

# SELF-REPORTED COGNITIVE FRAILTY PREDICTS ADVERSE HEALTH OUTCOMES FOR COMMUNITY-DWELLING OLDER ADULTS BASED ON AN ANALYSIS OF SEX AND AGE

M. OKURA<sup>1</sup>, M. OGITA<sup>2</sup>, H. ARAI<sup>3</sup>

1. Department of Human Health Sciences, Kyoto University Graduate School of Medicine, Kyoto, Japan; 2. Department of Clinical Nursing, Shiga University of Medical Science, Shiga, Japan; 3. National Center for Geriatrics and Gerontology, Aichi, Japan. Corresponding author: Mika Okura, Kyoto University, Kyoto, Kyoto Japan, okura.mika.2e@kyoto-u.ac.jp

**Abstract:** *Objectives:* The present study examined whether the combination of self-reported mobility decline (SR-MD) and cognitive decline (SR-CD) was associated with mortality and new long-term care insurance (LTCI) service certifications based on sex and age. *Design:* A prospective cohort study. *Setting and Participants:* We analyzed cohort data from a sample of older adult residents in Kami Town, Japan. The response rate was 94.3%, and we followed 5,094 older adults for 3 years. Full analyses were conducted on 5,076 participants. *Measures:* A total of four groups were determined through self-reported responses on the Kihon Checklist for SR-MD (a score of 3 or more on 5 items) and SR-CD (a score of 1 or more on 3 items): non-SR-cognitive frailty, non-SR-MD & SR-CD, SR-MD & non-SR-CD, and SR-cognitive frailty. *Results:* Main outcomes included mortality (n = 262) or new certifications for LTCI services (n = 708) during the 3-year period. Excluding overlapping, this included 845 older adults (16.6%). Among men, prevalence of non-SR-cognitive frailty, non-SR-MD & SR-CD, SR-MD & non-SR-CD, and SR-cognitive frailty (SR-MD & SR-CD) was 48.2%, 26.4%, 11.5%, and 13.8%, respectively. Respective rates for women were 45.7%, 15.5%, 23.1%, and 15.7%. Multivariate analyses revealed that for men, SR-MD & non-SR-CD significantly affected adverse health outcomes, leading to earlier negative outcomes relative to the non-SR-MD & SR-CD group. For women, non-SR-MD & SR-CD and SR-MD & non-SR-CD had similar slopes. *Conclusions:* The impact of SR-MD or SR-CD on adverse health outcomes differed as a function of age and sex. Thus, we need to consider preventive approaches according to these specific target group features.

**Key words:** Frailty, mobility disorders, cognitive impairment, long-term care insurance, mortality, older adults.

## Background

Living in harmony with physical, mental, and/or cognitive malfunction is challenging not only for older adults but also for local communities and Japan as a whole (1). Given that there is no widely accepted definition for mobility disorder, current estimates regarding the presence of mobility disorder range between 6% and 68% among community-dwelling older adults (2-5). Furthermore, mobility disorder is a consistent risk factor for falls, (6-10) disability (6, 7, 11), reduced health-related quality-of-life (12-14), hospitalization (including nursing home admission) (6,7), and mortality (6, 7, 11, 15-17). Mobility disorder is also associated with the following factors: decreased gait speed at one's usual pace (6, 7), decreased balance (6, 16), polypharmacy (6, 18), and having multimorbidity and severity of individual disease (6, 19, 20).

Similarly, the presence of cognitive impairment ranges between 12% and 40% among community-dwelling older adults (2, 3, 21-24). Cognitive impairment is also a consistent risk factor for dementia (3, 25), disability (7, 26), falls (27), reduced health-related quality-of-life (14), hospitalization (including nursing home admission) (3, 7), and mortality (6, 7, 21). However, it is also possible to reverse cognitive impairment to no-cognitive impairment (28, 29).

Furthermore, comorbid physical frailty (phenotype model) and cognitive impairment (clinical dementia rating = 0.5; excluded the presence of definite dementia and cognitive

impairment due to neurodegenerative disorders) was defined as "cognitive frailty" by the International Academy of Nutrition and Aging and the International Association of Gerontology and Geriatrics (30, 31). Arai and colleagues (31) described the following based on previous cross-sectional studies (21, 22, 32); the prevalence of cognitive frailty is estimated to be 1% to 5% by the original definition (physical frailty + clinical dementia rating = 0.5 or mild cognitive impairment) in community-dwelling older adults, although it differs depending on the operational definitions and the study subjects (e.g., the prevalence of cognitive frailty by Delrieu and colleagues (33) was 22%, because prefrailty was included in cognitive frailty). However, Shimada and colleagues (34) considered the criteria of cognitive frailty with low prevalence rates, which increased the risk of false-negative results, to be unsuitable for primary screening in the community; they then revised the prevalence of cognitive frailty to 9.8%. Therefore, the definition and prevalence of cognitive frailty may have not yet completely reached a consensus. One of the reasons is that the topic depends on the tool used for measurement by the researcher and the country (35).

Arai and colleagues (31) described the following based on the previous longitudinal studies (36-40): although the consensus of major outcomes of cognitive frailty is not determined, major outcomes that should be taken into account are incident dementia (36, 38-40), disability (37, 38), and mortality (37, 38). Other studies assessing cognitive frailty have revealed robust

associations between physical frailty and cognitive impairment with activities of daily living (ADLs) and instrumental activities of daily living (I-ADLs), poor quality of life (37) and hospitalization (2, 3) more strongly than results for each condition individually. From the above, it is clear that cognitive frailty is widely observed among older adults; it increases with age and is strongly predictive of adverse health outcomes.

In the present study, a self-completion questionnaire survey, which is one of the optimal methods for assessing public health activities, was used; they are less of a burden for the participants (less invasive, less time required, less movement to the measuring place) and to be easily answered for most older adults. It is one of the least expensive and most effective methods of collecting participant-based outcomes for health care researchers. The research question of the present study focused on whether a prognosis differs depending on self-reported-mobility decline (SR-MD) and self-reported-cognitive decline (SR-CD), individually or in combination. Additionally, we sought to clarify whether age and sex influenced the effects of SR-MD and/or SR-CD on mortality and new long-term care insurance (LTCI) service requirement certifications in Japan.

## Materials and methods

### *Study setting and participants*

Data were derived from a prospective cohort study. A baseline survey was conducted in April 2013 that comprised self-administered questionnaires mailed to 5,401 community-dwelling adults aged 65 years and older, excluding individuals who already had an LTCI service requirement certification ( $n = 1,283$ ), in Kami Town, Japan. The mailed response rate was 73.2% ( $n = 3,952$ ). Those who did not return the questionnaires by mail were then visited at home by nursing staff to retrieve the survey. The total number of mail and home visit respondents was 5,094 (94.3%). We further excluded individuals who did not answer more than half of the questionnaire items ( $n = 18$ ). Thus, a sample of 5,076 older adults was available for full analyses, and multiple imputation procedures were used to account for missing data.

This study was conducted in accordance with the guidelines proposed by the Declaration of Helsinki, and the study protocol was reviewed and approved by the Ethics Committee of our University Graduate School of Medicine (approved in August 2012; No. E1457).

### *Measures (questionnaire items)*

The Kihon Checklist (KCL) was used as a frailty screening index and comprised 25 items (yes/no) divided into seven categories: physical strength, nutrition, eating, socialization, memory, mood, and I-ADLs based on self-report. The cutoff for frailty was 8 points based on the total KCL score (sum of all 25 items) (41), and the following five domains were classified: SR-MD, SR-CD, SR-oral frailty, SR-isolation, and SR-depressive mood. The KCL was shown as one of the models

that covers multiple geriatric syndromes presently being used successfully by primary care professionals in the community (42). The KCL is reported to be an accurate self-reported diagnostic test among the instruments for screening community-dwelling older people for frailty (43). Additionally, the KCL was shown to be highly correlated with the 32-Frailty Index and the 68-Frailty Index as cumulative deficit models, a significant predictor of LTCI certification and/or mortality, and compatible with Frailty Index in the risk prediction (44). However, the KCL consists of smaller numbers of items than the standard 32-Frailty Index and the 68-Frailty Index. In addition, the KCL consists of all self-reported items and can be administered by non-health care professionals or by mail, email, or phone (44). Furthermore, it has been validated for predicting frailty and disability over a 2-year follow-up period (45).

The SR-MD index comprised five items (yes/no) such as “Do you normally climb stairs without using a handrail or wall for support?”, “Do you normally stand up from a chair without any aid?”, “Do you normally walk continuously for 15 minutes?”, “Have you experienced a fall in the past year?”, and “Do you have a fear of falling while walking?” An answer indicating a negative state was given 1 point; a score of 3 or more was indicative of SR-MD. The sensitivity and specificity of the SR-MD using the KCL for LTCI over the 12 months were 62.7% and 77.6%, respectively. Moreover, the negative answers to SR-MD using the KCL were found to be the best predictors for the certification for LTCI over the next 24 months (46).

The SR-CD index comprised three items (yes/no) as follows: “Do your family or your friends point out your memory loss?”, “Do you make a call by looking up phone numbers?”, and “Do you find yourself not knowing today’s date?”. As with SR-MD, an answer indicating a negative state was given 1 point, and any participant who gave an answer indicating a negative state to any of the three items was considered to have SR-CD. The sensitivity and specificity of the SR-CD using the KCL for LTCI over the 12 months were 71.4% and 61.6%, respectively (4). Additionally, the sensitivity and specificity of the SR-CD using the KCL for the incidence of dementia using the Dementia Scale (Degree of Independence in Daily Living for Elderly with Dementia), as per doctors’ reports during the 5.7-year study period, were 60.2% and 65.1%;<sup>47</sup> in another paper, those same measures were 71.4% and 61.6%, respectively (4).

From the above preceding studies, SR-MD and SR-CD using the KCL may be regarded as simple self-report screening tools that identify frailty and may avoid costs and unnecessary assessment.

Based on the total scores for SR-MD and SR-CD, participants were categorized into one of four groups as follows: non-SR-cognitive frailty, non-SR-MD & SR-CD, SR-MD & non-SR-CD, and SR-cognitive frailty.

SR-COGNITIVE FRAILTY AND ADVERSE HEALTH OUTCOMES

**Table 1**  
Baseline characteristics according to sex and age n(%)

Missing data	Overall (n=5,076)		65-74 yr. (n=2,274)		75-84 yr. (n=2,197)		≥85 yr. (n=605)		P value					
	Men n=2,113 (41.6%)	Women n=2,963 (58.4%)	Men n=974 (46.1%)	Women n=1,300 (43.9%)	Men n=922 (43.6%)	Women n=1,275 (43.0%)	Men n=217 (10.1%)	Women n=388 (13.1%)						
Self-reported-Mobility Decline (SR-MD)	189 (3.7)	1,685.8 (33.2)	536.2 (25.4)	1,149.6 (38.8)	<0.001	126.8 (13.0)	300.6 (23.1)	<0.001	289.4 (31.4)	602.8 (47.3)	<0.001	120.0 (60.5)	246.2 (63.5)	0.050
Do you normally climb stairs without using handrail or wall for support?; no	51 (1.0)	2,512.4 (49.5)	839.2 (39.7)	1,673.2 (56.5)	<0.001	246.4 (25.3)	501.8 (38.6)	<0.001	434.8 (47.2)	854.0 (67.0)	<0.001	158.0 (72.8)	317.4 (81.8)	0.009
Do you normally stand up from a chair without any aids?; no	32 (0.6)	1,455.2 (28.7)	453.4 (21.5)	1,001.8 (33.8)	<0.001	105.6 (10.8)	229.6 (17.7)	<0.001	250.8 (27.2)	538.0 (42.2)	<0.001	97.0 (44.7)	234.2 (60.4)	<0.001
Do you normally walk continuously for 15 minutes?; no	41 (0.8)	1,364.0 (26.9)	525.0 (24.8)	839.0 (28.3)	0.006	212.8 (21.8)	314.4 (24.2)	0.194	227.0 (24.6)	370.4 (29.1)	0.022	85.2 (39.3)	154.2 (39.7)	0.914
Have you experienced a fall in the past year?; yes	33 (0.7)	1,270.8 (25.0)	526.0 (24.9)	744.8 (25.1)	0.840	191.2 (19.6)	264.4 (20.3)	0.674	256.4 (27.8)	353.0 (27.7)	0.782	78.4 (36.1)	127.4 (32.8)	0.412
Do you have a fear of falling while walking?; yes	54 (1.1)	2,796.4 (55.1)	940.2 (44.5)	1,856.2 (62.6)	<0.001	301.4 (30.9)	637.8 (49.1)	<0.001	485.2 (52.6)	911.0 (71.5)	<0.001	153.6 (70.8)	307.4 (79.2)	0.019
Self-reported-Cognitive Decline (SR-CD)	85 (1.7)	1,773.8 (34.9)	850.4 (40.2)	923.4 (31.2)	<0.001	328.6 (33.7)	315.2 (24.2)	<0.001	405.6 (44.0)	436.8 (34.3)	<0.001	116.2 (47.5)	171.4 (44.2)	0.026
Do your family or your friends point out your memory loss? e.g. "You ask the same question over and over again."; yes	48 (0.9)	1,062.0 (20.9)	507.4 (24.0)	554.6 (18.7)	<0.001	187.6 (19.3)	176.2 (13.6)	<0.001	256.8 (27.9)	266.2 (20.9)	<0.001	63.0 (29.0)	112.2 (28.9)	0.956
Do you make a call by looking up phone numbers?; no	30 (0.6)	294.8 (5.9)	154.0 (7.3)	140.8 (4.8)	<0.001	43.4 (4.5)	26.0 (2.0)	0.001	73.2 (7.9)	54.6 (4.3)	<0.001	37.4 (17.2)	60.2 (15.5)	0.586
Do you find yourself not knowing today's date?; yes	16 (0.3)	1,033.8 (20.4)	491.4 (23.3)	542.4 (18.3)	<0.001	190.0 (19.5)	182.4 (14.0)	0.001	227.0 (24.6)	252.4 (19.8)	0.007	74.4 (34.3)	107.6 (27.7)	0.092
Four group of SR-MD and SR-CD	264 (5.2)													
non-SR-cognitive frailty		2,374.2 (46.8)	1,018.8 (48.2)	1,355.4 (45.7)	<0.001	579.2 (59.5)	784.8 (60.4)	<0.001	382.8 (41.5)	481.6 (37.8)	<0.001	56.8 (24.0)	89.0 (22.9)	0.010
non-SR-MD & SR-CD		1,016.0 (20.0)	558.0 (26.4)	458.0 (15.5)		268.0 (27.5)	214.6 (16.5)		249.8 (27.1)	190.6 (14.9)		40.2 (15.4)	52.8 (13.6)	
SR-MD & non-SR-CD		928.0 (18.3)	243.8 (11.5)	684.2 (23.1)		66.2 (6.8)	200.0 (15.4)		133.6 (14.5)	356.6 (28.0)		44.0 (28.4)	127.6 (32.9)	
SR-cognitive frailty		757.8 (14.9)	292.4 (13.8)	465.4 (15.7)		60.6 (6.2)	100.6 (7.7)		155.8 (16.9)	246.2 (19.3)		76.0 (32.2)	118.6 (30.6)	
Age (mean±SD)	0 (0.0)	75.9 ± 6.9	75.6 ± 6.8	76.1 ± 7.0	0.003	69.4 ± 2.8	69.7 ± 2.8	0.041	79.2 ± 2.8	79.1 ± 2.8	0.098	87.6 ± 2.7	88.0 ± 2.8	0.042
Living alone†	122 (2.4)	630.0 (12.7)	145.0 (6.9)	485.0 (16.3)	<0.001	64.0 (6.7)	157.0 (12.3)	<0.001	60.0 (6.7)	251.0 (20.2)	<0.001	21.0 (10.0)	77.0 (20.7)	0.001
SR-IADL decline	396 (7.8)	1,883.2 (37.1)	851.0 (40.3)	1,032.2 (34.8)	<0.001	355.0 (36.4)	312.0 (24.0)	<0.001	371.6 (40.3)	464.4 (36.4)	0.065	124.4 (57.3)	255.8 (65.9)	0.034
SR-Depressive mood	289 (5.7)	1,317.6 (26.0)	588.4 (27.8)	749.2 (25.3)	0.183	213.0 (21.9)	232.0 (17.8)	0.016	272.0 (29.5)	371.2 (29.1)	0.770	93.4 (38.4)	146.0 (37.6)	0.681
SR-Isolation	87 (1.7)	1,027.8 (20.2)	324.6 (15.4)	703.2 (23.7)	0.004	99.8 (10.2)	186.4 (14.3)	0.004	159.6 (17.3)	344.0 (27.0)	<0.001	65.2 (30.0)	172.8 (44.5)	0.001
SR-Oral frailty	114 (2.2)	999.8 (19.7)	460.6 (19.2)	539.2 (18.2)	0.002	178.4 (18.3)	157.4 (12.1)	<0.001	222.4 (24.1)	262.8 (20.6)	0.053	59.8 (27.6)	119.0 (30.7)	0.371
SR-Polypharmacy (>=5)†	945 (18.6)	929.0 (22.5)	439.0 (20.8)	490.0 (16.5)	<0.001	154.0 (21.0)	140.0 (14.0)	<0.001	219.0 (28.1)	251.0 (22.8)	0.009	66.0 (34.4)	99.0 (30.5)	0.356
SR-Serious disease (>=1)†‡	175 (3.4)	1,661.0 (33.9)	733.0 (32.7)	928.0 (32.6)	0.025	313.0 (32.8)	351.0 (27.9)	0.014	328.0 (36.8)	433.0 (35.6)	0.593	92.0 (44.0)	144.0 (38.4)	0.185
Self-rated health; bad†	24 (0.5)	1,037.0 (20.5)	576.0 (27.3)	731.0 (24.7)	0.037	237.0 (24.5)	269.0 (20.7)	0.035	265.0 (28.9)	342.0 (27.0)	0.340	74.0 (34.3)	120.0 (31.2)	0.437
Self-rated economic; bad†	140 (2.8)	2,960.0 (60.0)	1,319.0 (62.4)	1,641.0 (55.4)	<0.001	630.0 (65.8)	788.0 (62.7)	0.135	576.0 (63.7)	686.0 (55.8)	<0.001	113.0 (53.3)	167.0 (44.4)	0.038
SR-Familiar community activity (<2)§	522 (10.3)	1,511.8 (29.8)	649.6 (30.7)	862.2 (29.1)	0.270	228.8 (23.5)	285.0 (21.9)	0.402	306.6 (33.3)	359.6 (28.2)	0.017	114.2 (52.6)	217.6 (56.1)	0.395
Respose to survey; by home-visit (vs by mail)	0 (0.0)	1,138.0 (22.4)	476.0 (22.5)	662.0 (22.3)	0.876	221.0 (22.7)	282.0 (21.7)	0.571	209.0 (22.7)	285.0 (22.4)	0.861	46.0 (21.2)	95.0 (24.5)	0.359

Percent shows the proportion occupied by each person in each item in sex of each age group.† The results across 5 imputed data sets were combined by multiple imputation. However, household composition, SR-polypharmacy, SR-serious disease, self-rated health and self-rated economic were not used multiple imputation. ‡ SR-Serious disease implies more than one of the following: (1) heart attack or cerebrovascular disease within 6 months; (2) serious hypertension; (3) diabetes complications; (4) abnormal electrocardiogram within 1 year; (5) ordered to limit physical activities; (6) severe shortness of breath; or (7) hospitalization for 1 week or longer within 3 months; § SR-Familiar community activities at least once a week less than two of the following: (1) volunteer activity, (2) regional activity, (3) visit own friends (4) hobby or lesson, (5) work with some income, (6) farming or (7) daily shopping.

**Table 2**  
<Overall> SR-MD &SR-CI status predictions for new LTCI service requirement certifications or mortality during the 3-year follow-up period

	Total n	Case n (%)	Univariate HR (95% CI)	Multivariate† Model 1 HR (95% CI)	Multivariate‡ Model 2 HR (95% CI)	Survival time (day) mean ± SD	Log-rank
Overall	5 076,0	845.0 (16.6)				1,003.9 ± 3.3	
non-SR-MD	3 390,2	327.0 (9.6)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,049.0 ± 2.9	<0.001
SR-MD	1 685,8	518.0 (30.7)	3.69 ( 3.21 - 4.25 )	2.42 ( 2.09 - 2.81 )	1.83 ( 1.53 - 2.18 )	913.0 ± 7.8	
non-SR-CD	3 302,2	407.2 (12.3)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,031.3 ± 3.5	<0.001
SR-CD	1 773,8	437.8 (24.7)	2.17 ( 1.89 - 2.49 )	1.75 ( 1.52 - 2.00 )	1.50 ( 1.28 - 1.77 )	952.7 ± 6.9	
non-SR-cognitive frailty	2 374,2	177.8 (7.5)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,059.3 ± 3.0	<0.001
non-SR-MD & SR-CD	1 016,0	149.2 (14.7)	2.02 ( 1.62 - 2.51 )	1.75 ( 1.41 - 2.18 )	1.52 ( 1.18 - 1.96 )	1,024.8 ± 6.3	
SR-MD & non-SR-CD	928,0	229.4 (24.7)	3.66 ( 3.01 - 4.46 )	2.48 ( 2.03 - 3.03 )	1.84 ( 1.46 - 2.33 )	959.6 ± 9.2	
SR-cognitive frailty	757,8	288.6 (38.0)	6.36 ( 5.27 - 7.69 )	3.65 ( 3.00 - 4.45 )	2.65 ( 2.08 - 3.37 )	856.0 ±13.1	
65 - 74 years old	2 274,0	129.0 (5.7)				1,066.2 ± 2.9	
non-SR-MD	1 846,6	74.6 (4.0)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,075.8 ± 2.6	<0.001
SR-MD	427,4	54.4 (12.7)	3.31 ( 2.32 - 4.72 )	3.37 ( 2.34 - 4.83 )	1.99 ( 1.26 - 3.14 )	1,025.1 ±10.5	
non-SR-CD	1 630,2	76.8 (4.7)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,071.3 ± 3.1	0,002
SR-CD	643,8	52.2 (8.1)	1.75 ( 1.23 - 2.50 )	1.68 ( 1.18 - 2.40 )	1.37 ( 0.90 - 2.09 )	1,053.4 ± 6.7	
non-SR-cognitive frailty	1 364,0	45.8 (3.4)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,078.3 ± 2.9	<0.001
non-SR-MD & SR-CD	482,6	28.8 (6.0)	1.80 ( 1.12 - 2.87 )	1.68 ( 1.05 - 2.69 )	1.58 ( 0.91 - 2.76 )	1,068.6 ± 5.9	
SR-MD & non-SR-CD	266,2	31.0 (11.6)	3.61 ( 2.26 - 5.77 )	3.63 ( 2.26 - 5.83 )	2.32 ( 1.31 - 4.09 )	1,035.4 ±11.9	
SR-cognitive frailty	161,2	23.4 (14.5)	4.64 ( 2.79 - 7.70 )	4.49 ( 2.70 - 7.47 )	2.42 ( 1.28 - 4.59 )	1,008.0 ±20.0	
75 - 84 years old	2 197,0	441.0 (20.0)				987.0 ± 5.4	
non-SR-MD	1 304,8	174.4 (13.4)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,033.5 ± 5.2	<0.001
SR-MD	892,2	266.6 (29.9)	2.54 ( 2.10 - 3.09 )	2.47 ( 2.03 - 3.01 )	1.87 ( 1.48 - 2.36 )	919.0 ±10.5	
non-SR-CD	1 354,6	214.8 (15.9)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,015.0 ± 5.9	<0.001
SR-CD	842,4	226.2 (26.9)	1.82 ( 1.51 - 2.20 )	1.79 ( 1.48 - 2.16 )	1.56 ( 1.25 - 1.94 )	942.0 ±10.2	
non-SR-cognitive frailty	864,4	93.4 (10.8)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,047.3 ± 5.6	<0.001
non-SR-MD & SR-CD	440,4	81.0 (18.4)	1.76 ( 1.31 - 2.38 )	1.68 ( 1.25 - 2.28 )	1.41 ( 1.00 - 2.00 )	1,006.2 ±10.6	
SR-MD & non-SR-CD	490,2	121.4 (24.8)	2.53 ( 1.93 - 3.32 )	2.41 ( 1.83 - 3.17 )	1.73 ( 1.27 - 2.38 )	957.8 ±12.6	
SR-cognitive frailty	420,0	145.2 (34.6)	4.06 ( 3.12 - 5.28 )	3.79 ( 2.91 - 4.92 )	2.74 ( 1.99 - 3.76 )	871.6 ±17.4	
85 years old and more	605,0	275.0 (45.5)				830.2 ±14.3	
non-SR-MD	238,8	78.0 (32.7)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	927.0 ±18.4	<0.001
SR-MD	366,2	197.0 (53.8)	2.02 ( 1.56 - 2.63 )	1.93 ( 1.48 - 2.51 )	1.45 ( 1.04 - 2.02 )	767.0 ±19.8	
non-SR-CD	317,4	115.6 (36.4)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	895.3 ±17.8	<0.001
SR-CD	287,6	159.4 (55.4)	1.82 ( 1.43 - 2.31 )	1.74 ( 1.37 - 2.22 )	1.44 ( 1.03 - 2.01 )	758.2 ±22.3	
non-SR-cognitive frailty	145,8	38.6 (26.5)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	952.9 ±22.6	<0.001
non-SR-MD & SR-CD	93,0	39.4 (42.4)	1.72 ( 1.09 - 2.72 )	1.86 ( 1.18 - 2.94 )	1.72 ( 1.00 - 2.95 )	886.6 ±32.0	
SR-MD & non-SR-CD	171,6	77.0 (44.9)	1.92 ( 1.30 - 2.84 )	2.00 ( 1.35 - 2.96 )	1.63 ( 1.02 - 2.60 )	846.5 ±26.3	
SR-cognitive frailty	194,6	120.0 (61.7)	3.28 ( 2.27 - 4.73 )	3.00 ( 2.07 - 4.33 )	2.16 ( 1.35 - 3.47 )	696.5 ±28.3	

The results across 5 imputed data sets were combined by multiple imputation; Percent shows the percentage occupied by case in the total number of people in each item; †Model 1: Adjusted for sex and age; ‡ Model 2: Adjusted for sex, age, living alone, SR-IADL decline, SR-isolation, SR-oral frailty, SR-polypharmacy, SR-serious disease, responded method to survey and self-rated economic.

## SR-COGNITIVE FRAILTY AND ADVERSE HEALTH OUTCOMES

### Outcomes

The two main outcomes were mortality and new LTCI service requirement certifications (which indicates onset of a new disability during the 3 years following the baseline survey). Essentially, as a disability incident, we should use new LTCI service initiation instead of new LTCI service requirement certifications; however, in this research, we could not acquire these data. This information was collected from the local government office in Kami Town. When either of these outcomes appeared, we stopped the observation period for that respondent and calculated the survival time up to that point. However, if these outcomes overlapped during the observation period (i.e., death after a new LTCI service requirement certification or change in level to an LTCI service certification), we chose the outcome that emerged first (i.e., duplicates were not counted). We also accounted for individuals who moved away from Kami Town during the observation period.

### Additional variables considered in the analyses

Based on prior cognitive frailty research (including frailty), the following variables were identified as potential covariates in our main analyses: sex (5, 6, 15, 48, 49), age (6, 21, 48-50), living alone (15, 51), IADL decline (3, 6, 51) depressive mood (6, 51-53), isolation (6), oral frailty (54, 55), polypharmacy (6, 18, 51), multimorbidity and severity of individual disease (6, 19, 20), self-rated health (6, 49, 51, 56), self-rated economic status (6, 55), and familiar community activity (57, 58). SR-Serious disease was used as an alternative to multimorbidity and severity of individual disease. SR-Serious disease implies more than one of the following: 1) heart attack or cerebrovascular disease within 6 months; 2) serious hypertension; 3) diabetes complications; 4) abnormal electrocardiogram within 1 year; 5) ordered to limit physical activities; 6) severe shortness of breath; or 7) hospitalization for 1 week or longer within 3 months. Although the previous study did not show in which the responded method to survey and cognitive frailty were directly related, was added to one of the confounding factors. These items were recommended by the Ministry of Health, Labor and Welfare as an additional item to KCL from the previous year in this survey (59). For this reason, it is predicted that participants' characteristics such as age, degree of interest in health, and health condition would be different between postal-mail self-return and interview surveys conducted by home-visits (60-62). Unfortunately, however, marital status (6), household income (6,49), social network (51), education level (49, 50), sensory impairments (vision, hearing) (6), and malnutrition (63) could not be adjusted, as these were not included in the baseline survey.

### Statistical analyses

Participants' baseline characteristics were compared based on sex and age group. In subsequent analyses, survival time was defined as the time between enrollment (the date of the baseline survey) and either death, new LTCI service requirement

certification, or end of the follow-up period (March 31, 2016). Additionally (49). participants moved out during the follow-up period. We retained their data and treated their move away date as the survival end point.

Kaplan-Meier survival curves were calculated for the group newly determined to be at risk for mortality or in need of LTCI services. Analyses were stratified by the 4 SR-MD and SR-CD groups. Cox proportional hazards models were conducted to estimate hazard ratios (HRs), and 95% confidence intervals (95% CIs) regarding relationships between the four SR-MD and SR-CD groups and mortality or LTCI service requirement certification across univariate and multivariate analyses. Multivariate analyses were performed for each covariate, and adjustments for age and sex were made in Model 1. In Model 2 of the multivariate analysis, adjustments were made for age, sex, living alone, SR-IADL decline, SR-isolation, SR-oral decline, SR-polypharmacy, SR-serious disease, responded method to survey and self-rated economic status. The following three factors that were found to be weakly related to multiple confounding factors were excluded: SR-depressive mood, self-rated health, and SR-familiar community activity.

All analyses were conducted using SPSS software (SPSS version 24.0 and missing values; Inc, Tokyo). The significance threshold was set at  $P < 0.05$ .

## Results

Participants' mean age was 75.9 years, and 58.4% were women. For men, the prevalence of non-SR-cognitive frailty, non-SR-MD & SR-CD, SR-MD & non-SR-CD, and SR-cognitive frailty were 48.2%, 26.4%, 11.5%, and 13.8%, respectively. These rates were 45.7%, 15.5%, 23.1%, and 15.7%, respectively, among women. In addition, the rates of each condition/combination increased as a function of age for both men and women (Table 1).

During the 3 years of follow-up after the baseline survey of the participants, 708 participants obtained new LTCI service certifications and 262 died. Excluding overlapping, our main sample for assessing adverse health outcomes included 845 older adults (16.6%). Collapsing across gender, each of the 4 condition combinations influenced adverse health outcomes in the following order regarding relationship strength: non-SR-cognitive frailty, non-SR-MD & SR-CD, SR-MD & non-SR-CD, and SR-cognitive frailty; each HR (95%CI) adjusted age and sex was 1.0(ref.), 1.8(1.4-2.2), 2.5(2.0-3.0), and 3.7(3.0-4.5), respectively. Moreover, as age increased, the HRs for each group increased. Moreover, in all age groups, most trends of non-SR-cognitive frailty, non-SR-MD & SR-CD, SR-MD & non-SR-CD, and SR-cognitive frailty, in that order, nearly did not change, even after adjusting for many confounding factors as in model 2 (Table 2).

Similarly, in men each HR (95%CI) adjusted by age was 1.0(ref.), 1.3(0.9-1.7), 2.9(2.2-4.0), and 3.3(2.5-4.4), respectively. There was no significant difference in non-SR-

**Table 3**  
< Men > SR-MD & SR-CI status predictions for new LTCI service requirement certifications or mortality during the 3-year follow-up period

	Total	Case n (%)	Univariate HR (95% CI)	Multivariate† Model 1 HR (95% CI)	Multivariate‡ Model 2 HR (95% CI)	Survival time mean ± SD	Log-rank P value
< Men > Overall	2 113.0	369.0 (17.5)				1,003.8 ± 5.1	
non-SR-MD	1 576.8	164.6 (10.4)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,047.8 ± 4.1	<0.001
SR-MD	536.2	204.4 (38.1)	4.45 ( 3.62 - 5.48 )	2.82 ( 2.26 - 3.51 )	2.07 ( 1.59 - 2.69 )	874.0 ±14.6	
non-SR-CD	1 262.6	176.8 (14.0)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,024.2 ± 5.8	<0.001
SR-CD	850.4	192.2 (22.6)	1.70 ( 1.39 - 2.09 )	1.37 ( 1.12 - 1.69 )	1.26 ( 0.98 - 1.60 )	973.4 ± 9.1	
non-SR-cognitive frailty	1 018.8	93.8 (9.2)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,051.9 ± 5.0	<0.001
non-SR-MD & SR-CD	558.0	70.8 (12.7)	1.40 ( 1.03 - 1.91 )	1.28 ( 0.94 - 1.74 )	1.16 ( 0.81 - 1.67 )	1,040.4 ± 7.3	
SR-MD & non-SR-CD	243.8	83.0 (34.0)	4.36 ( 3.24 - 5.87 )	2.94 ( 2.17 - 3.97 )	1.97 ( 1.38 - 2.80 )	908.4 ±19.9	
SR-cognitive frailty	292.4	121.4 (41.5)	5.72 ( 4.36 - 7.51 )	3.27 ( 2.46 - 4.35 )	2.45 ( 1.73 - 3.47 )	845.1 ±20.8	
< Men > 65 - 74 years old	974.0	58.0 (6.0)				1,065.5 ± 4.4	
non-SR-MD	847.2	37.0 (4.4)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,076.0 ± 3.6	<0.001
SR-MD	126.8	21.0 (16.6)	4.13 ( 2.41 - 7.05 )	4.10 ( 2.40 - 7.01 )	2.58 ( 1.32 - 5.07 )	995.1 ±22.9	
non-SR-CD	645.4	33.0 (5.1)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,068.5 ± 5.1	0,127
SR-CD	328.6	25.0 (7.6)	1.51 ( 0.89 - 2.53 )	1.50 ( 0.89 - 2.51 )	1.11 ( 0.58 - 2.11 )	1,059.6 ± 8.4	
non-SR-cognitive frailty	579.2	24.0 (4.1)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,074.5 ± 4.7	<0.001
non-SR-MD & SR-CD	268.0	13.0 (4.9)	1.17 ( 0.60 - 2.27 )	1.16 ( 0.59 - 2.26 )	0.91 ( 0.39 - 2.10 )	1,079.4 ± 5.4	
SR-MD & non-SR-CD	66.2	9.0 (13.6)	3.49 ( 1.62 - 7.50 )	3.43 ( 1.59 - 7.38 )	2.10 ( 0.82 - 5.35 )	1,016.2 ±27.6	
SR-cognitive frailty	60.6	12.0 (19.8)	5.33 ( 2.66 -10.68 )	5.32 ( 2.66 -10.67 )	2.89 ( 1.18 - 7.11 )	972.0 ±37.1	
< Men > 75 - 84 years old	922.0	206.0 (22.3)				982.0 ± 8.3	
non-SR-MD	632.6	94.6 (15.0)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,029.8 ± 7.4	<0.001
SR-MD	289.4	111.4 (38.5)	3.06 ( 2.32 - 4.04 )	2.82 ( 2.13 - 3.74 )	2.17 ( 1.56 - 3.04 )	877.3 ±19.4	
non-SR-CD	516.4	99.0 (19.2)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,006.6 ± 9.6	0,006
SR-CD	405.6	107.0 (26.4)	1.46 ( 1.11 - 1.92 )	1.44 ( 1.10 - 1.90 )	1.26 ( 0.91 - 1.74 )	950.7 ±14.1	
non-SR-cognitive frailty	382.8	53.0 (13.8)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,037.8 ± 8.8	<0.001
non-SR-MD & SR-CD	249.8	41.6 (16.7)	1.23 ( 0.82 - 1.86 )	1.23 ( 0.82 - 1.85 )	1.04 ( 0.65 - 1.68 )	1,017.6 ±13.1	
SR-MD & non-SR-CD	133.6	46.0 (34.4)	2.86 ( 1.93 - 4.25 )	2.62 ( 1.76 - 3.90 )	1.79 ( 1.13 - 2.85 )	917.7 ±25.6	
SR-cognitive frailty	155.8	65.4 (42.0)	3.79 ( 2.63 - 5.47 )	3.51 ( 2.43 - 5.06 )	2.58 ( 1.65 - 4.03 )	842.9 ±28.3	
< Men > 85 years old and more	217.0	105.0 (48.4)				818.2 ±23.6	
non-SR-MD	97.0	33.0 (34.0)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	918.9 ±28.9	<0.001
SR-MD	120.0	72.0 (60.0)	2.28 ( 1.51 - 3.44 )	2.14 ( 1.41 - 3.24 )	1.35 ( 0.80 - 2.28 )	736.2 ±34.0	
non-SR-CD	100.8	44.8 (44.4)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	830.0 ±34.8	0,364
SR-CD	116.2	60.2 (51.8)	1.19 ( 0.81 - 1.76 )	1.18 ( 0.80 - 1.74 )	1.27 ( 0.78 - 2.07 )	808.1 ±32.2	
non-SR-cognitive frailty	56.8	16.8 (29.6)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	916.7 ±40.3	0,001
non-SR-MD & SR-CD	40.2	16.2 (40.3)	1.35 ( 0.68 - 2.69 )	1.43 ( 0.72 - 2.85 )	1.94 ( 0.87 - 4.33 )	922.1 ±41.2	
SR-MD & non-SR-CD	44.0	28.0 (63.6)	2.88 ( 1.57 - 5.28 )	2.83 ( 1.54 - 5.20 )	1.87 ( 0.89 - 3.90 )	716.8 ±56.0	
SR-cognitive frailty	76.0	44.0 (57.9)	2.47 ( 1.40 - 4.34 )	2.32 ( 1.31 - 4.09 )	1.75 ( 0.87 - 3.53 )	747.4 ±42.6	

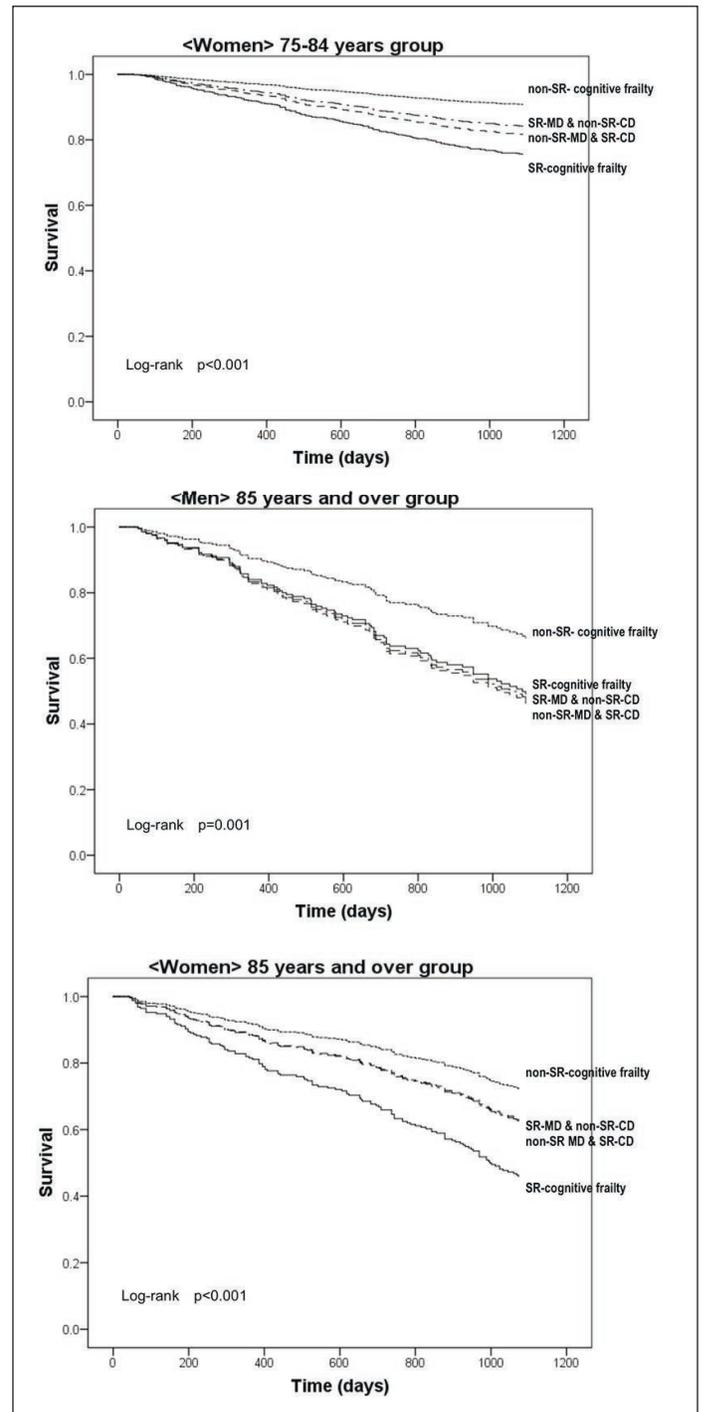
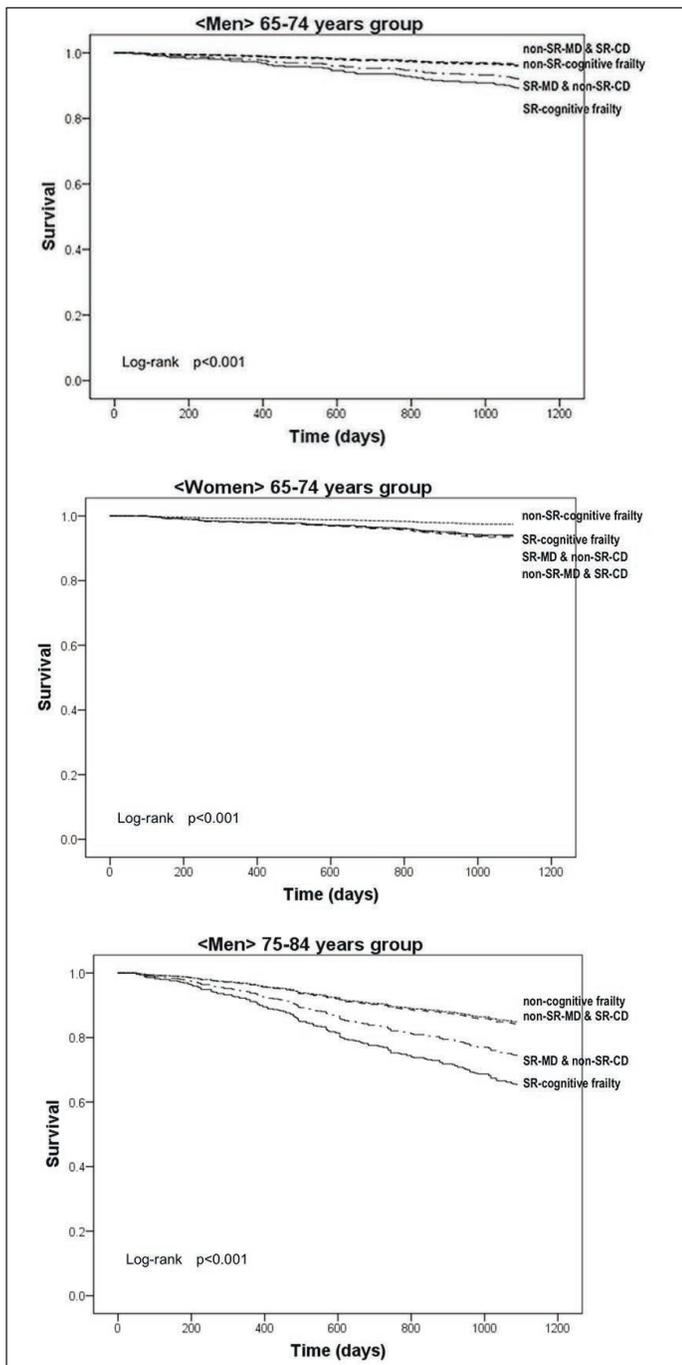
The results across 5 imputed data sets were combined by multiple imputation; Percent shows the percentage occupied by case in the total number of people in each item; † Model 1: Adjusted for age. ‡ Model 2: Adjusted for sex, age, living alone, SR-IADL decline, SR-isolation, SR-oral frailty, SR-polypharmacy, SR-serious disease, responded method to survey and self-rated economic.

SR-COGNITIVE FRAILTY AND ADVERSE HEALTH OUTCOMES

MD & SR-CD among the four groups in all age groups of men. Furthermore, particularly in men aged 85 years old and older, the SR-MD & non-SR-CD combination was more minimally influential on adverse health outcomes than SR-cognitive frailty (Table 3).

**Figure 1**

Kaplan-Meier survival curves according to the adverse health outcomes during three years, with the participants stratified into four groups based on self-reported-mobility decline and self-reported-cognitive decline by sex and age group



Adjusted for sex, age, living alone, self-reported-IADL decline, self-reported-isolation, self-reported-oral frailty, self-reported-polypharmacy, self-reported-serious disease, responded method to survey and self-rated economic.

Similarly, in women, each HR (95%CI) adjusted by age was 1.0(ref.), 2.5(1.8-3.4), 2.4(1.8-3.2), and 4.1(3.1-5.4), respectively. With the exception of the 65-74-year-old group among women, non-SR-MD & SR-CD more strongly affected adverse health outcomes than did SR-MD & non-SR-CD. In all age groups, women showed higher scores than did men (Table

**Table 4**

< Women > SR-MD & SR-CI status predictions for new LTCI service requirement certifications or mortality during the 3-year follow-up period

	Total n	Case n (%)	Univariate HR (95% CI)	Multivariate† Model 1 HR (95% CI)	Multivariate‡ Model 2 HR (95% CI)	Survival time (day) mean ± SD	Log-rank P value
< Women > Overall	2 963,0	476.0 (16.1)				1,003.9 ± 4.4	
non-SR-MD	1 813,4	162.4 (9.0)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,050.0 ± 4.0	<0.001
SR-MD	1 149,6	313.6 (27.3)	3.46 ( 2.86 - 4.19 )	2.17 ( 1.78 - 2.64 )	1.65 ( 1.30 - 2.09 )	931.2 ± 9.2	
non-SR-CD	2 039,6	230.4 (11.3)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,035.7 ± 4.3	<0.001
SR-CD	923,4	245.6 (26.6)	2.61 ( 2.18 - 3.13 )	2.09 ( 1.74 - 2.51 )	1.75 ( 1.40 - 2.17 )	933.7 ±10.3	
non-SR-cognitive frailty	1 355,4	84.0 (6.2)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,064.9 ± 3.7	<0.001
non-SR-MD & SR-CD	458,0	78.4 (17.1)	2.90 ( 2.13 - 3.95 )	2.48 ( 1.82 - 3.38 )	2.11 ( 1.47 - 3.04 )	1,005.9 ±10.8	
SR-MD & non-SR-CD	684,2	146.4 (21.4)	3.76 ( 2.88 - 4.93 )	2.40 ( 1.83 - 3.16 )	1.87 ( 1.36 - 2.58 )	977.8 ±10.1	
SR-cognitive frailty	465,4	167.2 (35.9)	7.19 ( 5.53 - 9.37 )	4.10 ( 3.12 - 5.38 )	2.92 ( 2.09 - 4.09 )	862.8 ±16.8	
< Women > 65 - 74 years old	1 300,0	71.0 (5.5)				1,066.8 ± 3.9	
non-SR-MD	999,4	37.6 (3.8)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,075.5 ± 3.8	<0.001
SR-MD	300,6	33.4 (11.1)	3.06 ( 1.90 - 4.93 )	2.88 ( 1.78 - 4.64 )	1.55 ( 0.84 - 2.84 )	1,037.7 ±11.4	
non-SR-CD	984,8	43.8 (4.4)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,073.1 ± 3.8	0,005
SR-CD	315,2	27.2 (8.6)	1.99 ( 1.23 - 3.23 )	1.82 ( 1.12 - 2.95 )	1.56 ( 0.89 - 2.75 )	1,047.0 ±10.5	
non-SR-cognitive frailty	784,8	21.8 (2.8)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,081.1 ± 3.6	<0.001
non-SR-MD & SR-CD	214,6	15.8 (7.4)	2.73 ( 1.41 - 5.26 )	2.49 ( 1.29 - 4.82 )	2.75 ( 1.29 - 5.85 )	1,055.2 ±11.3	
SR-MD & non-SR-CD	200,0	22.0 (11.0)	4.10 ( 2.21 - 7.62 )	3.87 ( 2.08 - 7.19 )	2.43 ( 1.16 - 5.10 )	1,041.7 ±12.9	
SR-cognitive frailty	100,6	11.4 (11.3)	4.28 ( 2.05 - 8.93 )	3.83 ( 1.83 - 8.00 )	1.87 ( 0.73 - 4.78 )	1,029.7 ±22.7	
< Women > 75 - 84 years old	1 275,0	235.0 (18.4)				990.7 ± 7.1	
non-SR-MD	672,2	79.8 (11.9)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,036.9 ± 7.3	<0.001
SR-MD	602,8	155.2 (25.7)	2.43 ( 1.85 - 3.19 )	2.19 ( 1.67 - 2.88 )	1.68 ( 1.22 - 2.32 )	939.0 ±12.4	
non-SR-CD	838,2	115.8 (13.8)	1.00 ( ref. )	1.00 ( ref. )	1.00 ( ref. )	1,020.2 ± 7.5	<0.001
SR-CD	436,8	119.2 (27.3)	2.15 ( 1.66 - 2.78 )	2.14 ( 1.65 - 2.78 )	1.86 ( 1.37 - 2.52 )	933.9 ±14.7	
non-SR-cognitive frailty	481,6	40.4 (8.4)	1.00 ( ref. )	1.00 ( ref. )	1.00 ( ref. )	1,054.9 ± 7.2	<0.001
non-SR-MD & SR-CD	190,6	39.4 (20.7)	2.58 ( 1.65 - 4.03 )	2.56 ( 1.64 - 4.01 )	2.13 ( 1.28 - 3.56 )	991.1 ±17.8	
SR-MD & non-SR-CD	356,6	75.4 (21.1)	2.75 ( 1.88 - 4.03 )	2.45 ( 1.67 - 3.59 )	1.82 ( 1.18 - 2.81 )	973.1 ±14.4	
SR-cognitive frailty	246,2	79.8 (32.4)	4.61 ( 3.14 - 6.75 )	4.21 ( 2.87 - 6.18 )	2.99 ( 1.91 - 4.70 )	889.7 ±21.8	
< Women > 85 years old and more	388,0	170.0 (43.8)				836.9 ±18.1	
non-SR-MD	141,8	45.0 (31.7)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	932.5 ±23.8	<0.001
SR-MD	246,2	125.0 (50.8)	1.92 ( 1.37 - 2.70 )	1.82 ( 1.29 - 2.56 )	1.44 ( 0.92 - 2.25 )	781.8 ±24.3	
non-SR-CD	216,6	70.8 (32.7)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	925.6 ±20.1	<0.001
SR-CD	171,4	99.2 (57.9)	2.29 ( 1.69 - 3.12 )	2.17 ( 1.59 - 2.95 )	1.52 ( 1.03 - 2.24 )	724.5 ±30.2	
non-SR-cognitive frailty	89,0	21.8 (24.5)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	976.1 ±26.1	<0.001
non-SR-MD & SR-CD	52,8	23.2 (43.9)	2.04 ( 1.11 - 3.72 )	2.27 ( 1.24 - 4.16 )	1.53 ( 0.73 - 3.23 )	859.5 ±46.1	
SR-MD & non-SR-CD	127,6	49.0 (38.4)	1.72 ( 1.03 - 2.86 )	1.80 ( 1.08 - 3.00 )	1.50 ( 0.80 - 2.79 )	890.5 ±28.5	
SR-cognitive frailty	118,6	76.0 (64.1)	3.94 ( 2.43 - 6.37 )	3.57 ( 2.20 - 5.79 )	2.42 ( 1.25 - 4.71 )	663.9 ±37.3	

The results across 5 imputed data sets were combined by multiple imputation; Percent shows the percentage occupied by case in the total number of people in each item; †Model 1: Adjusted for age; ‡ Model 2: Adjusted for sex, age, living alone, SR-IADL decline, SR-isolation, SR-oral frailty, SR-polypharmacy, SR-serious disease, responded method to survey and self-rated economic.

## SR-COGNITIVE FRAILTY AND ADVERSE HEALTH OUTCOMES

4).

Figure 1 shows the Kaplan-Meier survival curves according to mortality or new LTCI service requirement certification during the 3-year follow up, with participants stratified into four groups based on SR-MD and SR-CD. In the groups aged 65-74 years and 75-84 years among men, the survival curves of non-SR-cognitive frailty and non-SR-MD & SR-CD showed somewhat gentle downward slopes. However, in the age group of 85 years and older among men, the rate of deterioration of the three groups other than non-SR-cognitive frailty showed a very similar trend, was faster than non-SR-cognitive frailty at a remarkably gradient descent. In the group aged 65-74 years among women, the rate of deterioration of the three groups other than the non-SR-cognitive frailty group showed a very similar trend. However, in the group aged 75-84 years and 85 years and older among women, non-SR-MD & SR-CD and SR-MD & non-SR-CD had similar slopes.

### Discussion

First, we compared SR-MD and mobility disorder prevalence in our study with those reported in previous studies and tried to interpret the results. The prevalence of poor physical performance battery (SPPB<8; percentage of population) for men and women was 6-17% and 9-29%, respectively.<sup>5</sup> Similarly, difficulties in climbing a single flight (10 steps) of stairs without resting or walking 400m was experienced by 12%-40% men and 22%-68% women.<sup>5</sup> In that survey, the same measurement tool was used, and the research targeted almost the same male-female and age stratification ratio. However, it reported that each prevalence rate had a very broad range in five regions (5). On the other hand, regarding the prevalence of SR-MD determined through a self-reporting tool showed that difficulty in at least one of five mobility-related activities of daily living was experienced by 13%-30% men and 20%-45% women.<sup>5</sup> The prevalence of SR-MD using the KCL in another community was 24%, but gender-specific-data were not shown.<sup>4</sup> In other words, it is difficult to compare mobility disorder based on physical performance measurement in the present study, but it is almost the same as the proportion of SR-MD of at least the preceding study.

The self-reported questionnaire survey is not stronger than interview survey, but there is a tendency for participants to provide socially desirable response (64). In a survey on general frailty, women had a higher frailty score in self-reported measures, and men scored higher in test-based health measures (48). Likewise, women experienced faster accumulation of self-reported disability, but slower declines in the measured physical capacity than men (15). When it is socially desirable that older people are not mobility disorder, the characteristics of the self-reported survey are considered to be applicable to SR-MD for men. Moreover, our study found that women report more SR-MD than men do. This is because women were more likely to make the transition from having no disability to mild

disability, but less likely to make the transitions from having mild to no disability and from both mild and severe disability to death (15).

Second, we compared SR-CD and cognitive impairment prevalence found in our study with those reported in previous studies and tried to interpret the results. The prevalence of SR-CD using the KCL was 40%, remarkably higher than that in other surveys (5). However, the prevalence of cognitive impairment was measured with famous tools such as Mini-Mental State Examination (12-24%) (2, 3, 21). The sensitivity and specificity of SR-CD using the KCL were 60-71% and 62-65%, respectively (4, 47). These results could be considered to some extent as a public health screening tool (4, 46, 47). On the other hand, we must seriously consider the possibility of about 30%-40% differential misclassification, and this issue is one of the key limitations of the present study. In some of the neuropsychological tests, including tests of language ability to judge cognitive impairment, women display better results than do men. This result would support our analysis (37). However, age and education are more potent variables than are race and gender influencing performance on these language tests (50). In our analysis, education could not be controlled for. Furthermore, the prevalence of cognitive impairment among men was higher than that among women, contradicting the finding that about two-thirds of Alzheimer's disease patients are women (65). This sex difference may be due to the fact that women generally have a long lifespan. In addition, the effects of sex hormones in the early developmental stages may lead to inherent fragility of the female brain making them more vulnerable to developing Alzheimer's disease during older adulthood (65). The SR-CD in men was already over 30% in the 65-74 year-old group; perhaps this could be because that men are more likely to have anxiety about dementia than women; we need to explore background factors deeply in the future.

Third, it is harder for people to detect SR-CD than SR-MD in themselves, and family members may not be aware of the surrounding people; thus, the timing of LTCI system application may be delayed. Moreover, we cannot deny the possibility that sex difference in resistance to nursing care insurance application was affected.

The strength of our research is as follows. First, we have clarified whether the four groups that combined SR-cognitive frailty follow similar trajectories over time or whether the patterns of change differ by age and sex. It is important that, in addition to each impairment, we consider whether individuals can continue to perform physical and cognitive activities in order to examine their overlapping influence on adverse health outcomes (52, 66). In particular, it was suggested that for men, we should take a preventive approach to SR-MD, which strongly influences adverse health outcomes. In addition, it is necessary to explore the reasons for SR-CD, which had a high prevalence rate from the middle-aged individuals, and investigate effective approaches for the young adults.

The second strength of our research is that participants from the present study covered a wider sample, which included 94% of community dwelling-older adults within a Japanese rural municipality, and effective response rate was very high. Therefore, the present study might have more accurately observed frailty rates relative to previous work, which analyzed the data of participants who had high health consciousness, desirable health behavior, and maintained ADL.

The present study has the following limitations. First, the screening test used for assessing SR-cognitive frailty was self-reported questionnaire; no physical test, and no blood test. Second, we examined only one town in a rural area, then might be influenced by regional characteristics (67).

Future longitudinal research with a longer follow-up period could be analyzed with mortality or the stratified LTCI certification based on the grade of services.

### Conclusions and implications

The present results revealed a moderating role of age and sex on the impact of SR-MD and/or SR-CD on adverse health outcomes among community-dwelling older adults. Based on this information, we need to consider preventive approaches as a function of these various moderators in order to facilitate positive health and well-being in late life.

*Acknowledgements:* We are extremely grateful to all the study participants and staff from the Kami Town Hall, who assisted with this study.

*Conflicts of interest:* The authors declare no conflicts of interest.

*Funding sources:* This work received financial support from the Health, Labour and Welfare Sciences Research Grants (Comprehensive Research on Aging and Health, grant number H24-Chouju-Ippan-001; H28-Chouju-Policy research-28110101), Research Funding for Longevity Sciences from Japan Agency for Medical Research and Development (grant number 16dk0110019h0001), and Research Funding for Longevity Sciences from the National Center for Geriatrics and Gerontology (grant number 27-1; 30-6), Japan. No support was received from any corporate entity. The funding source played no role in the design or conduct of the research in terms of data collection, management, analysis, or interpretation, as well as preparation, review, or approval of this manuscript.

*Ethical standards:* This study was conducted in accordance with the guidelines proposed by the Declaration of Helsinki, and the study protocol was reviewed and approved by the Ethics Committee of the Kyoto University.

### References

1. Minister of Health, Labour and Welfare. A Basic-direction for Comprehensive Implementation of National Health Promotion. Ministerial Notification No. 430 of the Ministry of Health, Labour and Welfare. July 10, 2012. <http://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/0000047330.pdf> Accessed 8 June 2018.
2. Ensrud KE, Lui LY, Paudel ML, Schousboe JT, Kats AM, Cauley JA, McCulloch CE, Yaffe K, Cawthon PM, Hillier TA, Taylor BC; Study of Osteoporotic Fractures (SOF). Effects of mobility and cognition on risk of mortality in women in late life: a prospective study. *J Gerontol A Biol Sci Med Sci* 2016;71(6):759-765. doi: 10.1093/gerona/glv220.
3. Avila-Funes JA, Amieva H, Barberger-Gateau P, Le Goff M, Raoux N, Ritchie K, Carrière I, Tavernier B, Tzourio C, Gutiérrez-Robledo Dartigues JF. Cognitive impairment improves the predictive validity of the phenotype of frailty for adverse health outcomes: the three-city study. *J Am Geriatr Soc* 2009;57(3):453-461. doi: 10.1111/j.1532-5415.2008.02136.x.
4. Tomata Y, Hozawa A, Ohmori-Matsuda K, Nagai M, Sugawara Y, Nitta A, Kuriyama S, Tsuji I. Validation of the Kihon Checklist for predicting the risk of 1-year incident long-term care insurance certification: the Ohsaki Cohort 2006 Study. *Nihon Koshu Eisei Zasshi* 2011;58(1):3-13. (in Japanese)
5. Zunzunegua MV, Alvarado BE, Guerra R, Gómez JF, Ylli A, Guralnik JM; Imias Research Group. The mobility gap between older men and women: the embodiment of gender. *Arch Gerontol Geriatr* 2015;61(2):140-148. doi: 10.1016/j.archger.2015.06.005.
6. Lang PO, Michel JP, Zekry D. Frailty syndrome: a transitional state in a dynamic process. *Gerontology* 2009;55(5):539-549. doi: 10.1159/000211949.
7. Abellan van Kan G, Rolland Y, Andrieu S, Bauer J, Beauchet O, Bonnefoy M, Cesari M, Donini LM, Gillette Guyonnet S, Inzitari M, Nourhashemi F, Onder G, Ritz P, Salva A, Visser M, Vellas B. Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people: an International Academy on Nutrition and Aging (IANA) Task Force. *J Nutr Health Aging* 2009;13(10):881-889.
8. Reed-Jones RJ, Solis GR, Lawson KA, Loya AM, Cude-Islas D, Berger CS. Vision and falls: a multidisciplinary review of the contributions of visual impairment to falls among older adults. *Maturitas* 2013;75(1):22-28. doi: 10.1016/j.maturitas.2013.01.019.
9. Visschedijk J, Achterberg W, Van Balen R, Hertogh C. (2010) Fear of falling after hip fracture: a systematic review of measurement instruments, prevalence, interventions, and related factors. *J Am Geriatr Soc* 2010;58(9):1739-1748. doi: 10.1111/j.1532-5415.2010.03036.x.
10. Cheng MH, Chang SF. Frailty as a risk factor for falls among community dwelling people: evidence from a meta-analysis. *J Nurs Scholarsh* 2017;49(5):529-536. doi: 10.1111/jnu.12322.
11. Buchman AS, Wilson RS, Leurgans SE, Bennett DA, Barnes LL. Change in motor function and adverse health outcomes in older African-Americans. *Exp Gerontol*. 2015;70:71-7. doi: 10.1016/j.exger.2015.07.009.
12. Polis S, Fernandez R. Impact of physical and psychological factors on health-related quality of life in adult patients with liver cirrhosis: a systematic review protocol. *JBIR Database System Rev Implement Rep* 2015;13(1):39-51. doi: 10.11124/jbisr-2015-1987.
13. Pratali L, Mastorci F, Vitiello N, Sironi A, Gastaldelli A, Gemignani A. Motor activity in aging: an integrated approach for better quality of life. *Int Sch Res Notices* 2014;24:257248. doi: 10.1155/2014/257248.
14. Kojima G, Iliffe S, Jivraj S, Walters K. Association between frailty and quality of life among community-dwelling older people: a systematic review and meta-analysis. *J Epidemiol Community Health* 2016;70(7):716-721. doi: 10.1136/jech-2015-206717.
15. Botoseneanu A, Allore HG, Mendes de Leon CF, Gahbauer EA, Gill TM. Sex differences in concomitant trajectories of self-reported disability and measured physical capacity in older adults. *J Gerontol A Biol Sci Med Sci* 2016;71(8):1056-1062. doi: 10.1093/gerona/glw038.
16. Davis DH, Rockwood MR, Mitnitski AB, Rockwood K. Impairments in mobility and balance in relation to frailty. *Arch Gerontol Geriatr* 2011;53(1):79-83. doi: 10.1016/j.archger.2010.06.013.
17. Veronese N, Stubbs B, Fontana L, Trevisan C, Bolzetta F, Rui M, Sartori L, Musacchio E, Zambon S, Maggi S, Perissinotto E, Corti MC, Crepaldi G, Manzato E, Sergi G. A comparison of objective physical performance tests and future mortality in the elderly people. *J Gerontol A Biol Sci Med Sci* 2017;72(3):362-368. doi: 10.1093/gerona/glw139.
18. Hubbard RE, O'Mahony MS, Woodhouse KW. Medication prescribing in frail older people. *Eur J Clin Pharmacol* 2013;69(3):319-326. doi: 10.1007/s00228-012-1387-1392.
19. Villacampa-Fernández P, Navarro-Pardo E, Tarín JJ, Cano A. Frailty and multimorbidity: Two related yet different concepts. *Maturitas*. 2016;95:31-35. doi: 10.1016/j.maturitas.2016.10.008.
20. Boeckstaens P, Vaes B, Legrand D, Dalleur O, De Sutter A, Degryse JM. The relationship of multimorbidity with disability and frailty in the oldest patients: a cross-sectional analysis of three measures of multimorbidity in the BELFRAIL cohort. *Eur J Gen Pract*. 2015;21(1):39-44. doi: 10.3109/13814788.2014.914167.
21. Shimada H, Makizako H, Doi T, Yoshida D, Tsutsumimoto K, Anan Y, Uemura K, Ito T, Lee S, Park H, Suzuki T. Combined prevalence of frailty and mild cognitive impairment in a population of elderly Japanese people. *J Am Med Dir Assoc* 2013;14(7):518-524. doi: 10.1016/j.jaSR-MDa.2013.03.010.
22. Shimada H, Makizako H, Lee S, Doi T, Lee S, Tsutsumimoto K, Harada K, Hotta R, Bae S, Nakakubo S, Harada K, Suzuki T. Impact of cognitive frailty on daily Activities in older persons. *J Nutr Health Aging*. 2016;20(7):729-235. doi: 10.1007/s12603-016-0685-2.
23. Albala C, Lera L, Sanchez H, Angel B, Márquez C, Arroyo P, Fuentes P. Frequency of frailty and its association with cognitive status and survival in older Chileans. *Clin Interv Aging* 2017;12:995-1001. doi: 10.2147/CIA.S136906.
24. Su X, Shang L, Xu Q, Li N, Chen J, Zhang L, Zhang L, Hua Q. Prevalence and predictors of mild cognitive impairment in Xi'an: a community-based study among the elders. *PLoS One* 2014;9(1):e83217. doi: 10.1371/journal.pone.0083217.
25. Cooper C, Sommerlad A, Lyketsos CG, Livingston G. Modifiable predictors of dementia in mild cognitive impairment: a systematic review and meta-analysis. *Am J Psychiatry* 2015;172(4):323-334. doi: 10.1176/appi.ajp.2014.14070878.
26. Lindbergh CA, Dishman RK, Miller LS. Functional disability in mild cognitive impairment: a systematic review and meta-analysis. *Neuropsychol Rev* 2016;26(2):129-159. doi: 10.1007/s11065-016-9321-5.
27. Lipardo DS, Aseron AMC, Kwan MM, Tsang WW. Effect of exercise and cognitive training on falls and fall-related factors in older adults with mild cognitive impairment: a systematic review. *Arch Phys Med Rehabil* 2017;98(10):2079-2096. doi: 10.1016/j.apmr.2017.04.021.
28. Canevelli M, Grande G, Lacorte E, Quarchioni E, Cesari M, Mariani C, Bruno G, Vanacore N. Spontaneous reversion of mild cognitive impairment to normal cognition: A systematic review of literature and meta-analysis. *J Am Med Dir Assoc*

## SR-COGNITIVE FRAILTY AND ADVERSE HEALTH OUTCOMES

- 2016;17(10):943-938. doi: 10.1016/j.jaSR-MDa.2016.06.020.
29. Malek-Ahmadi M. Reversion from mild cognitive impairment to normal cognition: a meta-analysis. *Alzheimer Dis AssoSR-CDISord* 2016;30(4):324-330.
30. Kelaiditi E, Cesari M, Canevelli M, van Kan GA, Ousset PJ, Gillette-Guyonnet S, Ritz P, Duveau F, Soto ME, Provencher V, Nourhashemi F, Salvà A, Robert P, Andrieu S, Rolland Y, Touchon J, Fitten JL, Vellas B; IANA/IAGG. Cognitive frailty: rational and definition from an (I.A.N.A./I.A.G.G.) international consensus group. *J Nutr Health Aging*. 2013;17(9):726-734. doi: 10.1007/s12603-013-0367-2.
31. Arai H, Satake S, Kozaki K. Cognitive frailty in geriatrics. *Clin Geriatr Med*. 2018;34(4):667-675. doi: 10.1016/j.cger.2018.06.011.
32. Roppolo M, Mulasso A, Rabaglietti E. Cognitive frailty in Italian community-dwelling older adults: Prevalence rate and its association with disability. *J Nutr Health Aging*. 2017;21(6):631-636. doi: 10.1007/s12603-016-0828-5.
33. Delrieu J, Andrieu S, Pahor M, Cantet C, Cesari M, Ousset PJ, Voisin T, Fougère B, Gillette S, Carrie I, Vellas B. Neuropsychological profile of "cognitive frailty" subjects in MAPT Study. *J Prev Alzheimers Dis*. 2016;3(3):151-159.
34. Shimada H, Doi T, Lee S, Makizako H, Chen LK, Arai H. Cognitive frailty predicts incident dementia among community-dwelling older people. *J Clin Med*. 2018;7(9). pii: E250. doi: 10.3390/jcm7090250.
35. Fougère B, Delrieu J, Del Campo N, Soriano G, Sourdet S, Vellas B. Cognitive frailty: Mechanisms, tools to measure, prevention and controversy. *Clin Geriatr Med*. 2017;33(3):339-355. doi: 10.1016/j.cger.2017.03.001.
36. Montero-Odasso MM, Barnes M, Speechley M, Muir Hunter SW, Doherty TJ, Duque G, Gopaul K, Sposato LA, Casas-Herrero A, Borrie MJ, Camicioli R, Wells JL. Disentangling cognitive-frailty: Results from the gait and brain study. *J Gerontol A Biol Sci Med Sci*. 2016;71(11):1476-1482.
37. Feng L, Zin Nyunt MS, Gao Q, Feng L, Yap KB, Ng TP. Cognitive frailty and adverse health outcomes: Findings from the Singapore Longitudinal Ageing Studies (SLAS). *J Am Med Dir Assoc*. 2017;18(3):252-258. doi: 10.1016/j.jamda.2016.09.015.
38. Solfrizzi V, Scafato E, Lozupone M, Seripa D, Giannini M, Sardone R, Bonfiglio C, Abbrescia DI, Galluzzo L, Gandin C, Baldereschi M, Di Carlo A, Inzitari D, Daniele A, Sabbà C, Logroscino G, Panza F, Italian Longitudinal Study on Aging Working Group. Additive role of a potentially reversible cognitive frailty model and inflammatory state on the risk of disability: The Italian Longitudinal Study on Aging. *Am J Geriatr Psychiatry*. 2017;25(11):1236-1248. doi: 10.1016/j.jagp.2017.05.018.
39. Solfrizzi V, Scafato E, Seripa D, Lozupone M, Imbimbo BP, D'Amato A, Tortelli R, Schilardi A, Galluzzo L, Gandin C, Baldereschi M, Di Carlo A, Inzitari D, Daniele A, Sabbà C, Logroscino G, Panza F, Italian Longitudinal Study on Aging Working Group. Reversible cognitive frailty, dementia, and all-cause mortality. The Italian Longitudinal Study on Aging. *J Am Med Dir Assoc*. 2017;18(1):89.e1-89.e8. doi: 10.1016/j.jamda.2016.10.012.
40. Shimada H, Makizako H, Tsutsumimoto K, Doi T, Lee S, Suzuki T. Cognitive frailty and incidence of dementia in older persons. *J Prev Alzheimers Dis*. 2018;5(1):42-48. doi: 10.14283/jpad.2017.29.
41. Satake S, Senda K, Hong YJ, Miura H, Endo H, Sakurai T, Kondo I, Toba K. (2016) Validity of the Kihon Checklist for assessing frailty status. *Geriatr Gerontol Int* 2016;16(6):709-715. doi: 10.1111/ggi.12543.
42. Morley JE, Arai H, Cao L, Dong B, Merchant RA, Vellas B, Visvanathan R, Woo J. Integrated care: enhancing the role of the primary health care professional in preventing functional decline: a systematic review. *J Am Med Dir Assoc* 2017;18(6):489-494. doi: 10.1016/j.jaSR-MDa.2017.03.015.
43. Ambagtsheer RC, Thompson MQ, Archibald MM, Casey MG, Schultz TJ. Diagnostic test accuracy of self-reported frailty screening instruments in identifying community-dwelling older people at risk of frailty and pre-frailty: a systematic review protocol. *JBIS Database System Rev Implement Rep* 2017;15(10):2464-2468. doi: 10.11124/JBISRR-2017-003363.
44. Kojima G, Taniguchi Y, Kitamura A, Shinkai S. Are the Kihon Checklist and the Kaigo-Yobo Checklist compatible with the frailty index? *J Am Med Dir Assoc* 2018;19(9):797-800.e2. doi: 10.1016/j.jaSR-MDa.2018.05.012.
45. Fukutomi E, Okumiya K, Wada T, Sakamoto R, et al. Importance of cognitive assessment as part of the "Kihon Checklist" developed by the Japanese Ministry of Health, Labor and Welfare for prediction of frailty at a 2-year follow up. *Geriatr Gerontol Int* 2013;13(3):654-662. doi: 10.1111/j.1447-0594.2012.00959.x.
46. Fukutomi E, Okumiya K, Wada T, Sakamoto R, Ishimoto Y, Kimura Y, Kasahara Y, Chen WL, Imai H, Fujisawa M, Otuka K, Matsubayashi K. Relationships between each category of 25-item frailty risk assessment (Kihon Checklist) and newly certified older adults under Long-Term Care Insurance: a 24-month follow-up study in a rural community in Japan. *Geriatr Gerontol Int* 2015;15(7):864-871. doi: 10.1111/ggi.12360.
47. Tomata Y, Sugiyama K, Kaiho Y, Sugawara Y, Hozawa A, Tsuji I. Predictive ability of a simple subjective memory complaints scale for incident dementia: Evaluation of Japan's national checklist, the "Kihon Checklist". *Geriatr Gerontol Int* 2017;17(9):1300-1305. doi: 10.1111/ggi.12864.
48. Theou O, O'Connell SR-MD, King-Kallimanis BL, O'Halloran AM, Rockwood K, Kenny RA. Measuring frailty using self-report and test-based health measures. *Age Ageing* 2015;44(3):471-477. doi: 10.1093/ageing/afv010.
49. Kusumastuti S, Gerds TA, Lund R, Mortensen EL, Westendorp RGJ. Discrimination ability of comorbidity, frailty, and subjective health to predict mortality in community-dwelling older people: population based prospective cohort study. *Eur J Intern Med* 2017;42:29-38. doi: 10.1016/j.ejim.2017.05.016.
50. Snitz BE, Unverzagt FW, Chang CC, Bilt JV, Gao S, Saxton J, Hall KS, Ganguli M. Effects of age, gender, education and race on two tests of language ability in community-based older adults. *Int Psychogeriatr* 2009;21(6):1051-1062. doi: 10.1017/S1041610209990214.
51. Apóstolo J, Cooke R, Bobrowicz-Campos E, Santana S, Marcucci M, Cano A, Vollenbroek-Hutten M, Germini F, D'Avanzo B, Gwyther H, Holland C. Effectiveness of interventions to prevent pre-frailty and frailty progression in older adults: a systematic review. *JBIS Database System Rev Implement Rep* 2018;16(1):140-232. doi: 10.11124/JBISRR-2017-003382.
52. Potter R, Ellard D, Rees K, Thorogood M. A systematic review of the effects of physical activity on physical functioning, quality of life and depression in older people with dementia. *Int J Geriatr Psychiatry* 2011;26(10):1000-11. doi: 10.1002/gps.2641.
53. Huang CQ, Wang ZR, Li YH, Xie YZ, Liu QX. Cognitive function and risk for depression in old age: a meta-analysis of published literature. *Int Psychogeriatr* 2011;23(4):516-525. doi: 10.1017/S1041610210000049.
54. Shinsho F. New strategy for better geriatric oral health in Japan: 80/20 movement and Healthy Japan 21. *Int Dent* 2001;J51(3 Suppl):200-206.
55. Wright J, Baldwin C. Oral nutritional support with or without exercise in the management of malnutrition in nutritionally vulnerable older people: a systematic review and meta-analysis. *Clin Nutr* pii: 2017;S0261-5614(17)30319-9. doi: 10.1016/j.clnu.2017.09.004.
56. Iecovich E, Biderman A. Attendance in adult day care centers and its relation to loneliness among frail older adults. *Int Psychogeriatr* 2012;24(3):439-448. doi: 10.1017/S1041610211001840.
57. Okura M, Ogita M, Yamamoto M, Nakai T, Numata T, Arai H. The relationship of community activities with cognitive impairment and depressive mood independent of mobility disorder in Japanese older adults. *Arch Gerontol Geriatr* 2017;70:54-61. doi: 10.1016/j.archger.2016.12.010.
58. Okura M, Ogita M, Yamamoto M, Nakai T, Numata T, Arai H. Community activities predict disability and mortality in community-dwelling older adults. *Geriatr Gerontol Int* 2018;18(7):1114-1124. doi: 10.1111/ggi.13315.
59. Minister of Health, Labour and Welfare. Long-term care insurance latest information Vol. 181: About implementation method of secondary preventive project. March 11, 2011. <https://www.wam.go.jp/gyoseiShiryu-files/resources/bc344f83-6255-4263-90b0-2e3d99f0209e/%E4%BB%8B%E8%AD%B7%E4%BF%9D%E9%99%BA%E6%9C%80%E6%96%B0%E6%83%85%E5%A0%B1vol.181.pdf> Accessed 1 March 2019.
60. Nakash RA, Hutton JL, Jørstad-Stein EC, Gates S, Lamb SE. Maximising response to postal questionnaires—a systematic review of randomised trials in health research. *BMC Med Res Methodol*. 2006;6:5.
61. Edwards P, Roberts I, Clarke M, DiGiuseppi C, Pratap S, Wentz R, Kwan I, Cooper R. Methods to increase response rates to postal questionnaires. *Cochrane Database Syst Rev*. 2007;2:MR000008.
62. Edelman LS, Yang R, Guymon M, Olson LM. Survey methods and response rates among rural community dwelling older adults. *Nurs Res*. 2013;62(4):286-291. doi: 10.1097/NNR.0b013e3182987b32.
63. Wright J, Baldwin C. Oral nutritional support with or without exercise in the management of malnutrition in nutritionally vulnerable older people: a systematic review and meta-analysis. *Clin Nutr* pii: 2017;S0261-5614(17)30319-9. doi: 10.1016/j.clnu.2017.09.004.
64. Okamoto K, Ohsuka K, Shiraishi T, Hukazawa E, Wakasugi S, Furuta K. Comparability of epidemiological information between self- and interviewer-administered questionnaires. *J Clin Epidemiol* 2002;55(5):505-511.
65. Pike CJ. Sex and the development of Alzheimer's disease. *J Neurosci Res* 2017;95(1-2):671-680. doi: 10.1002/jnr.23827.
66. Hirvensalo M, Rantanen T, Heikkinen E. Mobility difficulties and physical activity as predictors of mortality and loss of independence in the community-living older population. *J Am Geriatr Soc* 2000;48(5):493-498.
67. Strobl R, Maier W, Ludyga A, Mielck A, Grill E. Relevance of community structures and neighbourhood characteristics for participation of older adults: a qualitative study. *Qual Life Res*. 2016;25(1):143-152. doi: 10.1007/s11136-015-1049-9.