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Complex multimorbidity and mortality in Japan: a prospective propensity-matched cohort study

Daisuke Kato ,[1] Ichiro Kawachi,[2] Junko Saito ,[3] Naoki Kondo[4]

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[1]Department of Family Medicine, Mie University Graduate School of Medicine Faculty of Medicine, Tsu, Mie, Japan
[2]Department of Social & Behavioral Sciences, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA
[3]Behavioral Science Division, Center for Public Health Sciences, National Cancer Center Japan, Chuo-ku, Tokyo, Japan
[4]Department of Social Epidemiology, Graduate School of Medicine and School of Public Health, Kyoto University, Kyoto, Japan

Correspondence to
Dr Daisuke Kato;
d.kato0417@gmail.com

ABSTRACT

Objectives There are limitations to defining multimorbidity (MM) based on a simple count of diseases. To address these limitations, the concept of complex MM (CMM) focuses on how many body systems are affected in a single patient, rather than counting comorbid conditions. This study compared the prediction of mortality among older Japanese adults between CMM and conventional MM.

Design A population-based prospective cohort study.

Setting The Japan Gerontological Evaluation Study, a nationwide longitudinal cohort study, which ran from 2010 to 2016.

Participants Functionally independent individuals who were older than 65 and had complete illness data at the time of baseline survey were eligible.

Outcomes measure CMM was defined as the coexistence of 3 or more body system disorders at baseline. We calculated the propensity for each individual to develop CMM based on a wide array of characteristics, including socioeconomic status and health behaviours. Individuals with and without CMM were then matched on their propensity scores before we estimated overall survival using a log-rank test.

Results Our 6-year follow-up included 38 889 older adults: 20 233 (52.0%) and 7565 (19.5%) adults with MM and CMM, respectively. In the MM-matched cohort (n=15 666 pairs), the presence of MM was significantly associated with increased mortality (HR 1.07; 95% CI 1.01 to 1.14; p=0.02 by the log-rank test). A similar mortality association was found in the CMM-matched cohort (n=7524 pairs, HR, 1.07; 95% CI 0.99 to 1.16; p=0.08 by the log-rank test).

Conclusion This is the first study to report the association between CMM and mortality among older adults in Japan. MM and CMM predict mortality in older adults to a similar degree. This finding needs to be replicated with more precision in larger samples.

Strengths and limitations of this study

- ► This is the first study to directly compare the associations between two alternative formulations of multimorbidity—conventional multimorbidity and complex multimorbidity—and survival in a nationwide cohort of older Japanese adults.
- ► We used propensity score matching to minimise confounding bias when comparing the survival of individuals with and without multimorbidity.
- ► One limitation is that we did not take into account the severity of disease at baseline, which may have underestimated the impact of comorbid conditions.

INTRODUCTION

There are limitations in defining multimorbidity (MM; the co-occurrence of diseases in the same person) based on a simple count of diseases,[1] and a new concept of 'complex MM' (CMM) has thus been proposed.[2] CMM focuses on the impact across the different body systems rather than counting comorbid conditions.

In CMM, diseases are categorised by the body system they affect. Because impairments of the same body system often have similar interventions, their impacts on patient prognosis are expected to be similar. Therefore, it makes biological sense to combine closely related diseases (eg, osteoporosis and fractures) as affecting a single body system (ie, musculoskeletal and connective disorders) rather than counting them as two separate diseases when evaluating the impact of multiple comorbid conditions. In turn, disorders of different body systems should be counted separately because they need more complex and extensive treatment, and the treatment of one disease may adversely affect another. Furthermore, from a methodological perspective, focusing on body system disorders may be more reliable method for collecting patient self-report data as patients are apt to misclassify individual conditions (eg, osteoarthritis vs rheumatoid arthritis or asthma vs COPD (chronic obstructive pulmonary disease)) but they are unlikely to mistake the affected body system. CMM is also likely to be a more reliable method as it may avoid issues of whether a clinician sees two very similar diseases as distinct and thereby avoids the issue of some clinicians recording a single condition while others record two.

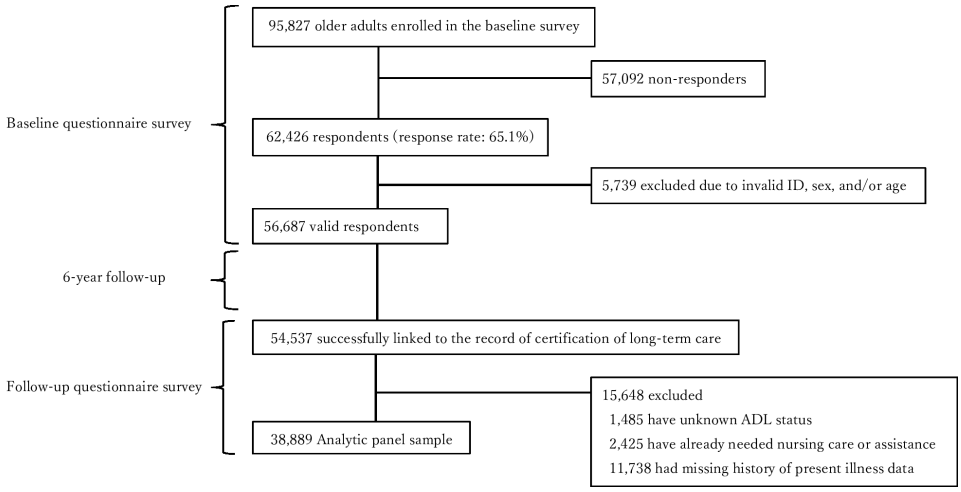

Figure 1 Flow diagram of the sample group. ADL, activities of daily living.

A growing number of studies have demonstrated the negative impact of MM on patient outcomes, showing that MM is associated with mortality, reduced quality of life, lower physical functioning and so on.[1 3–6] In many reports claiming these associations, researchers have attempted to weight diseases according to severity. Although the MM approach is better than conventional medical care that tends to focus on a single disease at a time, the new concept of CMM that focuses on multiple body system disorders is expected to result in stronger predictions of patient outcomes.

There is little evidence on the impact of CMM on mortality.[7] Although functional disability is associated with mortality, no previous studies have evaluated the impact of CMM by considering baseline activities of daily living status. Furthermore, previous reports that include both MM and CMM mainly performed descriptive statistics, not inferential statistics.[8–11] Against this background, we used CMM and conventional MM to compare the predictions of mortality among older Japanese adults.

Table 1 Definition of body system categories in CMM and diseases surveyed in JAGES

Category	Disease
Circulation disorder	► Heart disease (including arrhythmia) ► Stroke ► High blood pressure
Endocrine-metabolic disorder (general system)	► Diabetes (including mild type) ► Obesity ► Dyslipidaemia
Eye disorder	► Impaired vision
Gastrointestinal disorder	► Gastrointestinal disease ► Liver disease
Hearing disorder	► Impaired hearing
Mental and behavioural disorder	► Mental disease ► Sleep problem
Musculoskeletal and connective disorder	► Osteoporosis ► Joint disease/neuralgia ► Injury/fracture
Neoplasm	► Cancer
Respiratory disorder	► Respiratory disease

CMM, complex multimorbidity; JAGES, the Japan Gerontological Evaluation Study

METHODS

Data sources

We conducted this study using the longitudinal nationwide cohort data from the Japan Gerontological Evaluation Study (JAGES),[12] which was established in 2010. This study focuses on adults in Japan over 65 years of age and aims to establish a society of healthy longevity.

Study population

Self-administered questionnaires for the baseline survey were mailed to 95 827 older adults in Japan between August 2010 and January 2012. Adults were sampled from 13 municipalities in 7 of the 47 prefectures in Japan. All adults were functionally independent, which was defined as not receiving public long-term care (LTC) insurance. The municipalities were from three of the four major islands of Japan (Hokkaido, Honshu, Kyushu).

Among the target population, 62 426 individuals responded to the survey (response rate, 65.1%). We included individuals who were functionally independent and not receiving any nursing care or home care assistance to avoid reverse causality between MM and functional disability, which is a key factor in mortality. We included individuals who had valid ID, sex, and age information, and who were linked to LTC insurance certification registers. We excluded individuals whose functional disability status at baseline was unknown, or who were already receiving nursing care or home care assistance, or whose data on the history of present illness was missing. Finally, we identified a cohort of 38 889 individuals. Further details of the cohort flow diagram are shown in figure 1.

Table 2 Demographic characteristics of the cohort study

Characteristic	With MM		Without MM		With CMM		Without CMM	
Sample size	20 233		18 656		7565		31 324	
Age								
65–69	4087	43.4	5328	56.6	1205	12.8	8210	87.2
70–74	5673	49.7	5745	50.3	1955	17.1	9463	82.9
75–79	5413	56.7	4134	43.3	2162	22.6	7385	77.4
80–84	3418	59.2	2352	40.8	1485	25.7	4285	74.3
85–89	1322	60.3	870	39.7	605	27.6	1587	72.4
90+	320	58.5	227	41.5	153	28.0	394	72.0
Missing	0		0		0		0	
Sex								
Male	8803	49.3	9038	50.7	3051	17.1	14 790	82.9
Female	11 430	54.3	9618	45.7	4514	21.4	16 534	78.6
Missing	0		0		0		0	
No of natural teeth								
20 or more	5979	48.6	6313	51.4	2020	16.4	10 272	83.6
10–19	4946	51.3	4686	48.7	1807	18.8	7825	81.2
1–9	5478	54.5	4582	45.5	2170	21.6	7890	78.4
No natural teeth	3174	56.1	2484	43.9	1311	23.2	4347	76.8
Missing	656	52.6	591	47.4	257	20.6	990	79.4
Formal education years								
Less than 6 years	582	58.6	412	41.4	296	29.8	698	70.2
6–9 years	9812	54.2	8297	45.8	3818	21.1	14 291	78.9
10–12 years	6234	49.9	6250	50.1	2247	18.0	10 237	82.0
13 years or more	3091	49.1	3208	50.9	997	15.8	5302	84.2
Other	125	50.6	122	49.4	52	21.1	195	78.9
Missing	389	51.5	367	48.5	155	20.5	601	79.5
Marital status								
Married	13 555	50.4	13 328	49.6	4772	17.8	22 111	82.2
Widowed	5124	56.5	3944	43.5	2171	23.9	6897	76.1
Divorced	652	52.3	594	47.7	255	20.5	991	79.5
Never married	413	55.5	331	44.5	157	21.1	587	78.9
Other	108	50.2	107	49.8	48	22.3	167	77.7
Missing	381	52.0	352	48.0	162	22.1	571	77.9
Living arrangement								
Live alone	17 195	51.5	16 169	48.5	6300	18.9	27 064	81.1
Not alone	2730	56.1	2138	43.9	1159	23.8	3709	76.2
Missing	308	46.9	349	53.1	106	16.1	551	83.9
Financial insecurity (worries about unexpected expenses)								
None at all	1858	47.9	2018	52.1	608	15.7	3268	84.3
Slight	8218	49.6	8357	50.4	2817	17.0	13 758	83.0
Moderate	5556	54.2	4701	45.8	2144	20.9	8113	79.1
Severe	3431	57.9	2494	42.1	1554	26.2	4371	73.8
Missing	1170	51.9	1086	48.1	442	19.6	1814	80.4
Receiving pension								

Continued

Table 2 Continued

Characteristic	With MM		Without MM		With CMM		Without CMM	
No	19 191	51.9	17 779	48.1	7162	19.4	29 808	80.6
Yes	277	57.0	209	43.0	109	22.4	377	77.6
Missing	765	53.4	668	46.6	294	20.5	1139	79.5
Current employment status								
Has a paid job	3259	44.6	4055	55.4	952	13.0	6362	87.0
Retired	11 344	53.0	10 040	47.0	4315	20.2	17 069	79.8
Never had a job	2623	56.2	2043	43.8	1125	24.1	3541	75.9
Missing	3007	54.4	2518	45.6	1173	21.2	4352	78.8
Alcohol consumption								
Yes	5640	47.8	6164	52.2	1868	15.8	9936	84.2
Used to drink	840	57.2	628	42.8	354	24.1	1114	75.9
No	12 498	53.8	10 733	46.2	4844	20.9	18 387	79.1
Missing	1255	52.6	1131	47.4	499	20.9	1887	79.1
Smoking status								
Never smoked	10 990	52.8	9842	47.2	4195	20.1	16 637	79.9
Stopped smoking 5 or more years ago	4499	52.4	4086	47.6	1609	18.7	6976	81.3
Stopped smoking within the past 4 years	913	50.4	899	49.6	334	18.4)	1478	81.6
Current smoker	1632	46	1918	54	546	15.4	3004	84.6
Missing	2199	53.5	1911	46.5	881	21.4	3229	78.6

CMM, complex multimorbidity; MM, multimorbidity

MM and CMM

At baseline, 19 diseases were surveyed in the JAGES. Among them, as noted in table 1, we analysed the following 17 diseases to calculate MM and CMM: heart disease (including arrhythmia), stroke, high blood pressure, diabetes (including mild type), obesity, dyslipidaemia, impaired vision, gastrointestinal disease, liver disease, impaired hearing, mental disease, sleep problems, osteoporosis, joint disease/neuralgia, injury/fracture, cancer and respiratory disease. The remaining two symptoms, difficulty swallowing and difficulty with bowel movements, were excluded from the disease list in this study because they have aspects of dysfunction not disease. The JAGES did not survey diseases of the nervous system.

MM was defined as having two or more of the aforementioned diseases concurrently. For CMM, the diseases surveyed were categorised according to the body system they affected.[2 13] For example, heart disease and diabetes were individually categorised into disorders of the circulatory system and endocrine system. Next, CMM was defined as the coexistence of 3+ body system disorders at baseline (see table 1).

Outcome

The outcome of this study was the 6-year incidence of mortality. We ascertained vital status from 2010 to 2016 by linking the cohort participants to the mortality records of the national LTC insurance database (follow-up rate=96.2%). The mean follow-up period was 5.6 years, and we observed 5183 (13.3%) deaths during the period.

Statistical analysis

Estimation of missing data

Given that the missing data was missing at random, we conducted multiple imputations using a bootstrapping Expectation-Maximisation algorithm.[14] We analysed 20 multiply imputed datasets, taking the low missing rate of the cohort (approximately 5%) into consideration.[15] Lastly, we combined all estimators by Rubin's rule.[16]

Propensity score matching

We used propensity score matching to compare overall survival among individuals with and without MM/CMM. To address potential confounding bias, we conducted propensity score matching within a logistic regression framework. The participant information included in estimating the propensity score consisted of 44 variables: age, sex, smoking status, alcohol consumption, marital status, pension, dental health, employment status, consumption of meat of fish/fruits or vegetable, education, city code and so on (see online supplemental table S1).

We performed a 1:1 matching between individuals with and without MM/CMM using the nearest-neighbour

Table 3 Standardised mean differences with or without MM/CMM, before and after propensity score matching

	MM		CMM	
	SMD in multiply imputed data	SMD in matching data	SMD in multiply imputed data	SMD in matching data
Characteristic				
Age	0.24	0.002	0.327	0.025
Sex	0.099	0.001	0.139	0.004
Previous health check-up	0.01	0.015	0.02	0.005
No of natural teeth	0.11	0.019	0.16	0.005
Consumption of meat and fish	0.009	0.017	0.017	0.016
Consumption of fruits and vegetables	0.003	0.006	0.035	0.012
Formal educational years	0.093	0.045	0.151	0.004
Marital status	0.072	0.015	0.118	0.002
Living arrangement	0.06	0.033	0.1	0.011
Residence type	0.025	0.055	0.058	0.008
Architectural type of home	0.005	0.086	0.02	0.006
Financial insecurity	0.123	0.004	0.21	0.012
Receiving pension	0.023	0.022	0.022	0.006
Current working status	0.147	0.002	0.225	0.004
Eats meals alone	0.089	0.02	0.17	0.014
Alcohol consumption	0.107	0.015	0.145	0.013
Smoking status	0.079	0.014	0.098	0.016
Falls	0.223	0.004	0.307	0.013
Worries about falls	0.266	0.001	0.396	0.005
Goes upstairs without support	0.265	0.009	0.348	0.005
Gets up out of a chair without support	0.251	0.02	0.343	0.01
Average time to walk	0.16	<0.001	0.203	0.001
Frequency of going out	0.151	0.015	0.207	0.003
Decrease in the frequency of going out	0.243	0.001	0.352	0.006
Engagement in leisure activities	0.105	0.016	0.145	0.008
Trust in neighbours	0.079	0.027	0.135	0.009
Support from neighbours	0.074	0.015	0.109	0.002
Attachment to residence	0.053	0.036	0.086	0.002
Contribution to residence	0.095	0.009	0.129	0.007
Uneasiness about safety in residence	0.073	0.011	0.105	0.01
Participation in local events	0.085	0.009	0.114	0.008
Interactions with neighbourhood	0.02	0.031	0.049	0.007
Residential environment:				
Presence of graffiti or garbage	0.009	0.02	0.019	0.014
Parks or footpaths	0.059	0.045	0.097	<0.001
Locations difficult for walking	0.076	0.012	0.132	0.007
Risky roads or crossroads for traffic accidents	0.044	0.005	0.061	0.002

Continued

Table 3 Continued

	MM		CMM	
	SMD in multiply imputed data	SMD in matching data	SMD in multiply imputed data	SMD in matching data
Aesthetic views or buildings	0.04	<0.001	0.074	0.004
Shops selling fresh fruits and vegetables	0.074	0.023	0.091	0.001
Dangerous place to walk alone at night	0.013	0.019	0.016	<0.001
Comfortable house or facilities	0.066	0.024	0.107	0.011
Someone who listens to your concerns	0.019	0.01	0.075	0.007
Someone to provide care in case of illness	0.049	0.023	0.094	0.026
Attendance				
Sports group or club	0.063	0.008	0.117	0.031
Leisure activity group	0.06	0.006	0.088	0.007

CMM, complex multimorbidity; MM, multimorbidity; SMD, standardised mean difference

method within a calliper (0.2 of the SD of the logit of the propensity score).[17 18] We evaluated the covariate balance after matching using standardised differences. An absolute standardised difference of less than 0.1 was considered negligible in the groups (see tables 2 and 3).

Survival data analysis

We estimated the overall survival using Kaplan-Meier curves.[18] We also compared overall survival between matched with and without MM/CMM groups using a log-rank test.

Sensitivity analysis

While the definition of MM we adopted in this study is one of the most commonly used definitions in previous studies,[2] we analysed this cohort data with a more sensitive approach. Specifically, we analysed the association between the number of diseases or body system disorders and the mortality by multivariate analysis with the covariates used in the propensity score calculation. The results of this analysis did not change the direction or significance of the MM/CMM effect (data not shown).

We used R software packages (V.4.0.1) for all statistical analyses, and the statistical significance level was 0.05 for all analyses.

Patient and public involvement

This was a nationwide cohort study focusing on community-dwelling individuals. No patients and the public were involved in this research.

RESULTS

Baseline population characteristics

Among the current cohort study, 20 233 (52.0%) participants out of 38 889 had MM and 7565 (19.5%) had CMM. Table 2 presents the demographic characteristics of the

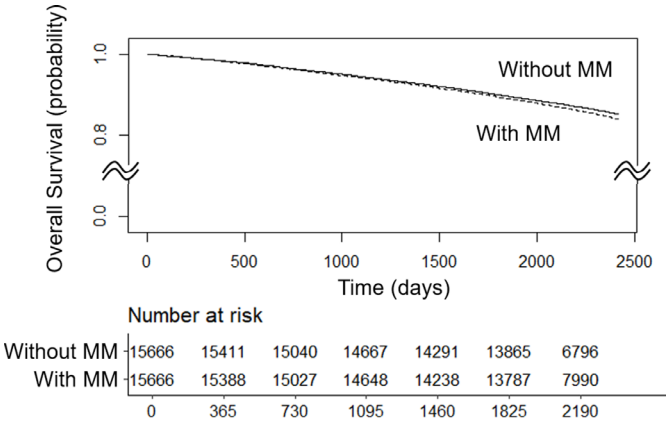

Figure 2 Kaplan-Meier curve for overall survival comparing patients with and without MM. MM, multimorbidity.

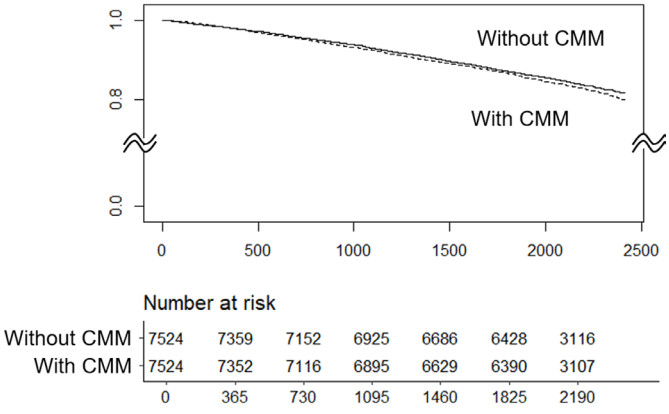

Figure 3 Kaplan-Meier curve for overall survival comparing patients with and without CMM. CMM, complex multimorbidity.

cohort study. Table 3 summarises the background characteristics of the participants between the two groups before and after matching. Populations with MM/CMM were more likely to be older, were more likely to have fewer teeth, and were more vulnerable to financial insecurity (worries about unexpected expenses) compared with those without MM/CMM. Furthermore, compared with populations with MM, populations with CMM were more likely to be female, to have lower education, to eat meals alone and to be unmarried.

MM outcome

After the 1:1 propensity score matching, 31 332 patients were recruited and evenly classified into propensity-matched MM and propensity-matched non-MM groups. The C-statistics before matching for evaluation of the discriminatory ability of the propensity score model was 0.64 (95% CI 0.63 to 0.64).[19] The two matched cohorts were well balanced (see table 3). The populations with MM had a 7% higher mortality than those without MM as shown in figure 2 (HR 1.07; 95% CI 1.01 to 1.14; p=0.02 by the log-rank test).

CMM outcome

After the 1:1 propensity score matching, 15 048 patients were recruited and evenly classified into propensity-matched CMM and propensity-matched non-CMM groups. The C-statistics before matching for evaluation of the discriminatory ability of the propensity score model was 0.69 (95% CI 0.68 to 0.69).[19] The two matched cohorts were well balanced (see table 3). The populations with CMM had slightly higher mortality than those without CMM as shown in figure 3 (HR, 1.07; 95% CI 0.99 to 1.16; p=0.08 by the log-rank test).

DISCUSSION

To the best of our knowledge, this is the first study to report the association between CMM and mortality among older adults in Japan. MM and CMM predict mortality in older adults to a similar degree.

MM is both an individual and a social issue. Low socioeconomic status (SES) individuals develop MM roughly 10–15 years earlier compared with high SES individuals.[20] Therefore, to evaluate whether the presence of MM/CMM is causally related to mortality, SES should be considered as a confounding factor. There were larger intergroup differences in baseline variables for the CMM-matched cohort compared with the MM-matched cohort. Although CMM was already known to be associated with lower SES,[21] the current findings indicate that CMM may be more closely related to social factors than MM.

We found that the impact of MM and CMM on mortality was similar. Furthermore, CMM was marginally statistically significantly associated with mortality. This may be partly because the current study did not consider disease severity or disease status except in the baseline survey. That is, it may not sufficiently represent body system disorders in terms of the number of disease groups affected. This finding needs to be replicated with more precision in larger samples.

There are several limitations to this study. First, the self-administered questionnaire was the basis for disease information, which may have led to recall bias. This reporting error may lead to bias in either direction because its extent depends on the type of disease and age.[22] Second, although the results are based on a nationwide cohort study, the participants were not nationally representative, and hence external generalisability is not assured. The response rate (around 65%) was comparable to that of other cohort studies for community-dwelling individuals. Third, because this study was observational, our findings cannot be interpreted as indicating causality. Nonetheless, we attempted to minimise confounding bias through the use of propensity score matching.[18]

CONCLUSION

Both MM and CMM predicted future mortality among older adults in Japan. These findings indicate the importance of the interactive effects of multiple diseases.

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Contributors All authors (DK, IK, JS and NK) made contributions to the conception and design of this study. DK analysed the data and authored the paper. IK checked the results and advised edits. All authors agreed on the final version of this manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval JAGES participants were informed that participation was voluntary and that their consent to participate in the study was shown by returning the questionnaire via mail. The Nihon Fukushi University Ethics Committee (no. 10-5), National Center for Geriatrics and Gerontology (no. 992-2), and Chiba University Ethics Committee (no. 2493) approved the parent JAGES protocol.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Data are from the JAGES study. All inquiries are to be addressed to the data management committee via email: dataadmin.ml@jages.net. All JAGES datasets have ethical and legal restrictions for public deposition due to the inclusion of sensitive information from human participants.

ORCID iDs
Daisuke Kato http://orcid.org/0000-0002-2449-0548
Junko Saito http://orcid.org/0000-0002-6923-7298

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