**	**<0.001**
Frail	**5.85**	**3.44–9.96**	**<0.001**	**4.65**	**2.63–8.22**	**<0.001**
Sub-items						
Slowness						
No	1			1		
Yes	**2.78**	**1.96–3.93**	**<0.001**	**2.32**	**1.62–3.33**	**<0.001**
Weakness						
No	1			1		
Yes	**2.09**	**1.49–2.94**	**<0.001**	**1.90**	**1.35–2.68**	**<0.001**
Exhaustion						
No	1			1		
Yes	**1.47**	**1.03–2.08**	**0.034**	1.15	0.79–1.69	0.462
Low activity						
No	1			1		
Yes	**1.44**	**1.05–1.97**	**0.024**	1.27	0.92–1.75	0.152
Weight loss						
No	1			1		
Yes	**1.87**	**1.31–2.66**	**0.001**	**1.61**	**1.13–2.31**	**0.009**

Adjusted for age and sex.

Adjusted for age, sex, body mass index, Mini-Mental State Examination, number of prescribed medications, hypertension, heart disease, diabetes mellitus, osteoporosis, and Geriatrics Depression Scale.

Figure 1 Incident disability rates during the two years after baseline assessment by frailty status and frailty components at baseline

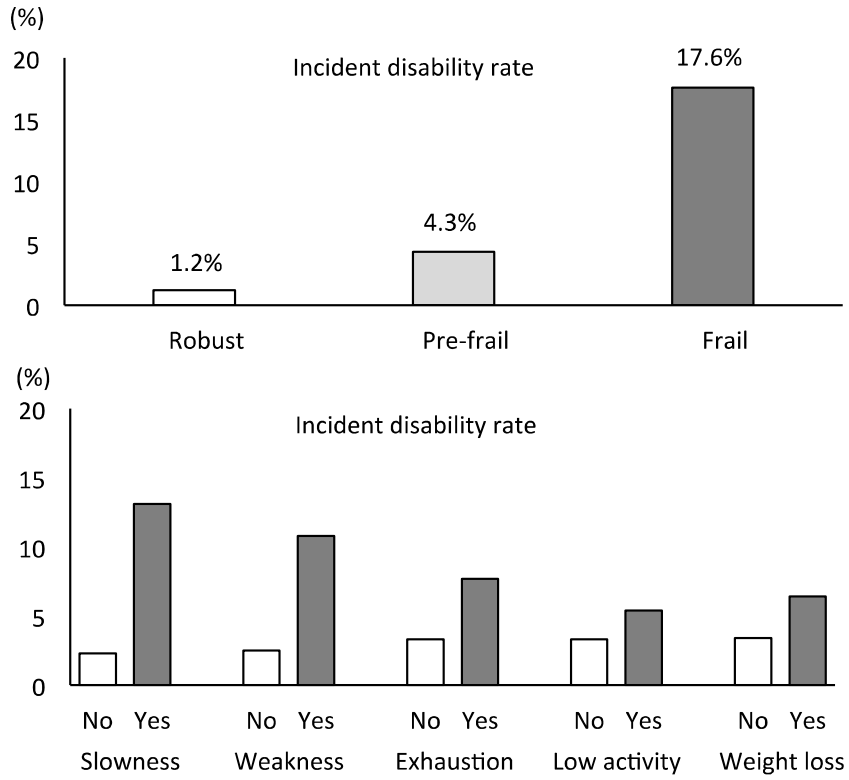


Figure 2 Kaplan-Meier estimates of cumulative incidence of disability according to frailty status

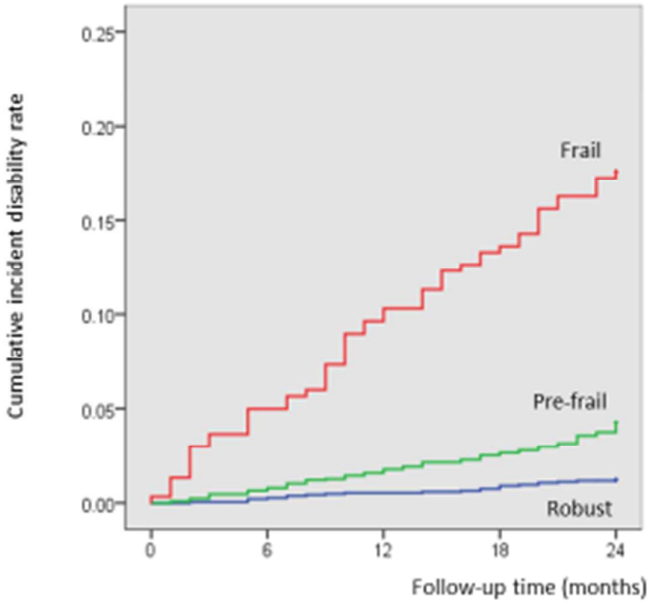


Figure 3 Kaplan-Meier estimates of cumulative incidence of disability according to components of frailty phenotype

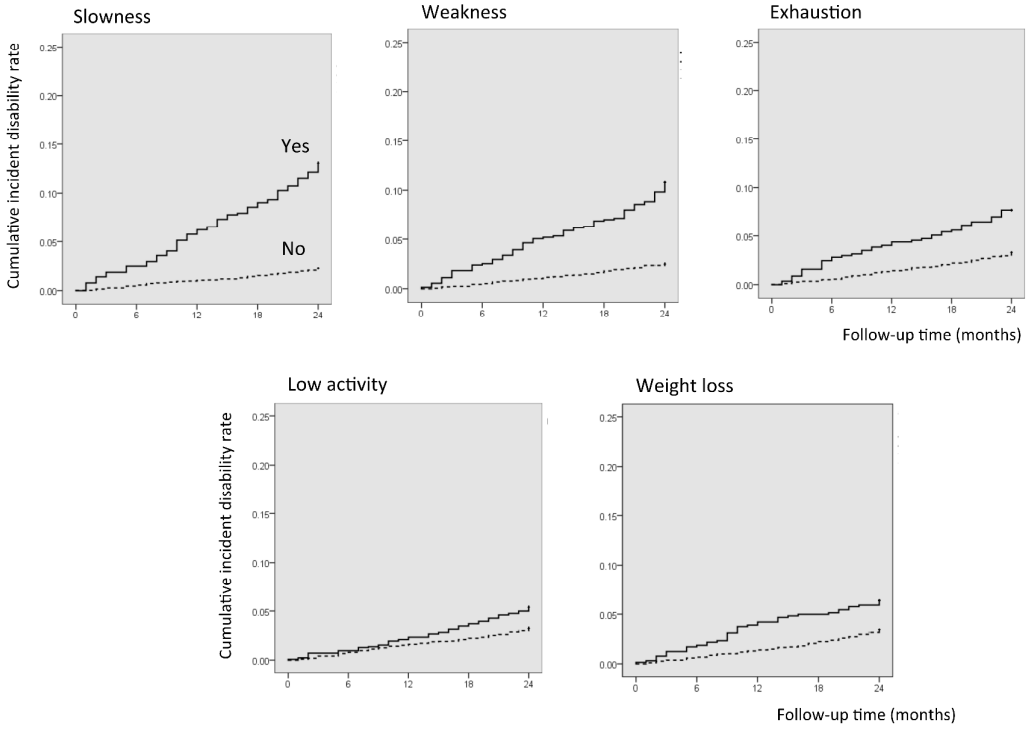
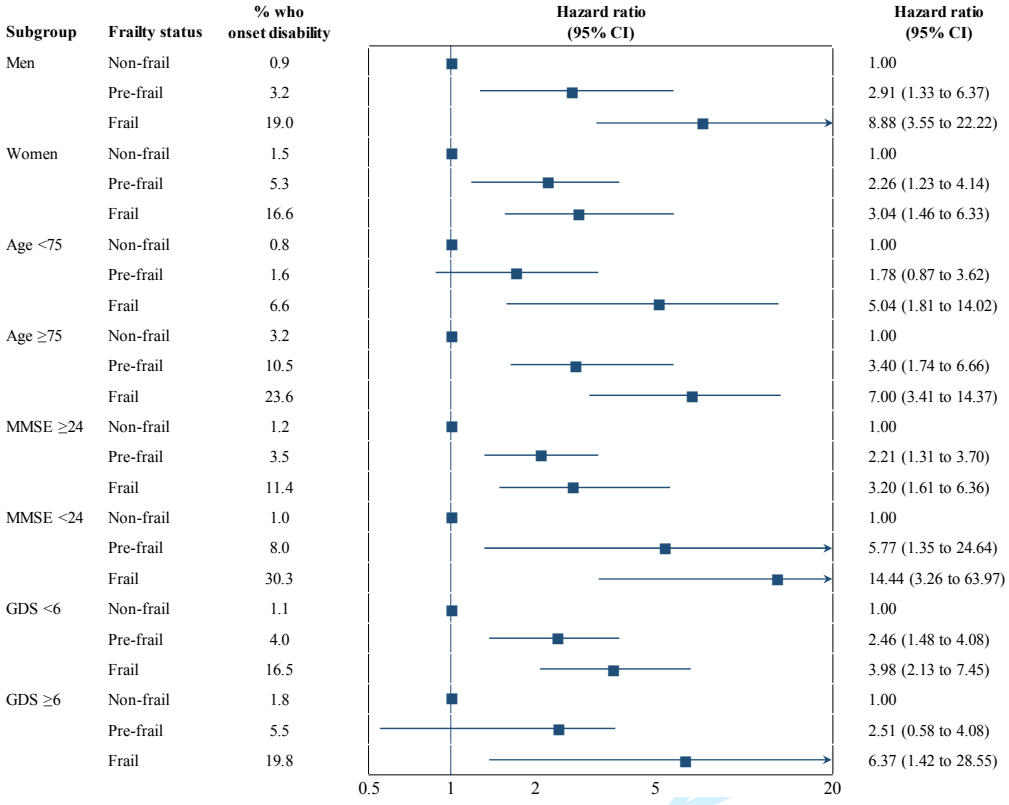


Figure 4 Hazard ratios estimate relative risk of incidence of disability in subgroups defined by sex, age, cognitive function, and depressive symptoms in stratified analyses



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	P1 & P2	**Title: The impact of physical frailty on disability in community-dwelling older adults: a prospective cohort study** **Design** Prospective cohort study.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	P2	Frailty, even being pre-frail, had a strong impact on the risk of future disability. Some components of frailty, such as slowness, weakness, and weight loss, are strongly associated with incident disability in community-dwelling older adults.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P3	Frailty is recognized as a biological syndrome associated with multisystem declines in physiologic reserve and increased vulnerability to stressors, resulting in an increased risk of adverse outcomes such as disability, hospitalization, and death.[2-4] Although there is a general consensus on the definition of frailty phenotype, which classifies it into robust, pre-fail, and frail,[2]

				many different ways to assess frailty have been reported.[5]
Objectives	3	State specific objectives, including any prespecified hypotheses	P3	We hypothesized that these components have differential effects on the incidence of disability. Thus, the purpose of this prospective cohort analysis was to evaluate the association between frailty phenotype and incidence of disability, and to identify the component(s) of frailty that has the most impact on disability among older adults (≥65 years) in Japan.
Methods				
Study design	4	Present key elements of study design early in the paper	P3	This prospective cohort study sampled 4341 community-dwelling elderly adults (≥65 years) enrolled in the Obu Study of Health Promotion for the Elderly (OSHPE).
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P3 & P4	OSHPE participants were recruited from Obu, a residential suburb of Nagoya, Japan. Inclusion criteria were age of ≥65 years at examination in 2011 or 2012, being a resident of Obu, participation in follow up assessments, and no previous participation in other studies.

				Between August 2011 and February 2012, 5104 community-dwelling elderly people participated in a baseline OSHPE assessment that included a face-to-face interview and measures of physical and cognitive function. Participants were then followed monthly and monitored for inclusion into the LTCI system for the next two years.
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	P3 & P4	Inclusion criteria were age of ≥65 years at examination in 2011 or 2012, being a resident of Obu, participation in follow up assessments, and no previous participation in other studies. Exclusion criteria were the need for support or care certified by the Japanese public long-term care insurance system (LTCI; care level ≥ 3/5), disability in basic activities of daily living (e.g., history of Parkinson's disease and stroke), and inability to undergo performance-based assessments (e.g., Mini-Mental State Examination (MMSE) score <18.[6, 7] Participants who died or who moved to another city during the two-year follow-up period were also excluded.

		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P4 & P5	**-Baseline assessments** **-Operationalization of the frailty phenotype** **-Outcomes**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P4 & P5	**-Baseline assessments** **-Operationalization of the frailty phenotype** **-Outcomes**
Bias	9	Describe any efforts to address potential sources of bias	P4	The mandatory social LTCI system was implemented in Japan on April 1, 2000.[8 9] Every Japanese person aged 65 and older is eligible for benefits (institutional and community-based services, but not cash) in cases of physical and/or mental disability. To assess eligibility for these benefits, the LTCI system conducts assessments on incident disability.
Study size	10	Explain how the study size was arrived at	NA	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P4	We considered the frailty phenotype to be characterized by limitations in three or more of the following five conditions based on those used in Fried's original studies[2]: slowness, weakness, exhaustion, low activity, and weight loss. Participants who had none of these components were considered to be robust; those with one or two components were considered to be pre-frail.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	P5 & P6	**-Statistical analyses**
		(*b*) Describe any methods used to examine subgroups and interactions	P5 & P6	**-Statistical analyses**
		(*c*) Explain how missing data were addressed	P6	Of 5104 participants who completed a baseline assessment from Aug 2011 to Feb 2012, 763 had a history of Parkinson's disease (n = 23), stroke (n = 281), MMSE scores of <18 (n = 31), missing data for frailty phenotype (n = 294), were already using the LTCI system (n = 124) at baseline, or had missing follow-up data (n = 55), and were excluded from further analyses.
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	P6	Of 5104 participants who completed a baseline assessment from Aug 2011 to Feb 2012, 763 had a history of Parkinson's disease (n = 23), stroke (n = 281), MMSE

				scores of <18 (n = 31), missing data for frailty phenotype (n = 294), were already using the LTCI system (n = 124) at baseline, or had missing follow-up data (n = 55), and were excluded from further analyses.
		(*e*) Describe any sensitivity analyses	NA	
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P6	Of 5104 participants who completed a baseline assessment from Aug 2011 to Feb 2012, 763 had a history of Parkinson's disease (n = 23), stroke (n = 281), MMSE scores of <18 (n = 31), missing data for frailty phenotype (n = 294), were already using the LTCI system (n = 124) at baseline, or had missing follow-up data (n = 55), and were excluded from further analyses. The mean (SD) age of the 4341 participants included in the study was 71.8 (5.4); 2241 (51.6%) were women. The prevalence rates of each component for determining frailty phenotype including slowness, weakness, exhaustion, low activity, and weight loss were 14.8%, 16.4%, 13.2%, 28.6%, and 14.8%, respectively. During the two-year follow-up period, 168

				participants (3.9 %) had incident disability and were certified as needing care or support according to LTCI criteria.
		(b) Give reasons for non-participation at each stage	NA	
		(c) Consider use of a flow diagram	NA	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P6 & Table 1	Table 1 presents participants' baseline characteristics by incidence of disability during follow-up.
		(b) Indicate number of participants with missing data for each variable of interest	P6	Of 5104 participants who completed a baseline assessment from Aug 2011 to Feb 2012, 763 had a history of Parkinson's disease (n = 23), stroke (n = 281), MMSE scores of <18 (n = 31), missing data for frailty phenotype (n = 294), were already using the LTCI system (n = 124) at baseline, or had missing follow-up data (n = 55), and were excluded from further analyses.
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	P6	Table 1 presents participants' baseline characteristics by incidence of disability during follow-up. Participants who developed disability during these two years were older, more often women, had more prescribed medications, and higher prevalence of hypertension, heart disease, and

				osteoporosis compared with those who remained independent.
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	P6	During the two-year follow-up period, 168 participants (3.9 %) had incident disability and were certified as needing care or support according to LTCI criteria.
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA	
		Cross-sectional study—Report numbers of outcome events or summary measures	NA	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	P7	In the first model (Model 1) that was adjusted for age and sex, participants classified as frail (HR 5.85, 95% CI 3.44 to 9.96) or pre-frail (HR 2.73, 95% CI 1.72 to 4.33) at the baseline assessment had an increased risk of incident disability compared with robust participants. All sub-items of frailty were significantly associated with increased risk of disability. The second model (Model 2) was adjusted for age, sex, BMI, MMSE, number of prescribed medications, hypertension, heart disease, diabetes mellitus, osteoporosis, and GDS. Both frail (HR 4.65, 95% CI 2.63 to 8.22) and pre-frail (HR 2.52, 95% CI 1.56 to 4.07) remained significantly associated with the incident of disability in Model 2. In Model 2, analyses for

			the sub-items of frailty showed that slowness (HR 2.32, 95% CI 1.62 to 3.33), weakness (HR 1.90, 95% CI 1.35 to 2.68), and weight loss (HR 1.61, 95% CI 1.13 to 2.31) were related to increased risk of incident disability. Exhaustion (HR 1.15, 95% CI 0.79 to 1.69) and low activity (HR 1.27, 95% CI 0.92 to 1.75) did not reach statistically significant levels in Model 2.
	(*b*) Report category boundaries when continuous variables were categorized	Table 1	
	(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	P7 & Fig 3	Figure 3 shows the results of the stratified analyses. Each status is defined by sex, age, cognitive function, and depressive symptoms. In all statuses, participants classified as frail had increased risk of incident disability across various strata defined by sex, age, cognitive function, and depressive symptoms, even after adjustment for age, sex, BMI, MMSE, number of prescribed medications, hypertension, heart disease, diabetes mellitus, osteoporosis, and GDS. Critically, participants with lower MMSE scores (<24 points) and who were classified as frail had the highest disability incidence rate (30/99, 30.3%) and those who were younger (<75 years) and classified as non-frail had the lowest disability incidence rate (12/1543, 0.8%) during the two years after baseline assessment.
Discussion				
Key results	18	Summarise key results with reference to study objectives	P10	In summary, the results of this prospective cohort study show that frailty, even being pre-frail, has a strong impact on increased risk of disability. Among the components of frailty, slowness, weakness, and

				weight loss are more strongly associated with incident disability in community-dwelling Japanese older adults. These findings indicate that frailty assessments including simple performance measurement (slowness, weakness) and questionnaires (exhaustion, low activity, and weight loss) could be combined for a more effective prediction of disability incidence in the Japanese older population.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P9	**-Strengths and limitations**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P8 & P9	**-Discussion**
Generalisability	21	Discuss the generalisability (external validity) of the study results	P8	**-Clinical and policy implications**
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P10	**Funding:** This work was supported by the National Center for Geriatrics and Gerontology (Research Funding for Longevity Sciences) [grant number 22-16 and 26-33].

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The impact of physical frailty on disability in community-dwelling older adults: a prospective cohort study

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Abstract

Objective To examine the relationship between physical frailty and risk of disability, and identify the component(s) of frailty with the most impact on disability in community-dwelling older adults.

Design Prospective cohort study.

Setting A Japanese community.

Participants 4341 older adults aged ≥65 living in the community participated in a baseline assessment from 2011 to 2012, and were followed for two years.

Main outcome measures Care-needs certification in the national long-term care insurance (LTCI) system of Japan, type of physical frailty (robust, pre-frail, frail), and sub-items (slowness, weakness, exhaustion, low activity, weight loss), adjusted for several potential confounders such as demographic characteristics; analysed with Kaplan-Meier survival curves for incidence of disability by frailty phenotype.

Results During the two-year follow-up period, 168 participants (3.9 %) began using the LTCI system for incidence of disability. Participants classified as frail (hazard ratio 4.65, 95% confidence interval: 2.63 to 8.22) or pre-frail (2.52, 1.56 to 4.07) at the baseline assessment had an increased risk of disability incidence compared with robust participants. Analyses for sub-items of frailty showed that slowness (2.32, 1.62 to 3.33), weakness (1.90, 1.35 to 2.68), and weight loss (1.61, 1.13 to 2.31) were related to increased risk of disability incidence. In stratified analyses, participants classified as frail and who had lower cognitive function had the highest percentage (30.3%) of disability incidence during the two years after baseline assessment.

Conclusion Physical frailty, even being pre-frail, had a strong impact on the risk of future disability. Some components of frailty, such as slowness, weakness, and weight loss, are strongly associated with incident disability in community-dwelling older adults.

Strengths and limitations of this study

- This study included a large-scale prospective sample of community-dwelling Japanese older adults and the application of a comprehensive measure of physical frailty including not only questionnaires but physical performance measurements.
- Physical frailty, even being pre-frail, strongly predicts increased risk of disability in the Japanese older population.
- Modified cutoff values for slowness (walking speed <1.0 m/s) and weakness (handgrip strength <26 kg for men and <18 kg for women) are appropriate criteria for physical frailty assessments in the Japanese older population.
- Slowness, weakness, and weight loss are particularly associated with incident disability.
- This study did not determine the causes of the incident of disability.

Introduction

Japan has a rapidly aging population, and assessing frailty earlier in this population could help identify those more at risk for disability earlier to implement a more effective intervention.

Disability is an adverse outcome of frailty.[1] Frailty is recognized as a biological syndrome associated with multisystem declines in physiologic reserve and increased vulnerability to stressors, resulting in an increased risk of adverse outcomes such as disability, hospitalization, and death.[2-4] Although there is a general consensus on the definition of frailty phenotype, which classifies it into robust, pre-fail, and frail,[2] many different ways to assess frailty have been reported.[5]

The well-known concept of physical frailty model includes slowness, weakness, exhaustion, low activity, and weight loss.[4] Moreover, these components could have an additive effect on adverse outcomes such as disability.[2 3] We hypothesized that these components have differential effects on the incidence of disability. Thus, the purpose of this prospective cohort analysis was to evaluate the association between physical frailty phenotype and incidence of disability, and to identify the component(s) of frailty that has the most impact on disability among older adults (≥65 years) in Japan.

Methods

This prospective cohort study sampled 4341 community-dwelling elderly adults (≥65 years) enrolled in the Obu Study of Health Promotion for the Elderly (OSHPE). OSHPE participants were recruited from Obu, a residential suburb of Nagoya, Japan. Inclusion criteria were age of ≥65 years at examination in 2011 or 2012, being a resident of Obu, participation in follow up assessments, and no previous participation in other studies. Exclusion criteria were the need for support or care certified by the Japanese public long-term care insurance system (LTCI; care level ≥ 3/5), disability in basic activities of daily living (self-feeding, personal hygiene and grooming, walking, stairs, and bathing), and inability to undergo performance-based assessments (e.g., severe hypertension, balance impairment, or pain). We also excluded participants with a history of Parkinson's disease, stroke, depression, Alzheimer's disease, or those with Mini-Mental State Examination (MMSE) scores <18.[6, 7] Participants who died or who moved to another city during the two-year follow-up period were also excluded. Between August 2011 and February 2012, 5104 community-dwelling elderly people participated in a

baseline OSHPE assessment that included a face-to-face interview and measures of physical and cognitive function.

Participants were then followed monthly and monitored for inclusion into the LTCI system for the next two years. The mandatory social LTCI system was implemented in Japan on April 1, 2000.[8 9] To assess eligibility for these benefits, the LTCI system conducts assessments on incident disability. Informed consent was obtained from all participants prior to their inclusion in the study, and the Ethics Committee of the National Center for Gerontology and Geriatrics approved the study protocol (#490).

Baseline assessments

Licensed nurses recorded demographic data, including age, sex, number of prescribed medications, and medical history in face-to-face interviews. Participants were asked about their history regarding the following diagnoses: stroke, Parkinson's disease, hypertension, heart disease, diabetes mellitus, and osteoporosis. We measured participants' height and weight and calculated their body mass index (BMI). Global cognitive function was assessed using the MMSE,[7] with a cut-off point of 23/24.[10] Depressive symptoms were measured using the 15-item Geriatric Depression Scale (GDS).[11] The cut-off score of ≥6 has a sensitivity of 82% and a specificity of 75% with a structured clinical interview for depression.[12]

Operationalization of the physical frailty phenotype

We considered the physical frailty phenotype to be characterized by limitations in three or more of the following five conditions based on those used in Fried's original studies[2]: slowness, weakness, exhaustion, low activity, and weight loss. Participants who had none of these components were considered to be robust; those with one or two components were considered to be pre-frail.

A majority of previous prospective cohort studies seem to agree with the use of walking speeds for health predictors in aging. [13] Walking speed was measured in seconds using a stopwatch. Participants were asked to walk on a flat and straight surface at a comfortable walking speed. Two markers were used to indicate the start and end of a 2.4-m walk path, with a 2-m section to be traversed before passing the start marker, such that participants were walking at a comfortable pace by the time they reached the timed path. Participants were asked to continue walking for an additional 2 m past the

end of the path to ensure a consistent walking pace while on the timed path. Slowness was established according to a pre-determined cutoff (<1.0 m/s).[6] Together with slowness, low handgrip strength is considered an important indicator of health outcome such as fractures,[14] disability,[15] and death.[16] Weakness was defined using maximum grip strength. Grip strength was measured in kilograms using a Smedley-type handheld dynamometer (GRIP-D; Takei Ltd., Niigata, Japan). In addition, weakness was established according to a sex-specific cutoff (<26 kg for men and <18 kg for women).[17] Exhaustion was considered present if the participant responded "yes" to the following questions, taken from the Kihon-Checklist, a self-reported comprehensive health checklist developed by the Japanese Ministry of Health, Labour and Welfare[18]: "In the last two weeks, have you felt tired for no reason?" We evaluated the role of physical activity by asking the following questions about time spent engaged in sports and exercise: (1) "Do you engage in moderate levels of physical exercise or sports aimed at health?" and (2) "Do you engage in low levels of physical exercise aimed at health?" Participants who answered "no" to both of these questions were classified as low activity.[6] Weight loss was assessed by a response of "yes" to the question, "Have you lost 2 kg or more in the past six months?"[18]

Outcomes

Participants were followed monthly for incident certification of need of care according to the LTCI system during the two years after the baseline assessment. Japan implemented a mandatory social LTCI system on April 1, 2000.[8 9] Every Japanese citizen aged 65 and older is eligible for benefits (institutional and community-based services, but not cash) in cases of physical and/or mental disability. The computer-aided standardized needs-assessment system used by the mandatory social LTCI system categorizes people into seven levels of needs.[9] We defined onset of disability as the point at which a participant was certified as needing care according to LTCI classification.

Statistical analyses

Student's t test and Pearson's chi-square test were used to test differences in baseline characteristics between participants with incidence of disability during the two years after baseline assessment and those without.

We calculated the cumulative incidence of disability during follow-up according to baseline frailty status (frail, pre-frail, and robust) and corresponding to each frailty

component (slowness, weakness, exhaustion, low activity, and weight loss) with Kaplan-Meier curves. Intergroup differences were estimated by the log-rank test.

Cox proportional hazards regression models were used to analyse the associations between frailty phenotype and disability risk. The first model (Model 1) was adjusted for age and sex. We then used a multiple adjustment model adjusted for age, sex, BMI, MMSE, number of prescribed medications, hypertension, heart disease, diabetes mellitus, osteoporosis, and GDS (Model 2). These covariates were included as categorical (age, sex, and diagnoses) and continuous variables (BMI, MMSE, number of prescribed medications, and GDS). We estimated adjusted hazard ratios (HRs) for incidence of disability and their 95% confidence intervals (95% CIs).

Stratified analyses were performed to examine the relationship between frailty and disability risk in different subgroups defined by sex, age (74/75 years old), cognitive function (MMSE score 23/24), and depressive symptoms (GDS score 5/6).[12] Adjusted HRs for incidence of disability and their 95% confidence intervals were also estimated in the stratified analyses.

All analyses were conducted using IBM SPSS Statistics 19.0 (IBM Japan Tokyo). The level of statistical significance was set at $P < 0.05$.

Results

Of 5104 participants who completed a baseline assessment from Aug 2011 to Feb 2012, 763 had a history of Parkinson's disease (n = 23), stroke (n = 281), MMSE scores of <18 (n = 31), missing data for frailty phenotype (n = 249), were already using the LTCI system (n = 124) at baseline, or had missing follow-up data (n = 55), and were excluded from further analyses (Figure 1). The mean (SD) age of the 4341 participants included in the study was 71.8 (5.4); 2241 (51.6%) were women. The prevalence rates of each component for determining frailty phenotype including slowness, weakness, exhaustion, low activity, and weight loss were 14.8%, 16.4%, 13.2%, 28.6%, and 14.8%, respectively. The prevalence of frailty and pre-frailty were 6.9% and 49.6%, respectively. During the two-year follow-up period, 168 participants (3.9 %) had incident disability and were certified as needing care or support according to LTCI criteria. Figure 2 shows the incident disability rates of frailty status and components.

Table 1 presents participants' baseline characteristics by incidence of disability during

follow-up. Participants who developed disability during these two years were older, more often women, had more prescribed medications, and higher prevalence of hypertension, heart disease, and osteoporosis compared with those who remained independent. Those with incident disability exhibited lower MMSE and higher GDS scores compared to those in the independent group at baseline. The prevalence of frailty in those who developed disability within these two years was 31.5% and approximately five-fold compare with in those who remained independent (5.9%).

Figure 3 and 4 shows the cumulative risk of disability based on frailty status and components. Survival analyses with the Kaplan-Meier log-rank test showed that the probability of incidence of disability was significantly higher in participants categorized as frail compared to those categorized as pre-frail or robust ($P < 0.001$). Furthermore, there was a significant difference in the incidence of disability between pre-frail and robust individuals ($P < 0.001$). Survival analysis performed for frailty components showed significant differences in the incident of disability, according to the presence of frailty sub-items at baseline ($P < 0.001$) (Figure 4).

Cox proportional hazards regression models were used to analyse associations between frail categories and disability risk (Table 2). In the first model (Model 1) that was adjusted for age and sex, participants classified as frail (HR 5.85, 95% CI 3.44 to 9.96) or pre-frail (HR 2.73, 95% CI 1.72 to 4.33) at the baseline assessment had an increased risk of incident disability compared with robust participants. All sub-items of frailty were significantly associated with increased risk of disability. The second model (Model 2) was adjusted for age, sex, BMI, MMSE, number of prescribed medications, hypertension, heart disease, diabetes mellitus, osteoporosis, and GDS. Both frail (HR 4.65, 95% CI 2.63 to 8.22) and pre-frail (HR 2.52, 95% CI 1.56 to 4.07) remained significantly associated with the incident of disability in Model 2. In Model 2, analyses for the sub-items of frailty showed that slowness (HR 2.32, 95% CI 1.62 to 3.33), weakness (HR 1.90, 95% CI 1.35 to 2.68), and weight loss (HR 1.61, 95% CI 1.13 to 2.31) were related to increased risk of incident disability. Exhaustion (HR 1.15, 95% CI 0.79 to 1.69) and low activity (HR 1.27, 95% CI 0.92 to 1.75) did not reach statistically significant levels in Model 2.

Figure 5 shows the results of the stratified analyses. Each status is defined by sex, age, cognitive function, and depressive symptoms. In all statuses, participants classified as frail had increased risk of incident disability across various strata defined by sex, age,

cognitive function, and depressive symptoms, even after adjustment for age, sex, BMI, MMSE, number of prescribed medications, hypertension, heart disease, diabetes mellitus, osteoporosis, and GDS. Critically, participants with lower MMSE scores (<24 points) and who were classified as frail had the highest disability incidence rate (30/99, 30.3%) and those who were younger (<75 years) and classified as non-frail had the lowest disability incidence rate (12/1543, 0.8%) during the two years after baseline assessment.

Discussion

Clinical and policy implications

Many different ways to assess physical frailty were reported in previous studies from around the world,[5] with the majority of cohort studies conducted in Western countries.[19] Thus, it might be inappropriate to extend the results of these studies to Asian countries. Indeed, the European Working Group on Sarcopenia in Older People [20] and Asian Working Group for Sarcopenia (AWGS) [17] have different diagnostic cutoffs for the frailty phenotype. Thus, assessing frailty phenotype in an Asian population would develop a more comprehensive definition of the concept and lead to better-designed studies on its effect on the risk of disability among community-dwelling older adults in Asian countries. In this prospective cohort study of community-dwelling older adults, individuals with frail or pre-frail phenotype at baseline had an increased risk of disability incidence during the two years after baseline assessment. These results support findings from previous cohort studies with large samples.[2 3] Regarding the components of frailty, slowness, weakness, and weight loss were more strongly associated with incident disability than the other components. The associations between frailty and the incident of disability remained across various strata defined by sex, age, cognitive function, and depressive symptoms. Specifically, participants with both frail phenotype and lower cognitive function (MMSE scores <24) had the highest disability incidence rate (30.3%) during the two years after baseline assessment (Figure 3). Thus, physical frailty and lower cognitive function could have additive effects on the risk for disability incidence.

The results of this prospective study showed that participants with the slowness component (defined as having a walking speed slower than 1.0 m/s) had more than a two-fold higher risk of disability. However, there is no consensus regarding the cutoff point for walking speed as an indicator of slowness [21-23]. Although additional studies are

necessary to determine the optimal cutoff values, slowness defined as a walking speed slower than 1.0 m/s could be useful as a component of frailty for predicting disability and preventing functional decline among community-dwelling older adults who are relatively well functioning. In this study, weakness was also determined using modified cutoff values of handgrip strength for Asian populations suggested in a consensus report from AWGS. The AWGS recommends using <26 kg for men and <18 kg for women as the cutoff values for handgrip strength among community-dwelling older adults in Asia.[17] Our findings indicated that low handgrip strength suggested by AWGS was independently associated with incident of disability after adjustment for potential covariates; thus, these modified cutoff values would be appropriate for diagnosing frailty in Asian populations.

Two components of frailty, exhaustion and weight loss, assessed using items in the Kihon Checklist, identified prevalence rates similar to those reported in a previous cohort study sampling more than 5000 community-dwelling older adults [2]. Although physical activity was assessed by two simple questions according to participation in sports or physical exercises in this study, we should recognize that many other kinds of activities such as domestic tasks and gardening could play important roles with regard to physical activity in older people. We thus need to consider these points, despite the fact that the total prevalence of frailty in our study was very similar to that reported in the Cardiovascular Health Study [2]. There seems to be general consensus on the essential components of physical frailty phenotype, and the present study also indicated these impacts on incident disability in the Japanese older samples. Frailty is due to an accumulation of deficits in areas including physical and cognitive impairment, and psychosocial risk factors [24]. However, the social and psychological dimensions of assessments for frailty have not been sufficiently verified [25]. Therefore, further studies on frailty that focus on not only physical but also cognitive and psychosocial domains will be needed.

Taken together, our findings indicate that combining questionnaires and performance-based assessments could be an effective method to identify older adults with frailty phenotype as a way to predict risk for disability incidence. Indeed, slowness and weakness assessed by performance-based methods were strongly associated with incident disability in our study. Thus, combining questionnaires with performance-based assessments would be more accurate in identifying older individuals

with higher risks for disability incidence. Furthermore, assessments of walking speed and handgrip strength are very simple and easy to implement in community settings, and are good predictors for health outcomes.[26] A notable point of our findings is that older adults with both physical frailty and lower cognitive function (MMSE scores <24) concurrently represented the highest percentage, more than 30%, of incident disability in stratified analyses. Previous studies have indicated the association between physical frailty and cognitive impairment among non-demented community-dwelling older adults [27-29] and showed that cognitive decline leads to higher risks of poor health [30]. Our findings also suggest that physical frailty and lower cognitive function have additive effects on disability incidence.

Strengths and limitations

A major strength of this study is the application of a monthly follow-up of disability using a mandatory social LTCI in Japan. Because most frailty models were developed in white populations, different cutoffs for frailty should be considered when examining different populations.[4] Although few prospective cohort studies regarding frailty phenotype and disability have been reported in Asia, this study included a large scale prospective sample of community-dwelling Japanese older adults and the application of a comprehensive measure of physical frailty including not only questionnaires but physical performance measurements.

Nevertheless, several limitations should be considered. In the multivariate analyses, although some diagnoses, such as hypertension, heart disease, diabetes mellitus, and osteoporosis, were included, several potential clinical confounders, such as hematologic diseases including anemia, oncological diseases, and eye diseases causing severe visual impairment were not included. In addition, these clinical conditions were based on self-report. We should therefore consider these issues carefully in interpreting the results. This study involved community-dwelling older people who were relatively well functioning and able to participate in the assessments at the community centre on their own. Therefore, this is likely to lead to an underestimation of the actual incidence of disability. In addition, our follow-up period was shorter than that in previous studies.[2 3 31 32] Another limitation is that the causes of the incident of disability were not determined. The major causes of incident disability certification by the LTCI include post-stroke, dementia, and severe stage of frailty. Moreover, anybody aged 65 and older (and anyone aged 40 to 64 with an aging-related disability) is eligible for LTCI.[33] Thus,

future studies examining causes of disability incidence and the longitudinal relationships between frailty and disability using longer follow-up data would be helpful for the development of preventive strategies for disability.

Conclusion

In summary, the results of this prospective cohort study show that physical frailty, even being pre-frail, has a strong impact on increased risk of disability. Among the components of physical frailty, slowness, weakness, and weight loss are more strongly associated with incident disability in community-dwelling Japanese older adults. These findings indicate that physical frailty assessments including simple performance measurement (slowness, weakness) and questionnaires (exhaustion, low activity, and weight loss) could be combined for a more effective prediction of disability incidence in the Japanese older population.

Contributors: HM and HS conceived and designed the study. HM performed the analyses and drafted the manuscript. HS, TD, KT, and TS revised the manuscript. TD and KT prepared the data. All authors participated in interpreting the results. All authors had full access to the data and are guarantors for the study.

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Figure legends

Figure 1 Flow chart of participant recruitment process

Figure 2 Incident disability rates during the two years after baseline assessment by frailty status and frailty components at baseline

Frailty phenotype containing three or more of the following was defined as frail, one or two as pre-frail, and none as robust: slowness, weakness, exhaustion, low activity, and weight loss

Figure 3 Kaplan-Meier estimates of cumulative incidence of disability according to frailty status

Frailty phenotype containing three or more of the following was defined as frail, one or two as pre-frail, and none as robust: slowness, weakness, exhaustion, low activity, and weight loss

Figure 4 Kaplan-Meier estimates of cumulative incidence of disability according to components of frailty phenotype

Cutoffs for definition of slowness (walking speed) were <1.0 m/s and weakness (handgrip strength) were <26 kg for men and <18 kg for women

Figure 5 Hazard ratios estimate relative risk of incidence of disability in subgroups defined by sex, age, cognitive function, and depressive symptoms in stratified analyses

Hazard ratios estimate relative risk of disability incidence in those classified as pre-frail or frail compared with those classified as robust (reference group) in different subgroup defined by sex, age (74/75 years), cognitive function (MMSE score 23/24), and depressive symptoms (GDS score 5/6)

Table 1 Baseline characteristics of participants by incidence of disability during the two years after baseline assessment

Characteristics	Overall (n = 4341)	Missing	Independent (n = 4173)	Incident disability (n = 168)	P value*
Age (years)	71.8±5.4	0	71.5±5.2	78.1±6.3	<0.001
Sex, women, n (%)	2241 (51.6)	0	2139 (51.3)	102 (60.7)	0.016
BMI (kg/m^2)	23.2±3.6	2	23.2±3.5	23.0±4.1	0.485
MMSE (score)	26.4±2.6	0	26.4±2.5	24.7±2.9	<0.001
GDS (score)	2.7±2.5	12	2.7±2.5	3.8±2.8	<0.001
Prescribed medications (number)	1.9±2.0	0	1.9±2.0	2.7±2.3	<0.001
Hypertension, n (%)	1930 (44.5)	0	1841 (44.1)	89 (53.0)	0.023
Heart disease, n (%)	689 (15.9)	0	652 (15.6)	37 (22.0)	0.026
Diabetes mellitus, n (%)	561 (12.9)	0	535 (12.8)	26 (15.5)	0.314
Osteoporosis, n (%)	457 (10.5)	2	426 (10.2)	31 (18.5)	0.001
Frail, n (%)	301 (6.9)	0	248 (5.9)	53 (31.5)	<0.001

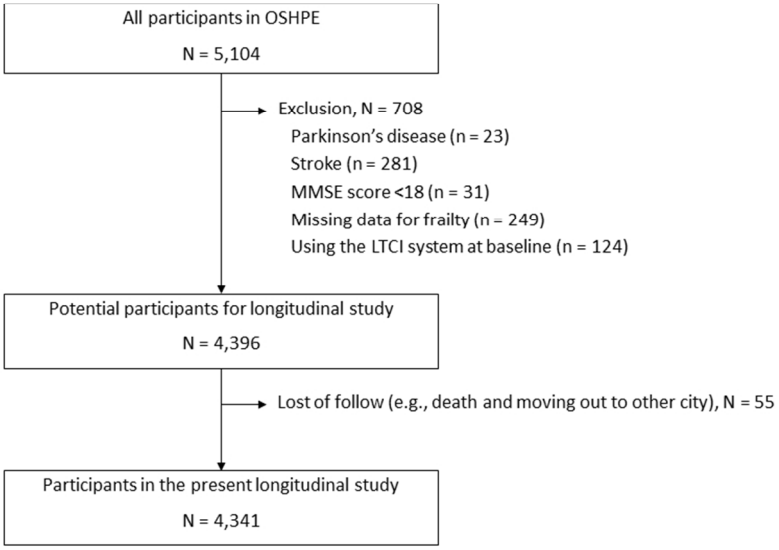
* χ^2 test for proportions and Student's t test for continuous measures.

Table 2 Hazard ratios for incident disability two years after baseline assessment according to frailty status and sub-items (n = 4341)

	Model 1			Model 2		
	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*
Frailty status						
Robust	1			1		
Pre-frail	**2.73**	**1.72–4.33**	**<0.001**	**2.52**	**1.56–4.07**	**<0.001**
Frail	**5.85**	**3.44–9.96**	**<0.001**	**4.65**	**2.63–8.22**	**<0.001**
Sub-items						
Slowness						
No	1			1		
Yes	**2.78**	**1.96–3.93**	**<0.001**	**2.32**	**1.62–3.33**	**<0.001**
Weakness						
No	1			1		
Yes	**2.09**	**1.49–2.94**	**<0.001**	**1.90**	**1.35–2.68**	**<0.001**
Exhaustion						
No	1			1		
Yes	**1.47**	**1.03–2.08**	**0.034**	1.15	0.79–1.69	0.462
Low activity						
No	1			1		
Yes	**1.44**	**1.05–1.97**	**0.024**	1.27	0.92–1.75	0.152
Weight loss						
No	1			1		
Yes	**1.87**	**1.31–2.66**	**0.001**	**1.61**	**1.13–2.31**	**0.009**

Adjusted for age and sex.

Adjusted for age, sex, body mass index, Mini-Mental State Examination, number of prescribed medications, hypertension, heart disease, diabetes mellitus, osteoporosis, and Geriatrics Depression Scale.



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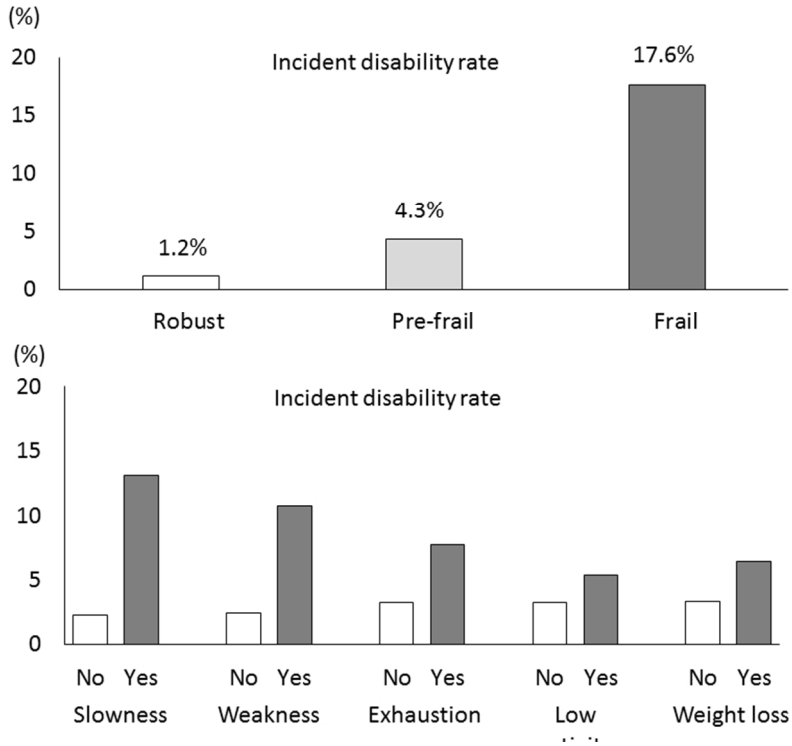

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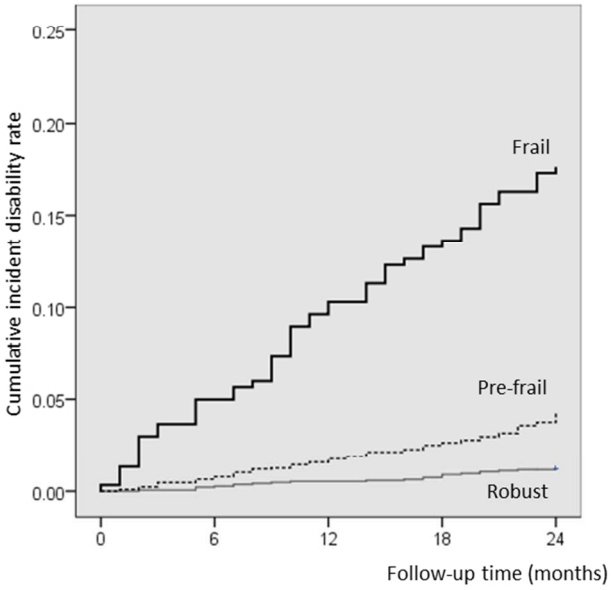

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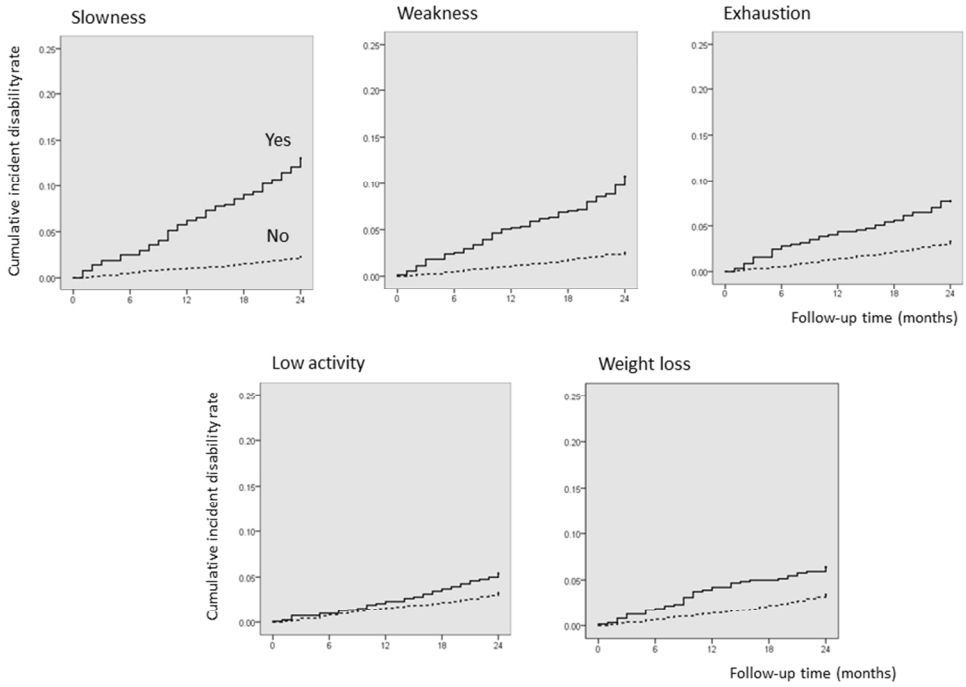

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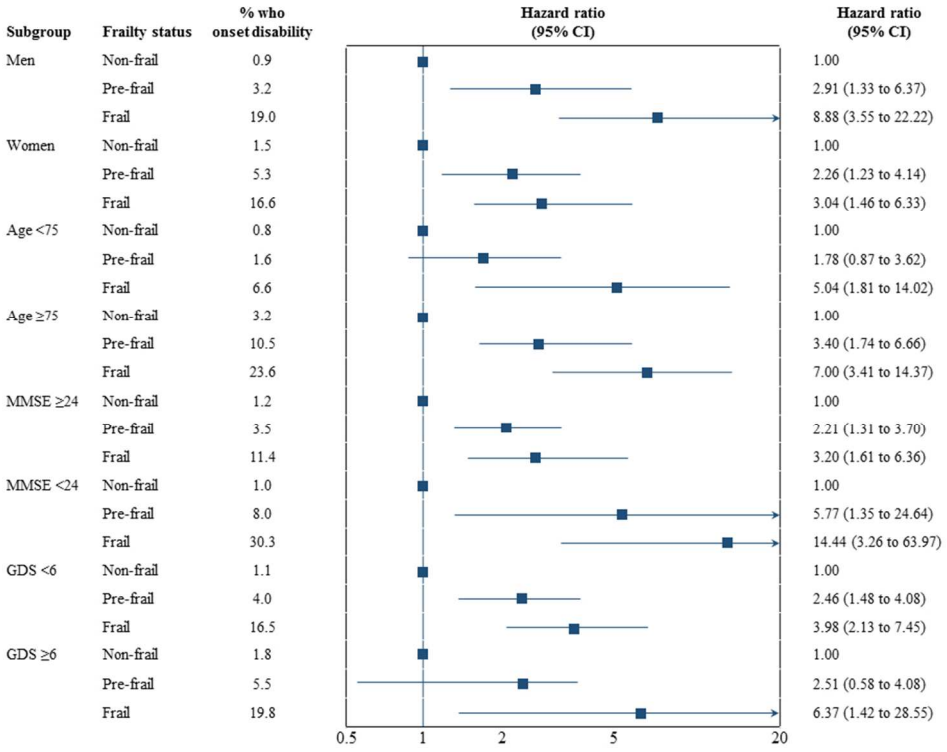

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The impact of physical frailty on disability in community-dwelling older adults: a prospective cohort study

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Abstract

Objective To examine the relationship between physical frailty and risk of disability, and identify the component(s) of frailty with the most impact on disability in community-dwelling older adults.

Design Prospective cohort study.

Setting A Japanese community.

Participants 4341 older adults aged ≥65 living in the community participated in a baseline assessment from 2011 to 2012, and were followed for two years.

Main outcome measures Care-needs certification in the national long-term care insurance (LTCI) system of Japan, type of physical frailty (robust, pre-frail, frail), and sub-items (slowness, weakness, exhaustion, low activity, weight loss), adjusted for several potential confounders such as demographic characteristics; analysed with Kaplan-Meier survival curves for incidence of disability by frailty phenotype.

Results During the two-year follow-up period, 168 participants (3.9 %) began using the LTCI system for incidence of disability. Participants classified as frail (hazard ratio 4.65, 95% confidence interval: 2.63 to 8.22) or pre-frail (2.52, 1.56 to 4.07) at the baseline assessment had an increased risk of disability incidence compared with robust participants. Analyses for sub-items of frailty showed that slowness (2.32, 1.62 to 3.33), weakness (1.90, 1.35 to 2.68), and weight loss (1.61, 1.13 to 2.31) were related to increased risk of disability incidence. In stratified analyses, participants classified as frail and who had lower cognitive function had the highest percentage (30.3%) of disability incidence during the two years after baseline assessment.

Conclusion Physical frailty, even being pre-frail, had a strong impact on the risk of future disability. Some components of frailty, such as slowness, weakness, and weight loss, are strongly associated with incident disability in community-dwelling older adults.

Strengths and limitations of this study

- This study included a large-scale prospective sample of community-dwelling Japanese older adults and the application of a comprehensive measure of physical frailty including not only questionnaires but physical performance measurements.
- Physical frailty, even being pre-frail, strongly predicts increased risk of disability in the Japanese older population.
- Modified cutoff values for slowness (walking speed <1.0 m/s) and weakness (handgrip strength <26 kg for men and <18 kg for women) are appropriate criteria for physical frailty assessments in the Japanese older population.
- Slowness, weakness, and weight loss are particularly associated with incident disability.
- This study did not determine the causes of the incident of disability.

Introduction

Japan has a rapidly aging population, and assessing frailty earlier in this population could help identify those more at risk for disability earlier to implement a more effective intervention.

Disability is an adverse outcome of frailty.[1] Frailty is recognized as a biological syndrome associated with multisystem declines in physiologic reserve and increased vulnerability to stressors, resulting in an increased risk of adverse outcomes such as disability, hospitalization, and death.[2-4] Although there is a general consensus on the definition of frailty phenotype, which classifies it into robust, pre-fail, and frail,[2] many different ways to assess frailty have been reported.[5]

The well-known concept of physical frailty model includes slowness, weakness, exhaustion, low activity, and weight loss.[4] Moreover, these components could have an additive effect on adverse outcomes such as disability.[2 3] We hypothesized that these components have differential effects on the incidence of disability. Thus, the purpose of this prospective cohort analysis was to evaluate the association between physical frailty phenotype and incidence of disability, and to identify the component(s) of frailty that has the most impact on disability among older adults (≥65 years) in Japan.

Methods

This prospective cohort study sampled 4341 community-dwelling elderly adults (≥65 years) enrolled in the Obu Study of Health Promotion for the Elderly (OSHPE). OSHPE participants were recruited from Obu, a residential suburb of Nagoya, Japan. Inclusion criteria were age of ≥65 years at examination in 2011 or 2012, being a resident of Obu, participation in follow up assessments, and no previous participation in other studies. Exclusion criteria were the need for support or care certified by the Japanese public long-term care insurance system (LTCI; care level ≥ 3/5), disability in basic activities of daily living (self-feeding, personal hygiene and grooming, walking, stairs, and bathing), and inability to undergo performance-based assessments (e.g., severe hypertension, balance impairment, or pain). We also excluded participants with a history of Parkinson's disease, stroke, depression, Alzheimer's disease, or those with Mini-Mental State Examination (MMSE) scores <18.[6, 7] Participants who died or who moved to another city during the two-year follow-up period were also excluded. Between August 2011 and February 2012, 5104 community-dwelling elderly people participated in a

baseline OSHPE assessment that included a face-to-face interview and measures of physical and cognitive function.

Participants were then followed monthly and monitored for inclusion into the LTCI system for the next two years. The mandatory social LTCI system was implemented in Japan on April 1, 2000.[8 9] To assess eligibility for these benefits, the LTCI system conducts assessments on incident disability. Informed consent was obtained from all participants prior to their inclusion in the study, and the Ethics Committee of the National Center for Gerontology and Geriatrics approved the study protocol (#490).

Baseline assessments

Licensed nurses recorded demographic data, including age, sex, number of prescribed medications, and medical history in face-to-face interviews. Participants were asked about their history regarding the following diagnoses: stroke, Parkinson's disease, hypertension, heart disease, diabetes mellitus, and osteoporosis. We measured participants' height and weight and calculated their body mass index (BMI). Global cognitive function was assessed using the MMSE,[7] with a cut-off point of 23/24.[10] Depressive symptoms were measured using the 15-item Geriatric Depression Scale (GDS).[11] The cut-off score of ≥6 has a sensitivity of 82% and a specificity of 75% with a structured clinical interview for depression.[12]

Operationalization of the physical frailty phenotype

We considered the physical frailty phenotype to be characterized by limitations in three or more of the following five conditions based on those used in Fried's original studies[2]: slowness, weakness, exhaustion, low activity, and weight loss. Participants who had none of these components were considered to be robust; those with one or two components were considered to be pre-frail.

A majority of previous prospective cohort studies seem to agree with the use of walking speeds for health predictors in aging. [13] Walking speed was measured in seconds using a stopwatch. Participants were asked to walk on a flat and straight surface at a comfortable walking speed. Two markers were used to indicate the start and end of a 2.4-m walk path, with a 2-m section to be traversed before passing the start marker, such that participants were walking at a comfortable pace by the time they reached the timed path. Participants were asked to continue walking for an additional 2 m past the

end of the path to ensure a consistent walking pace while on the timed path. Slowness was established according to a pre-determined cutoff (<1.0 m/s).[6] Together with slowness, low handgrip strength is considered an important indicator of health outcome such as fractures,[14] disability,[15] and death.[16] Weakness was defined using maximum grip strength. Grip strength was measured in kilograms using a Smedley-type handheld dynamometer (GRIP-D; Takei Ltd., Niigata, Japan). In addition, weakness was established according to a sex-specific cutoff (<26 kg for men and <18 kg for women).[17] Exhaustion was considered present if the participant responded "yes" to the following questions, taken from the Kihon-Checklist, a self-reported comprehensive health checklist developed by the Japanese Ministry of Health, Labour and Welfare[18]: "In the last two weeks, have you felt tired for no reason?" We evaluated the role of physical activity by asking the following questions about time spent engaged in sports and exercise: (1) "Do you engage in moderate levels of physical exercise or sports aimed at health?" and (2) "Do you engage in low levels of physical exercise aimed at health?" Participants who answered "no" to both of these questions were classified as low activity.[6] Weight loss was assessed by a response of "yes" to the question, "Have you lost 2 kg or more in the past six months?"[18]

Outcomes

Participants were followed monthly for incident certification of need of care according to the LTCI system during the two years after the baseline assessment. Japan implemented a mandatory social LTCI system on April 1, 2000.[8 9] Every Japanese citizen aged 65 and older is eligible for benefits (institutional and community-based services, but not cash) in cases of physical and/or mental disability. The computer-aided standardized needs-assessment system used by the mandatory social LTCI system categorizes people into seven levels of needs.[9] To determine an individual's level of nursing care need, a trained local government official visits that individual's home and administers a questionnaire on current physical and mental status (73 items in 7 dimensions; e.g., paralysis and limitation of joint movement, movement and balance, complex movement, conditions requiring special assistance, activities of daily living/instrumental activities of daily living, communication and cognition, behavioral problems) and use of medical procedures (12 items). The results of this questionnaire are then entered into the computer to calculate the applicant's standardized scores for the seven dimensions of physical and mental status and the estimated time for nine categories of care (grooming/bathing, eating, toileting, transferring, eating, assistance with instrumental activities of daily living, behavioral problems, rehabilitation, and

medical services), after which a care needs level based on the total estimated time taken for care is assigned. After this, the Nursing Care Needs Certification Board, which comprises physicians, nurses, and other experts in health and social services, reviews and confirms the care needs level [9]. We defined onset of disability as the point at which a participant was certified as needing care according to LTCI classification.

Statistical analyses

Student's t test and Pearson's chi-square test were used to test differences in baseline characteristics between participants with incidence of disability during the two years after baseline assessment and those without.

We calculated the cumulative incidence of disability during follow-up according to baseline frailty status (frail, pre-frail, and robust) and corresponding to each frailty component (slowness, weakness, exhaustion, low activity, and weight loss) with Kaplan-Meier curves. Intergroup differences were estimated by the log-rank test.

Cox proportional hazards regression models were used to analyse the associations between frailty phenotype and disability risk. The first model (Model 1) was adjusted for age and sex. We then used a multiple adjustment model adjusted for age, sex, BMI, MMSE, number of prescribed medications, hypertension, heart disease, diabetes mellitus, osteoporosis, and GDS (Model 2). These covariates were included as categorical (age, sex, and diagnoses) and continuous variables (BMI, MMSE, number of prescribed medications, and GDS). We estimated adjusted hazard ratios (HRs) for incidence of disability and their 95% confidence intervals (95% CIs).

Stratified analyses were performed to examine the relationship between frailty and disability risk in different subgroups defined by sex, age (74/75 years old), cognitive function (MMSE score 23/24), and depressive symptoms (GDS score 5/6).[12] Adjusted HRs for incidence of disability and their 95% confidence intervals were also estimated in the stratified analyses.

All analyses were conducted using IBM SPSS Statistics 19.0 (IBM Japan Tokyo). The level of statistical significance was set at $P < 0.05$.

Results

Of 5104 participants who completed a baseline assessment from Aug 2011 to Feb 2012,

763 had a history of Parkinson's disease (n = 23), stroke (n = 281), MMSE scores of <18 (n = 31), missing data for frailty phenotype (n = 249), were already using the LTCI system (n = 124) at baseline, or had missing follow-up data (n = 55), and were excluded from further analyses (Figure 1). The mean (SD) age of the 4341 participants included in the study was 71.8 (5.4); 2241 (51.6%) were women. The prevalence rates of each component for determining frailty phenotype including slowness, weakness, exhaustion, low activity, and weight loss were 14.8%, 16.4%, 13.2%, 28.6%, and 14.8%, respectively. The prevalence of frailty and pre-frailty were 6.9% and 49.6%, respectively. During the two-year follow-up period, 168 participants (3.9 %) had incident disability and were certified as needing care or support according to LTCI criteria. Figure 2 shows the incident disability rates of frailty status and components.

Table 1 presents participants' baseline characteristics by incidence of disability during follow-up. Participants who developed disability during these two years were older, more often women, had more prescribed medications, and higher prevalence of hypertension, heart disease, and osteoporosis compared with those who remained independent. Those with incident disability exhibited lower MMSE and higher GDS scores compared to those in the independent group at baseline. The prevalence of frailty in those who developed disability within these two years was 31.5% and approximately five-fold compare with in those who remained independent (5.9%).

Figure 3 and 4 shows the cumulative risk of disability based on frailty status and components. Survival analyses with the Kaplan-Meier log-rank test showed that the probability of incidence of disability was significantly higher in participants categorized as frail compared to those categorized as pre-frail or robust ($P < 0.001$). Furthermore, there was a significant difference in the incidence of disability between pre-frail and robust individuals ($P < 0.001$). Survival analysis performed for frailty components showed significant differences in the incident of disability, according to the presence of frailty sub-items at baseline ($P < 0.001$) (Figure 4).

Cox proportional hazards regression models were used to analyse associations between frail categories and disability risk (Table 2). In the first model (Model 1) that was adjusted for age and sex, participants classified as frail (HR 5.85, 95% CI 3.44 to 9.96) or pre-frail (HR 2.73, 95% CI 1.72 to 4.33) at the baseline assessment had an increased risk of incident disability compared with robust participants. All sub-items of frailty were significantly associated with increased risk of disability. The second model (Model

2) was adjusted for age, sex, BMI, MMSE, number of prescribed medications, hypertension, heart disease, diabetes mellitus, osteoporosis, and GDS. Both frail (HR 4.65, 95% CI 2.63 to 8.22) and pre-frail (HR 2.52, 95% CI 1.56 to 4.07) remained significantly associated with the incident of disability in Model 2. In Model 2, analyses for the sub-items of frailty showed that slowness (HR 2.32, 95% CI 1.62 to 3.33), weakness (HR 1.90, 95% CI 1.35 to 2.68), and weight loss (HR 1.61, 95% CI 1.13 to 2.31) were related to increased risk of incident disability. Exhaustion (HR 1.15, 95% CI 0.79 to 1.69) and low activity (HR 1.27, 95% CI 0.92 to 1.75) did not reach statistically significant levels in Model 2.

Figure 5 shows the results of the stratified analyses. Each status is defined by sex, age, cognitive function, and depressive symptoms. In all statuses, participants classified as frail had increased risk of incident disability across various strata defined by sex, age, cognitive function, and depressive symptoms, even after adjustment for age, sex, BMI, MMSE, number of prescribed medications, hypertension, heart disease, diabetes mellitus, osteoporosis, and GDS. Critically, participants with lower MMSE scores (<24 points) and who were classified as frail had the highest disability incidence rate (30/99, 30.3%) and those who were younger (<75 years) and classified as non-frail had the lowest disability incidence rate (12/1543, 0.8%) during the two years after baseline assessment.

Discussion

This study adds the following to the available evidence in the field. First, slowness and weakness as assessed by performance-based assessments are strongly associated with incident disability. Second, the modified cutoff values for slowness (walking speed <1.0 m/s) and weakness (handgrip strength <26 kg for men and <18 kg for women) appear to be appropriate criteria for physical frailty assessments in the Japanese older population. Finally, both physical frailty and lower cognitive function concurrently represent a higher risk of incident disability within two years.

Clinical and policy implications

Many different ways to assess physical frailty were reported in previous studies from around the world,[5] with the majority of cohort studies conducted in Western countries.[19] Thus, it might be inappropriate to extend the results of these studies to Asian countries. Indeed, the European Working Group on Sarcopenia in Older People [20] and Asian Working Group for Sarcopenia (AWGS) [17] have different diagnostic cutoffs for the

frailty phenotype. Thus, assessing frailty phenotype in an Asian population would develop a more comprehensive definition of the concept and lead to better-designed studies on its effect on the risk of disability among community-dwelling older adults in Asian countries. In this prospective cohort study of community-dwelling older adults, individuals with frail or pre-frail phenotype at baseline had an increased risk of disability incidence during the two years after baseline assessment. These results support findings from previous cohort studies with large samples.[2 3] Regarding the components of frailty, slowness, weakness, and weight loss were more strongly associated with incident disability than the other components. The associations between frailty and the incident of disability remained across various strata defined by sex, age, cognitive function, and depressive symptoms. Specifically, participants with both frail phenotype and lower cognitive function (MMSE scores <24) had the highest disability incidence rate (30.3%) during the two years after baseline assessment (Figure 3). Thus, physical frailty and lower cognitive function could have additive effects on the risk for disability incidence.

The results of this prospective study showed that participants with the slowness component (defined as having a walking speed slower than 1.0 m/s) had more than a two-fold higher risk of disability. However, there is no consensus regarding the cutoff point for walking speed as an indicator of slowness [21-23]. Although additional studies are necessary to determine the optimal cutoff values, slowness defined as a walking speed slower than 1.0 m/s could be useful as a component of frailty for predicting disability and preventing functional decline among community-dwelling older adults who are relatively well functioning. In this study, weakness was also determined using modified cutoff values of handgrip strength for Asian populations suggested in a consensus report from AWGS. The AWGS recommends using <26 kg for men and <18 kg for women as the cutoff values for handgrip strength among community-dwelling older adults in Asia.[17] Our findings indicated that low handgrip strength suggested by AWGS was independently associated with incident of disability after adjustment for potential covariates; thus, these modified cutoff values would be appropriate for diagnosing frailty in Asian populations.

Two components of frailty, exhaustion and weight loss, assessed using items in the Kihon Checklist, identified prevalence rates similar to those reported in a previous cohort study sampling more than 5000 community-dwelling older adults [2]. Although physical activity was assessed by two simple questions according to participation in

sports or physical exercises in this study, we should recognize that many other kinds of activities such as domestic tasks and gardening could play important roles with regard to physical activity in older people. We thus need to consider these points, despite the fact that the total prevalence of frailty in our study was very similar to that reported in the Cardiovascular Health Study [2]. There seems to be general consensus on the essential components of physical frailty phenotype, and the present study also indicated these impacts on incident disability in the Japanese older samples. Frailty is due to an accumulation of deficits in areas including physical and cognitive impairment, and psychosocial risk factors [24].

Although frailty has generally been regarded as an important concept and several multidimensional instruments have been developed to measure frailty in its totality, there is still considerable variety in how the concept is defined and measured. Specifically, there appear to be two major approaches to defining and measuring frailty: namely, regarding it as either a multifactorial construct (comprising social, psychological, and physical aspects) or a mainly physical one. Thus far, the social and psychological dimensions of frailty have not been sufficiently verified [25]. For instance, there is insufficient evidence regarding the operational definition of cognitive frailty and the validity of measurements of it [26]. A recent conference defined cognitive frailty as a clinical entity characterized by cognitive impairment related to physical causes with potential reversibility [27], making it a useful target for the secondary prevention of cognitive problems in older people [27]. Indeed, considering physical frailty and cognitive impairment as a single complex phenotype may be central to the prevention of dementia and its subtypes, although this should be confirmed with secondary preventive trials on cognitively frail older subjects [28]. In addition, according to the integral conceptual model of frailty, whereby frailty is affected by physical, psychological, and social factors, life-course determinants such as sociodemographic characteristics, lifestyle, life events, and environment-related factors can directly influence frailty as well as the onset of diseases that lead to frailty [29]. Therefore, further studies on frailty that focus on not only physical but also cognitive and psychosocial domains will be needed.

Another contentious point in defining and measuring frailty is whether to include performance-based measurements, especially for the identification of physical frailty [5]. Frailty questionnaires appear to be a highly feasible method for obtaining data from large samples and for assessing participants in a busy clinical practice setting; however,

slowness and weakness as assessed by performance-based methods were more strongly associated with incident disability in our study. Our findings indicate that combining questionnaires and performance-based assessments could be an effective method to identify older adults with frailty phenotype as a way to predict risk for disability incidence. Furthermore, assessments of walking speed and handgrip strength are very simple and easy to implement in community settings, and are good predictors for health outcomes.[30] A notable point of our findings is that older adults with both physical frailty and lower cognitive function (MMSE scores <24) concurrently represented the highest percentage, more than 30%, of incident disability in stratified analyses. Previous studies have indicated the association between physical frailty and cognitive impairment among non-demented community-dwelling older adults [31-33] and showed that cognitive decline leads to higher risks of poor health [34]. Our findings also suggest that physical frailty and lower cognitive function have additive effects on disability incidence.

Strengths and limitations

A major strength of this study is the application of a monthly follow-up of disability using a mandatory social LTCI in Japan. Because most frailty models were developed in white populations, different cutoffs for frailty should be considered when examining different populations.[4] Although few prospective cohort studies regarding frailty phenotype and disability have been reported in Asia, this study included a large scale prospective sample of community-dwelling Japanese older adults and the application of a comprehensive measure of physical frailty including not only questionnaires but physical performance measurements.

Nevertheless, several limitations should be considered. In the multivariate analyses, although some diagnoses, such as hypertension, heart disease, diabetes mellitus, and osteoporosis, were included, several potential clinical confounders, such as hematologic diseases including anemia, oncological diseases, and eye diseases causing severe visual impairment were not included. In addition, these clinical conditions were based on self-report. We should therefore consider these issues carefully in interpreting the results. This study involved community-dwelling older people who were relatively well functioning and able to participate in the assessments at the community centre on their own. Therefore, this is likely to lead to an underestimation of the actual incidence of disability. In addition, our follow-up period was shorter than that in previous studies.[2 3 35 36] Another limitation is that the causes of the incident of disability were not determined. The major causes of incident disability certification by the LTCI include

post-stroke, dementia, and severe stage of frailty. Moreover, anybody aged 65 and older (and anyone aged 40 to 64 with an aging-related disability) is eligible for LTCI.[37] Thus, future studies examining causes of disability incidence and the longitudinal relationships between frailty and disability using longer follow-up data would be helpful for the development of preventive strategies for disability.

Conclusion

In summary, the results of this prospective cohort study show that physical frailty, even being pre-frail, has a strong impact on increased risk of disability. Among the components of physical frailty, slowness, weakness, and weight loss are more strongly associated with incident disability in community-dwelling Japanese older adults. These findings indicate that physical frailty assessments including simple performance measurement (slowness, weakness) and questionnaires (exhaustion, low activity, and weight loss) could be combined for a more effective prediction of disability incidence in the Japanese older population.

Contributors: HM and HS conceived and designed the study. HM performed the analyses and drafted the manuscript. HS, TD, KT, and TS revised the manuscript. TD and KT prepared the data. All authors participated in interpreting the results. All authors had full access to the data and are guarantors for the study.

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Data sharing: No additional data available.

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Figure legends

Figure 1 Flow chart of participant recruitment process

Figure 2 Incident disability rates during the two years after baseline assessment by frailty status and frailty components at baseline

Frailty phenotype containing three or more of the following was defined as frail, one or two as pre-frail, and none as robust: slowness, weakness, exhaustion, low activity, and weight loss

Figure 3 Kaplan-Meier estimates of cumulative incidence of disability according to frailty status

Frailty phenotype containing three or more of the following was defined as frail, one or two as pre-frail, and none as robust: slowness, weakness, exhaustion, low activity, and weight loss

Figure 4 Kaplan-Meier estimates of cumulative incidence of disability according to components of frailty phenotype

Cutoffs for definition of slowness (walking speed) were <1.0 m/s and weakness (handgrip strength) were <26 kg for men and <18 kg for women

Figure 5 Hazard ratios estimate relative risk of incidence of disability in subgroups defined by sex, age, cognitive function, and depressive symptoms in stratified analyses

Hazard ratios estimate relative risk of disability incidence in those classified as pre-frail or frail compared with those classified as robust (reference group) in different subgroup defined by sex, age (74/75 years), cognitive function (MMSE score 23/24), and depressive symptoms (GDS score 5/6)

Table 1 Baseline characteristics of participants by incidence of disability during the two years after baseline assessment

Characteristics	Overall (n = 4341)	Missing	Independent (n = 4173)	Incident disability (n = 168)	P value*
Age (years)	71.8±5.4	0	71.5±5.2	78.1±6.3	<0.001
Sex, women, n (%)	2241 (51.6)	0	2139 (51.3)	102 (60.7)	0.016
BMI (kg/m^2)	23.2±3.6	2	23.2±3.5	23.0±4.1	0.485
MMSE (score)	26.4±2.6	0	26.4±2.5	24.7±2.9	<0.001
GDS (score)	2.7±2.5	12	2.7±2.5	3.8±2.8	<0.001
Prescribed medications (number)	1.9±2.0	0	1.9±2.0	2.7±2.3	<0.001
Hypertension, n (%)	1930 (44.5)	0	1841 (44.1)	89 (53.0)	0.023
Heart disease, n (%)	689 (15.9)	0	652 (15.6)	37 (22.0)	0.026
Diabetes mellitus, n (%)	561 (12.9)	0	535 (12.8)	26 (15.5)	0.314
Osteoporosis, n (%)	457 (10.5)	2	426 (10.2)	31 (18.5)	0.001
Frail, n (%)	301 (6.9)	0	248 (5.9)	53 (31.5)	<0.001

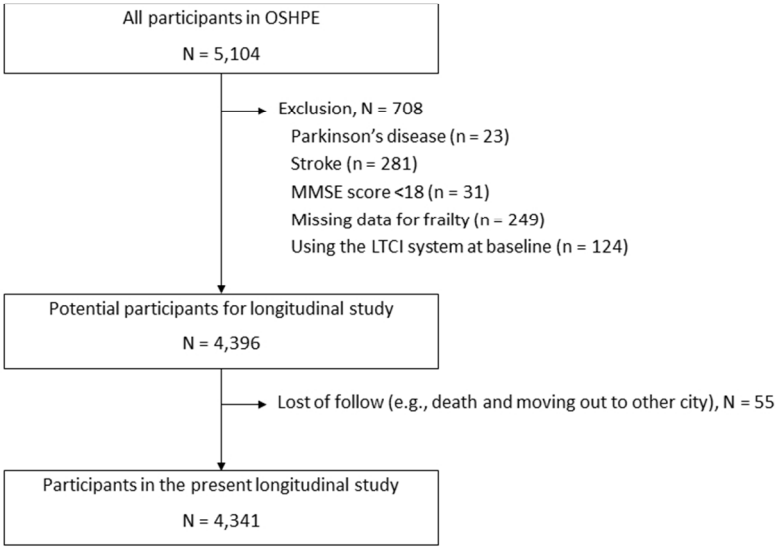
* χ^2 test for proportions and Student's t test for continuous measures.

Table 2 Hazard ratios for incident disability two years after baseline assessment according to frailty status and sub-items (n = 4341)

	Model 1			Model 2		
	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*
Frailty status						
Robust	1			1		
Pre-frail	**2.73**	**1.72–4.33**	**<0.001**	**2.52**	**1.56–4.07**	**<0.001**
Frail	**5.85**	**3.44–9.96**	**<0.001**	**4.65**	**2.63–8.22**	**<0.001**
Sub-items						
Slowness						
No	1			1		
Yes	**2.78**	**1.96–3.93**	**<0.001**	**2.32**	**1.62–3.33**	**<0.001**
Weakness						
No	1			1		
Yes	**2.09**	**1.49–2.94**	**<0.001**	**1.90**	**1.35–2.68**	**<0.001**
Exhaustion						
No	1			1		
Yes	**1.47**	**1.03–2.08**	**0.034**	1.15	0.79–1.69	0.462
Low activity						
No	1			1		
Yes	**1.44**	**1.05–1.97**	**0.024**	1.27	0.92–1.75	0.152
Weight loss						
No	1			1		
Yes	**1.87**	**1.31–2.66**	**0.001**	**1.61**	**1.13–2.31**	**0.009**

Adjusted for age and sex.

Adjusted for age, sex, body mass index, Mini-Mental State Examination, number of prescribed medications, hypertension, heart disease, diabetes mellitus, osteoporosis, and Geriatrics Depression Scale.



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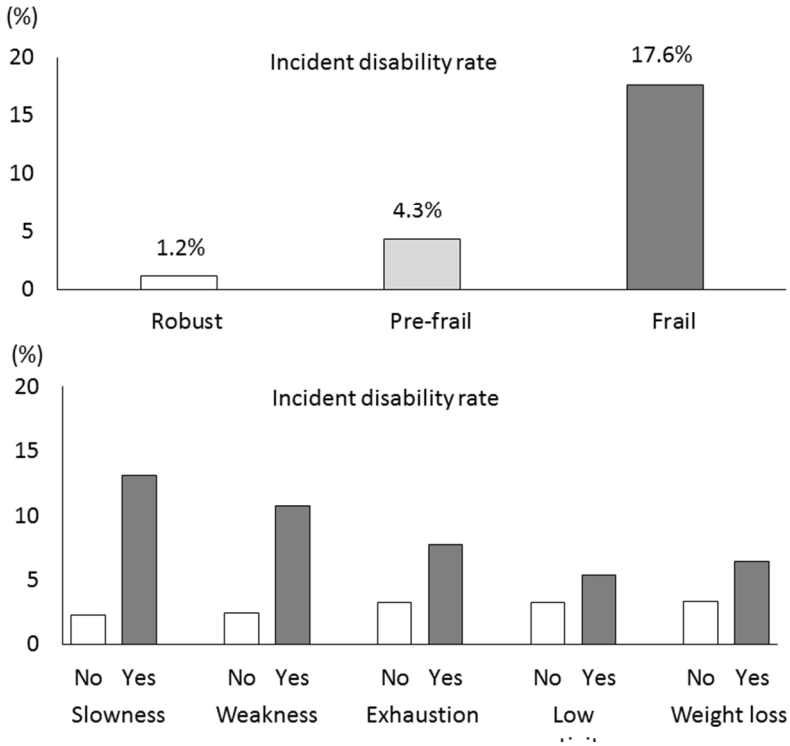

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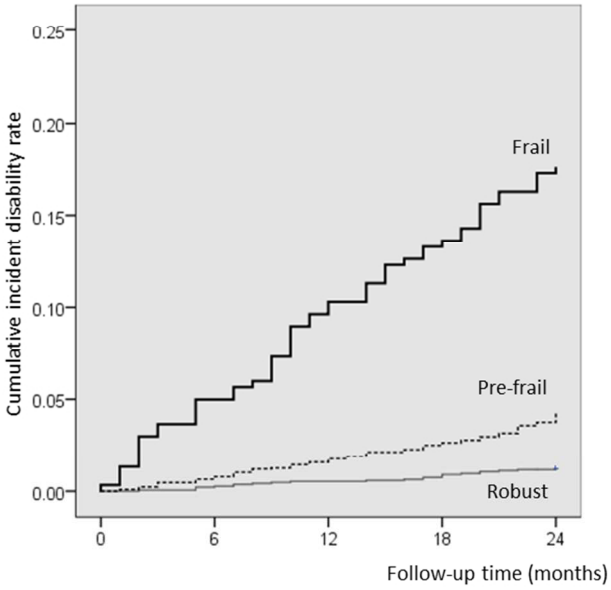

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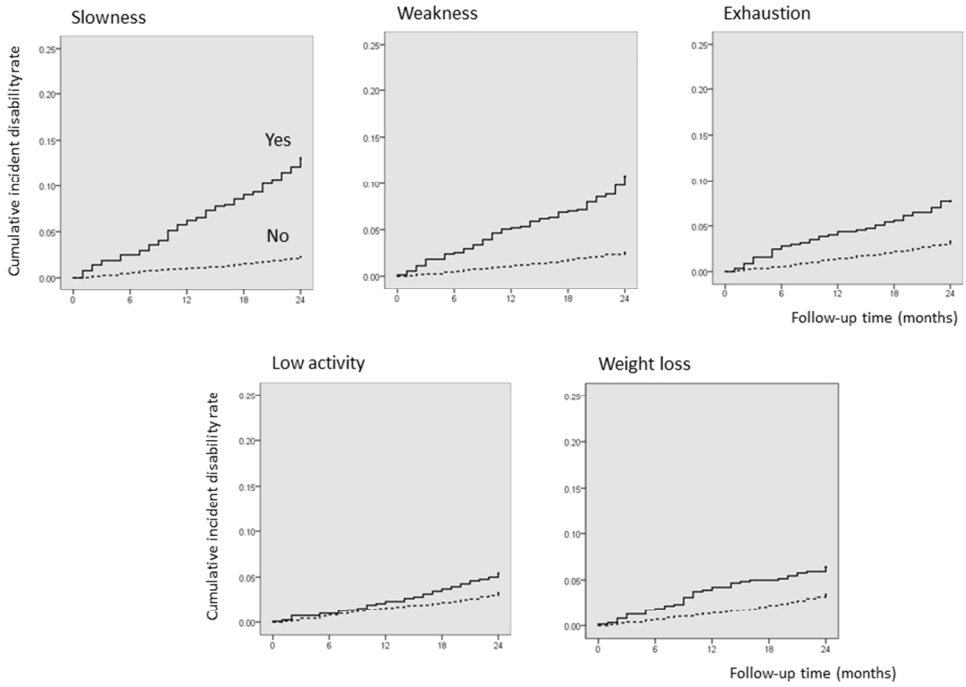

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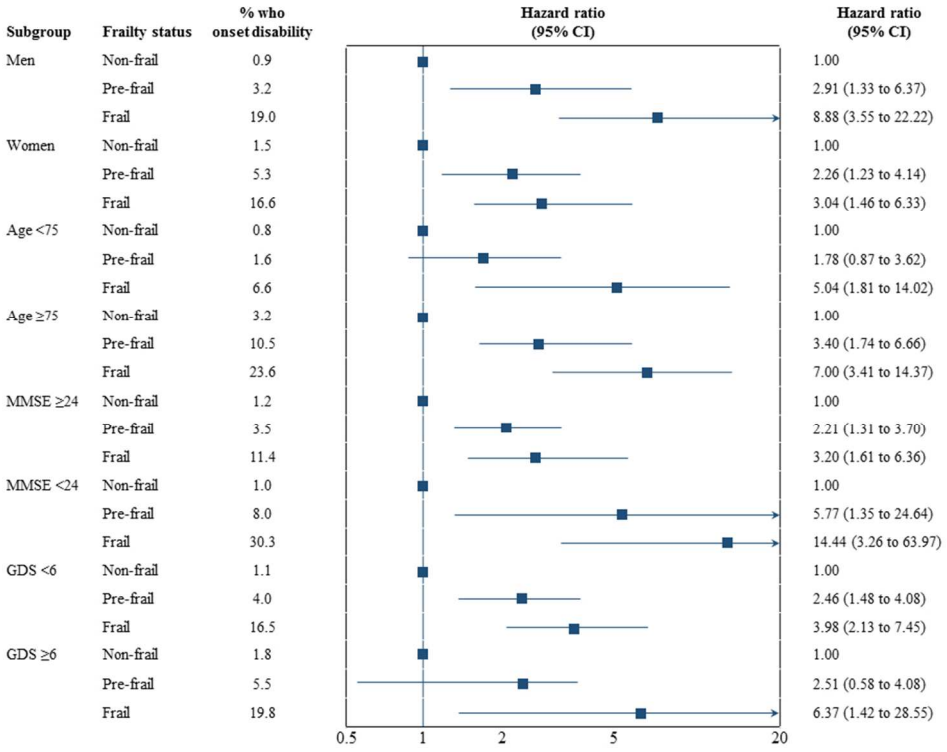

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	P1 & P2	**Title: The impact of physical frailty on disability in community-dwelling older adults: a prospective cohort study** **Design** Prospective cohort study.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	P2	Frailty, even being pre-frail, had a strong impact on the risk of future disability. Some components of frailty, such as slowness, weakness, and weight loss, are strongly associated with incident disability in community-dwelling older adults.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P3	Frailty is recognized as a biological syndrome associated with multisystem declines in physiologic reserve and increased vulnerability to stressors, resulting in an increased risk of adverse outcomes such as disability, hospitalization, and death.[2-4] Although there is a general consensus on the definition of frailty phenotype, which classifies it into robust, pre-fail, and frail,[2]

				many different ways to assess frailty have been reported.[5]
Objectives	3	State specific objectives, including any prespecified hypotheses	P3	We hypothesized that these components have differential effects on the incidence of disability. Thus, the purpose of this prospective cohort analysis was to evaluate the association between frailty phenotype and incidence of disability, and to identify the component(s) of frailty that has the most impact on disability among older adults (≥65 years) in Japan.
Methods				
Study design	4	Present key elements of study design early in the paper	P3	This prospective cohort study sampled 4341 community-dwelling elderly adults (≥65 years) enrolled in the Obu Study of Health Promotion for the Elderly (OSHPE).
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P3 & P4	OSHPE participants were recruited from Obu, a residential suburb of Nagoya, Japan. Inclusion criteria were age of ≥65 years at examination in 2011 or 2012, being a resident of Obu, participation in follow up assessments, and no previous participation in other studies.

				Between August 2011 and February 2012, 5104 community-dwelling elderly people participated in a baseline OSHPE assessment that included a face-to-face interview and measures of physical and cognitive function. Participants were then followed monthly and monitored for inclusion into the LTCI system for the next two years.
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	P3 & P4	Inclusion criteria were age of ≥65 years at examination in 2011 or 2012, being a resident of Obu, participation in follow up assessments, and no previous participation in other studies. Exclusion criteria were the need for support or care certified by the Japanese public long-term care insurance system (LTCI; care level ≥ 3/5), disability in basic activities of daily living (e.g., history of Parkinson's disease and stroke), and inability to undergo performance-based assessments (e.g., Mini-Mental State Examination (MMSE) score <18.[6, 7] Participants who died or who moved to another city during the two-year follow-up period were also excluded.

		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P4 & P5	**-Baseline assessments** **-Operationalization of the frailty phenotype** **-Outcomes**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P4 & P5	**-Baseline assessments** **-Operationalization of the frailty phenotype** **-Outcomes**
Bias	9	Describe any efforts to address potential sources of bias	P4	The mandatory social LTCI system was implemented in Japan on April 1, 2000.[8 9] Every Japanese person aged 65 and older is eligible for benefits (institutional and community-based services, but not cash) in cases of physical and/or mental disability. To assess eligibility for these benefits, the LTCI system conducts assessments on incident disability.
Study size	10	Explain how the study size was arrived at	NA	

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Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P4	We considered the frailty phenotype to be characterized by limitations in three or more of the following five conditions based on those used in Fried's original studies[2]: slowness, weakness, exhaustion, low activity, and weight loss. Participants who had none of these components were considered to be robust; those with one or two components were considered to be pre-frail.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	P5 & P6	**-Statistical analyses**
		(*b*) Describe any methods used to examine subgroups and interactions	P5 & P6	**-Statistical analyses**
		(*c*) Explain how missing data were addressed	P6	Of 5104 participants who completed a baseline assessment from Aug 2011 to Feb 2012, 763 had a history of Parkinson's disease (n = 23), stroke (n = 281), MMSE scores of <18 (n = 31), missing data for frailty phenotype (n = 294), were already using the LTCI system (n = 124) at baseline, or had missing follow-up data (n = 55), and were excluded from further analyses.
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	P6	Of 5104 participants who completed a baseline assessment from Aug 2011 to Feb 2012, 763 had a history of Parkinson's disease (n = 23), stroke (n = 281), MMSE

				scores of <18 (n = 31), missing data for frailty phenotype (n = 294), were already using the LTCI system (n = 124) at baseline, or had missing follow-up data (n = 55), and were excluded from further analyses.
		(*e*) Describe any sensitivity analyses	NA	
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P6	Of 5104 participants who completed a baseline assessment from Aug 2011 to Feb 2012, 763 had a history of Parkinson's disease (n = 23), stroke (n = 281), MMSE scores of <18 (n = 31), missing data for frailty phenotype (n = 294), were already using the LTCI system (n = 124) at baseline, or had missing follow-up data (n = 55), and were excluded from further analyses. The mean (SD) age of the 4341 participants included in the study was 71.8 (5.4); 2241 (51.6%) were women. The prevalence rates of each component for determining frailty phenotype including slowness, weakness, exhaustion, low activity, and weight loss were 14.8%, 16.4%, 13.2%, 28.6%, and 14.8%, respectively. During the two-year follow-up period, 168

				participants (3.9 %) had incident disability and were certified as needing care or support according to LTCI criteria.
		(b) Give reasons for non-participation at each stage	NA	
		(c) Consider use of a flow diagram	NA	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P6 & Table 1	Table 1 presents participants' baseline characteristics by incidence of disability during follow-up.
		(b) Indicate number of participants with missing data for each variable of interest	P6	Of 5104 participants who completed a baseline assessment from Aug 2011 to Feb 2012, 763 had a history of Parkinson's disease (n = 23), stroke (n = 281), MMSE scores of <18 (n = 31), missing data for frailty phenotype (n = 294), were already using the LTCI system (n = 124) at baseline, or had missing follow-up data (n = 55), and were excluded from further analyses.
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	P6	Table 1 presents participants' baseline characteristics by incidence of disability during follow-up. Participants who developed disability during these two years were older, more often women, had more prescribed medications, and higher prevalence of hypertension, heart disease, and

				osteoporosis compared with those who remained independent.
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	P6	During the two-year follow-up period, 168 participants (3.9 %) had incident disability and were certified as needing care or support according to LTCI criteria.
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA	
		Cross-sectional study—Report numbers of outcome events or summary measures	NA	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	P7	In the first model (Model 1) that was adjusted for age and sex, participants classified as frail (HR 5.85, 95% CI 3.44 to 9.96) or pre-frail (HR 2.73, 95% CI 1.72 to 4.33) at the baseline assessment had an increased risk of incident disability compared with robust participants. All sub-items of frailty were significantly associated with increased risk of disability. The second model (Model 2) was adjusted for age, sex, BMI, MMSE, number of prescribed medications, hypertension, heart disease, diabetes mellitus, osteoporosis, and GDS. Both frail (HR 4.65, 95% CI 2.63 to 8.22) and pre-frail (HR 2.52, 95% CI 1.56 to 4.07) remained significantly associated with the incident of disability in Model 2. In Model 2, analyses for

			the sub-items of frailty showed that slowness (HR 2.32, 95% CI 1.62 to 3.33), weakness (HR 1.90, 95% CI 1.35 to 2.68), and weight loss (HR 1.61, 95% CI 1.13 to 2.31) were related to increased risk of incident disability. Exhaustion (HR 1.15, 95% CI 0.79 to 1.69) and low activity (HR 1.27, 95% CI 0.92 to 1.75) did not reach statistically significant levels in Model 2.
	(*b*) Report category boundaries when continuous variables were categorized	Table 1	
	(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2	

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Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	P7 & Fig 3	Figure 3 shows the results of the stratified analyses. Each status is defined by sex, age, cognitive function, and depressive symptoms. In all statuses, participants classified as frail had increased risk of incident disability across various strata defined by sex, age, cognitive function, and depressive symptoms, even after adjustment for age, sex, BMI, MMSE, number of prescribed medications, hypertension, heart disease, diabetes mellitus, osteoporosis, and GDS. Critically, participants with lower MMSE scores (<24 points) and who were classified as frail had the highest disability incidence rate (30/99, 30.3%) and those who were younger (<75 years) and classified as non-frail had the lowest disability incidence rate (12/1543, 0.8%) during the two years after baseline assessment.
Discussion				
Key results	18	Summarise key results with reference to study objectives	P10	In summary, the results of this prospective cohort study show that frailty, even being pre-frail, has a strong impact on increased risk of disability. Among the components of frailty, slowness, weakness, and

				weight loss are more strongly associated with incident disability in community-dwelling Japanese older adults. These findings indicate that frailty assessments including simple performance measurement (slowness, weakness) and questionnaires (exhaustion, low activity, and weight loss) could be combined for a more effective prediction of disability incidence in the Japanese older population.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P9	**-Strengths and limitations**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P8 & P9	**-Discussion**
Generalisability	21	Discuss the generalisability (external validity) of the study results	P8	**-Clinical and policy implications**
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P10	**Funding:** This work was supported by the National Center for Geriatrics and Gerontology (Research Funding for Longevity Sciences) [grant number 22-16 and 26-33].

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.