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Association of trajectories of cognitive function with cause-specific mortality and medical and long-term care costs

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Aim: Cognitive decline increases mortality risk through dementia-related pathways and might be associated with increased healthcare costs. Using up to 12 years of repeated measures data, we identified trajectories in cognitive function among community-dwelling older Japanese adults. We then examined whether these trajectories were associated with all-cause and cause-specific mortality, and differences in healthcare costs.

Methods: A total of 1736 adults aged ≥65 years who were free of disabling dementia completed annual assessments during 2002–2014. Cognitive function was assessed with the Mini-Mental State Examination. The average number of follow-up assessments was 3.9, and the total number of observations was 6824 during the follow-up period.

Results: We identified five trajectory patterns in cognitive function (high, second, third, fourth, and low) during the 12-year follow-up period. The low (2.0%) and fourth (2.2%) trajectory groups had higher hazard ratios for cardiovascular disease mortality, and hazard ratios for other cause mortality were significantly higher for the third (16.8%) and second (38.8%) trajectory groups than for the high trajectory group (40.3%). Until 5 years of follow up, participants in the two lower-trajectory groups had higher mean combined monthly medical and long-term care costs. After 8 years of follow up, mean costs were highest for the third trajectory.

Conclusions: The risk of death from cardiovascular disease was higher in the two lower-trajectory groups in cognitive function, and they showed higher healthcare costs during the first 5 years of follow up. After 8 years of follow up, the third trajectory had the highest healthcare costs, perhaps because of hospitalizations attributable to gradual cognitive decline. **Geriatr Gerontol Int 2019; ••: ••–••.**

Keywords: cognition, health service, successful aging.

Introduction

Many people experience age-related functional decline. Cognitive function, too, typically deteriorates in later life.[1] Memory performance at age 80 years is approximately 1–1.5 standard deviations below that of young adults,[2] whereas global cognition is relatively stable, before declining moderately in the last 3–4 years of life.[3] Using repeated measures analysis, we previously identified three distinct trajectory patterns in cognitive aging among community-dwelling older Japanese adults.[4] Approximately half the participants had normal cognitive aging, 43% began to decline after age 80 years and the remaining 5% showed a rapid decline after age 65 years.

Cognitive impairment, might result from the process of cerebrovascular disease [5] (i.e. cerebral infarction and cerebral hemorrhage), and is a risk factor for cerebrovascular dementia[6] and prodromal Alzheimer's disease. Cognitive decline might increase the mortality risk through dementia-related pathways, and several studies have reported an association between cognitive status and mortality. Declines in memory and executive function were reported to be significant predictors of mortality in a younger-old group, and decline in processing was a strong mortality predictor in an older-old group.[7] The main causes of death among persons with low cognitive scores were cancer and cardiovascular diseases.[8] In addition, cognition was inversely associated with death from cancer, cardiovascular disease, death from other causes and respiratory illness.[9] Previous findings suggest that trajectories of cognitive function might predict mortality and cause-specific mortality; however, the present evidence is insufficient to confirm this hypothesis.[7–9]

The World Alzheimer Report estimated that the annual global cost of dementia is $818 billion, 85% of which is related to family and social burdens rather than to medical care.[5–10] We hypothesized that declining cognitive trajectories might be associated with increased healthcare costs, such as medical or long-term care costs.

The present prospective study of community-dwelling older adults used repeated measures data on cognitive function from a 13-year longitudinal study of rural Kusatsu Town, Japan. We examined local registries to ascertain deaths from any cause and linked these data with national vital statistics. Then, we obtained data on medical expenses and long-term care expenditures during the follow-up period. The three objectives were to identify trajectories in cognitive function among a general population of community-dwelling older Japanese adults, to determine whether these trajectories were associated with all-cause and cause-specific mortality, and to examine differences in healthcare costs (medical and long-term care costs) between trajectories. Furthermore, a preliminary analysis examined the association of hospitalization with trajectory.

Methods

Participants

In collaboration with the government of Kusatsu Town, Gunma Prefecture, Japan, we launched a longitudinal study of aging and health in 2001. In addition to an annual preventive health checkup for all residents aged ≥40 years, participants aged ≥70 years (≥65 years after 2006) underwent a geriatric assessment from 2002 through 2014. All older residents were invited to participate in annual assessments, which were all carried out in the same manner. The details of the study design have been previously reported.[4,11–16] All participants undergoing geriatric assessment provided written informed consent under conditions approved by the ethics committee at Tokyo Metropolitan Institute of Gerontology.

To be eligible for the study among a general population of community-dwelling older Japanese adults, individuals had to be free of disabling dementia at baseline, as assessed by the long-term care insurance system.[4,15] Briefly, disabling dementia was defined as level II or higher dementia in an observer-based rating for older adults with dementia, as this is the level at which applicants can receive insurance benefits, including institutional, home, respite and day care, and equipment loans.[17,18] The data source for the present study was 1736 adults aged ≥65 years living in Kusatsu Town who completed annual assessments at least once during the period from June 2002 through July 2014. The average number of follow-up assessments was 3.9, and the total number of observations was 6824 during the follow-up period (Fig. S1).

Measurement of cognitive function

Cognitive function was assessed with the Mini-Mental State Examination (MMSE), a widely used brief screening test for dementia and a measure of global cognitive function. The MMSE encompasses orientation, memory, concentration, language and praxis. It comprises 11 questions, and the score ranges from 0 to 30, with lower scores indicating worse global cognitive ability.[4] Well-trained personnel administered the annual examination. We used MMSE data from annual assessments during the study period from 2002 through 2014.

Cause-specific mortality

The underlying cause of death was coded by using the International Classification of Diseases, Tenth Edition (ICD-10). The relevant ICD-10 codes were I00–I99 for cardiovascular disease (CVD) and C00–C97 for cancer; all other codes were classified as "other." Local registries recorded 401 (23.6%) incident deaths among the 1736 participants during the period through December 2016. The median duration of follow up for incident death was 8.3 years. Among the 401 incident deaths, 391 (97.5%) were linked with Japanese national vital statistics (121 CVD deaths, 100 cancer deaths and 170 other deaths).

Healthcare costs (medical and long-term care costs)

All Japanese citizens have access to medical care and long-term care coverage under the universal health insurance system. The official medical insurance system includes the National Health Insurance and health insurance for older people, and these insurances cover almost all medical treatment and medical provider fees. Payments from insured persons to medical providers are made on a fee-for-service basis, in which the price of each service is determined by a uniform national fee schedule.[15,19,20] The Japanese Long-Term Care Insurance (LTCI) system provides long-term care services, community-based services and in-facility services. All primary insured persons aged ≥65 years are candidates for care. When insured persons need to use LTCI, they submit a request to the municipal government for their primary physicians to assess, and evaluate their physical and mental status. Using these results, a local Long-Term Care Needs Certification Board determines eligibility and the care level required for insured residents. Care services using allotted benefits are coordinated by a care manager, in collaboration with the insured person and their family.[15,21]

Using insurance claims data from the National Health Insurance, health insurance for older people and data on LTCI beneficiaries in Kusatsu Town, we calculated monthly medical costs, and the combined monthly medical and long-term care costs. Because the frequency of long-term care costs was low, we elected not to analyze these costs separately. The period of these costs for each participant corresponded with the follow-up period for MMSE (from June 2002 through July 2014). Costs are expressed in $US ($US1 = ¥111.02 on 11 July 2018). Other variables are shown in File S1.

Statistical analysis

First, we identified trajectory groups in cognitive function by estimating latent class group-based trajectory models for MMSE score. The procedure was implemented in SAS Proc Traj (SAS Institute, Cary, NC, USA),[22] as reported elsewhere.[4,14,15,23,24] For a fixed number of latent groups, cubic trajectory models were fitted, and posterior probabilities for each group membership assignment were calculated for each individual. We chose a model of five latent groups because of the interpretability of the trajectories and Bayesian information criterion of the models. After assigning the group with the highest posterior probability to each participant, we compared cause-specific mortality (i.e. death from cardiovascular disease, cancer or other causes) between the trajectory groups by using Fine and Gray subdistribution hazards models that controlled for baseline sex, age, years of education, frequency of going outdoors, self-rated health, body mass index, grip strength, Tokyo Metropolitan Institute of Gerontology Index of Competence score and Geriatric Depression Scale.[25] The

underlying time-scale in the hazards models starts from first participation (from June 2002 through July 2014) until death or the end of follow up (December 2016), whichever came first. Finally, we fitted the group-stratified Poisson generalized estimating equation (GEE) models for changes in healthcare costs and the group-stratified logistic GEE models for probability of hospitalization, including quadratic or cubic terms for follow-up time and the first-order autoregressive correlation structure, after combining the two smallest groups (the fourth and low trajectory groups) into one group. Statistical analyses were carried out with SPSS (version 23.0; IBM Corporation, Armonk, NY, USA) and SAS (version 9.4; SAS Institute).

Results

Data from the baseline survey showed that the mean age of participants was 71.5 years (SD 5.9 years), and 56.6% were women. The average number of years of education was 10.0 (SD 2.7 years), and 82.9% of participants reported a self-rated health of good or very good.

We identified five trajectory patterns in cognitive function: 40.3% of participants were in the high trajectory group, 38.8% in the second group, 16.8% in the third group, 2.2% in the fourth group and 2.0% were in the low trajectory group (Fig. 1). The two higher-trajectory groups (high and second groups) had consistently higher scores during the entire follow-up period. Mean scores in the third group remained relatively constant during the first few years, gradually decreased after 3 years and had an MMSE score <23 points within 10 years. The two lower-trajectory groups (fourth and low trajectory groups) had an MMSE score <23 points at baseline and showed gradual declines during the follow-up period. The average posterior probability of allocating each participant into the four groups was 0.65–0.95, indicating a good fit of the model of group trajectories to individual trajectories.

Table 1 shows the baseline demographic and health characteristics of the participants in relation to cognitive trajectory. At baseline, participants in the high trajectory group were younger, had more years of education, were likely to have hyperlipidemia, went outdoors more frequently, and had greater grip strength, higher Tokyo Metropolitan Institute of Gerontology Index of Competence scores, higher MMSE scores and lower Geriatric Depression Scale Short Form scores.

As compared with the high trajectory group, the second, third, fourth and low trajectory groups had hazard ratios (HR) of 1.31 (95% confidence interval [CI] 0.99–1.74), 1.38 (95% CI 0.99–1.92), 1.10 (95% CI 0.55–2.20) and 2.01 (95% CI 1.04–3.88), respectively, for all-cause mortality, after adjustment for several covariates (Table 2). For cause-specific death, the low trajectory group had a significantly higher HR for CVD mortality. CVD mortality risk was slightly higher for the fourth trajectory group than for the high trajectory group, but the difference was not significant. The HR for other cause mortality (non-CVD death and non-cancer death) were significantly higher for the second and third trajectory groups than for the high trajectory group.

Among the 1736 participants, 1095 (63.1%) incurred monthly medical costs and 89 (5.1%) incurred monthly long-term care costs during follow up. The GEE models showed trajectory-specific changes in monthly medical costs, and combined medical and long-term care costs (Figs 2, 3). Mean monthly medical costs in the fourth and low trajectory groups were higher than in the three higher-trajectory groups until 5 years of follow up, but decreased linearly thereafter. In contrast, the three higher-trajectory groups showed increases in monthly medical costs after the baseline survey; in particular, the third trajectory group had a dramatic increase during the second half of follow up, and mean monthly medical costs were estimated at $619.6 after 12 years of follow up. Combined monthly medical and long-term care costs were slightly higher than monthly medical costs alone. Interestingly, mean costs were highest in the third trajectory group, which had the highest monthly medical and long-term care costs after 8 years of follow up (the combined costs were estimated at $884.8 after 12 years of follow up).

Fitted logistic GEE models for the probability of hospitalization in the five trajectory groups showed several distinct patterns (Fig. S2). The probability during follow up was relatively constant for the two higher-trajectory groups, but gradually decreased for the two lower-trajectory group. In contrast, the probability rapidly increased in the third trajectory group during the last 4 years of follow up.

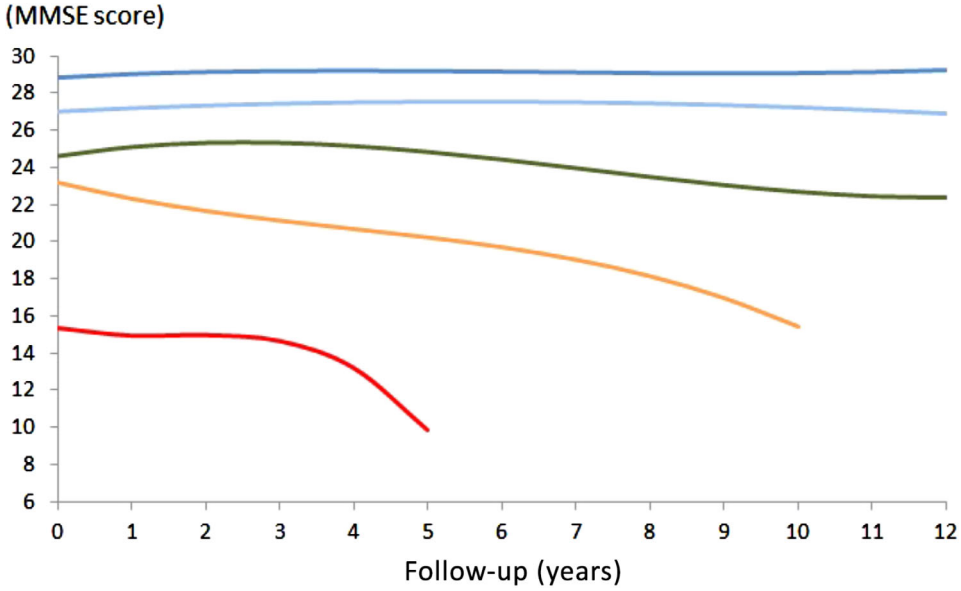

Figure 1 Trajectory patterns for cognitive function. The solid lines are estimated values. (——), High group (40.3%); (——) Second group (38.8%); (——) Third group (16.8%); (——) Fourth group (2.2%); (——) Low group (2.0%). MMSE, Mini-Mental State Examination.

Table 1 Associations of baseline demographic and health characteristics with Mini-Mental State Examination trajectory groups in community-dwelling older adults

Variable	MMSE trajectory					
	High (n = 700, 40.3%)	Second (n = 673, 38.8%)	Third (n = 291, 16.8%)	Fourth (n = 38, 2.2%)	Low (n = 34, 2.0%)	P-value
Sex, women (%)	59.7	52.5	56.4	63.2	70.6	0.864
Age (years)	69.6 ± 4.5	71.4 ± 5.6	74.4 ± 6.8	75.9 ± 7.1	80.0 ± 7.8	<0.001
Years of education	11.0 ± 2.7	9.7 ± 2.5	8.6 ± 2.3	8.6 ± 3.1	7.0 ± 2.4	<0.001
Frequency of going outdoors, at least once a day (%)	85.6	84.2	76.4	78.9	62.5	0.036
Self-rated health, very good or good (%)	84.3	83.1	79.7	76.3	84.4	0.384
Chronic disease (%)						
Hypertension	34.4	36.3	44.6	39.5	31.3	0.712
Hyperlipidemia	20.1	17.5	14.1	15.8	3.1	0.002
Stroke (cerebral hemorrhage, subarachnoid hemorrhage)	4.2	6.8	8.3	7.9	9.1	0.110
Heart disease (angina, myocardial infarction, arrhythmia e.g. ventricular extrasystole, others)	9.7	10.5	8.7	13.2	6.1	0.196
Diabetes mellitus	8.5	10.1	9.7	10.5	15.6	0.182
BMI (kg/m^2)	23.2 ± 3.1	23.4 ± 3.1	23.2 ± 3.5	22.6 ± 2.8	21.9 ± 3.5	0.787
Handgrip strength (kg)	27.4 ± 8.8	26.3 ± 9.1	23.7 ± 9.3	21.6 ± 10.1	16.8 ± 5.6	<0.001
Instrumental Activities of daily living (score)	4.9 ± 0.4	4.9 ± 0.6	4.7 ± 0.9	4.7 ± 0.7	4.0 ± 1.5	<0.001
Effectance (score)	3.7 ± 0.7	3.5 ± 0.8	3.1 ± 1.0	3.0 ± 1.1	2.0 ± 1.4	<0.001
Social role (score)	3.6 ± 1.8	3.5 ± 0.9	3.3 ± 1.0	2.8 ± 1.2	2.2 ± 1.4	<0.001
TMIG-IC (score)	12.2 ± 1.3	11.8 ± 1.7	11.1 ± 2.2	10.5 ± 2.3	8.1 ± 3.3	<0.001
GDS Short Form (score)	3.1 ± 2.8	3.7 ± 2.9	4.0 ± 3.0	5.8 ± 3.8	6.0 ± 2.9	<0.001
MMSE (score)	29.1 ± 1.3	26.9 ± 1.7	24.4 ± 2.1	23.2 ± 2.4	15.2 ± 3.5	<0.001

Data presented as the mean ± SD. P-values were calculated based on the cumulative logit model for Mini-Mental State Examination (MMSE) trajectory groups as an outcome after adjusting for baseline age and sex. BMI, body mass index; GDS, Geriatric Depression Scale, TMIG-IC, Tokyo Metropolitan Institute of Gerontology Index of Competence.

Discussion

Traditionally, an MMSE cut-off of 23 out of 24 has been used to screen persons with suspected cognitive impairment or dementia,[26] and MMSE scores <20 have been used to identify psychosis of dementia. In the present 12-year longitudinal study of 1736 older adults without disabling dementia at baseline, approximately 80% were classified in the two higher-trajectory groups (40.3% in the high trajectory and 38.8% in the second trajectory), and they retained higher cognitive function during the entire follow-up period. The cognitive function of the 16.8% of participants in the third trajectory group remained relatively constant for the first few years, gradually decreased after 3 years and was consistent with dementia within 10 years of follow up. Both the fourth trajectory (2.2%) and low trajectory (2.0%) groups had cognitive impairment at baseline, and would likely have developed severe dementia had follow up been longer. The participants in the two lower-trajectory groups had lower physical, psychological and social function, fewer years of education, and were older. These findings suggest that efforts to address cognition-associated controllable factors (i.e. physical, psychological and social function) might improve individual cognitive trajectories.

Cognitive trajectories were associated with mortality and confirmed the putative relationship between cognition and mortality. As compared with the high trajectory group, participants in the low trajectory group had an adjusted HR of 2.01 for all-cause mortality and a significantly higher HR for CVD mortality; the fourth trajectory group also had a slightly higher HR, but the difference was non-significant. We carried out a preliminary analysis for cerebrovascular disease mortality (ICD-10 codes, I60–I69). Competing-risk subdistribution regression showed HR of 4.97 (95% CI 1.42–17.50) in the low trajectory group and 5.51 (95% CI 1.89–16.10) in the fourth trajectory group, as compared with the high trajectory group. These findings show that older persons with severe dementia are at higher risk for death from cardiovascular diseases, such as cerebrovascular disease. In contrast, as compared with the high trajectory group, participants in the third and second trajectory groups had HR of 2.29 and 1.80 for other cause mortality, respectively. In a preliminary analysis of respiratory mortality (ICD-10 codes J00–J99), the HR was 5.25 (95% CI 2.34–11.77) for the third trajectory group and 2.49 (95% CI 1.12–5.56) for the second trajectory group, as compared with the high trajectory group. These results suggest that older persons with gradual cognitive decline have a higher risk of non-cancer death, such as respiratory disease.

We hypothesized that lower cognitive trajectory might be associated with increased healthcare costs. In fact, although the mean monthly medical and long-term care costs were higher in the two lower-trajectory groups during the first 5 years of follow up, they decreased linearly thereafter. The period of decreasing healthcare costs in these two groups after 5 years of follow up overlapped the period when their MMSE scores were <20. Specifically, the present findings suggest two potential mechanisms by which

Table 2 Independent associations of Mini-Mental State Examination trajectory groups with all-cause and cause-specific mortality in community-dwelling older adults

MMSE trajectory	All-cause mortality		CVD mortality		Cancer mortality		Other mortality	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
High[§] (*n* = 97/700, 13.9%)	1	1	1	1	1	1	1	1
Second (*n* = 164/673, 24.4%)	1.53 (1.19–1.97)**	1.31 (0.99–1.74)	1.00 (0.63–1.59)	0.84 (0.50–1.43)	1.47 (0.94–2.29)	1.20 (0.73–1.95)	1.94 (1.13–8.45)*	1.80 (1.10–2.95)*
Third (*n* = 109/291, 37.5%)	2.23 (1.69–2.93)**	1.38 (0.99–1.92)	1.79 (1.10–2.89)*	1.08 (0.59–2.00)	0.96 (0.53–1.75)	0.69 (0.35–1.38)	3.53 (2.30–5.87)**	2.29 (1.36–3.87)*
Fourth (*n* = 12/38, 31.6%)	1.89 (1.04–23.45)*	1.10 (0.55–2.20)	3.01 (1.31–6.91)**	2.31 (0.97–5.50)	-	-	2.04 (0.71–5.87)	0.75 (0.16–3.46)
Low (*n* = 19/34, 55.9%)	5.32 (3.25–8.70)**	2.01 (1.04–3.88)*	8.81 (4.51–17.21)**	5.10 (2.18–12.44)**	0.59 (0.08–4.45)	0.51 (0.06–4.60)	3.09 (1.13–8.45)*	0.38 (0.05–2.89)

*$P < 0.05$. **$P < 0.01$. Number of all-cause deaths/number of each trajectory group. Cox's proportional hazards model was run for all-cause mortality. For the cause-specific outcomes (cardiovascular disease [CVD], cancer and other cause of death), Fine–Gray subdistribution hazard models were fit to account for competing events. Adjusted for sex, age, years of education, frequency of going outdoors, self-rated health, history of hyperlipidemia, body mass index, grip strength, Tokyo Metropolitan Institute of Gerontology Index of Competence and Geriatric Depression Scale. [§]Reference group; CI, confidence interval; HR, hazard ratio; MMSE, Mini-Mental State Examination.

healthcare costs decrease for older persons with progressive dementia. First, older persons with progressive dementia might have difficulty reporting their subjective symptoms, which could lead to undertreatment or inappropriate treatment. The probability of hospitalization linearly decreased during follow up in the two lower-trajectory groups, which suggests that reporting subjective symptoms is difficult for older persons with progressive dementia. Second, physicians might alter treatment plans in accordance with patients' cognitive function. For example, the International Diabetes Federation and Japan Diabetes Society recommend less rigorous glycated hemoglobin limits for older adults with cognitive impairment, and the goals of glycemic control are adjusted in relation to the cognitive status of older patients. To better address the healthcare needs of patients in the 21st century, medical care might evolve to a more individualized and integrated model.[27] The present third trajectory group had the highest monthly medical and long-term care costs after 8 years of follow up. Sharma *et al.* reported that one-third of people with dementia had falls leading to hospitalization, necessitating action in clinical practice.[28] This suggests that the high healthcare costs of the third trajectory group were caused by fall-related hospitalizations attributable to gradual cognitive decline. A USA study reported that healthcare expenditures were substantially higher for persons with dementia than for those with other diseases.[29] Attempts to prevent dementia and reduce social security costs for persons at high risk of dementia should target people with gradual cognitive decline, especially those with an MMSE score <23 points.

The present study had strengths that warrant mention. First, our large sample and repeated measures data from a general population of community-dwelling older adults allowed us to use a group-based semiparametric mixture model, which yielded potential trajectories in cognitive function during follow up. Second, data on medical and long-term care costs were derived from the Japanese National Health Insurance, health insurance for older people and the LTCI database. Because Japan has a universal health insurance system, we were able to link age trajectories in cognitive function, cause of death, and medical and long-term care costs. The present findings might aid policies for health promotion and preventive care initiatives in the many countries with growing social security cost burdens.

The present study also had limitations. First, the Japanese health insurance system is completely different from the Medicare and Medicaid programs in the USA, and programs in other Western countries.[30] Thus, the estimated healthcare costs in the present study might differ from those in other countries. However, because older persons such as those in the present study population are the people who participate in community-based health checkups and seek care in clinical settings, the present trajectory-specific changes in healthcare costs will likely be applicable to them. Second, the data source for the present study was limited to one rural town and participants in the annual preventive health checkup. To confirm the present findings, data from other study sites or nationally representative data for Japan are required. Third, we calculated monthly medical costs and combined monthly medical and long-term care costs. Although the detailed costs of medical expenses, such as drug prescriptions and underlying disease, might be important in understanding the reasons for the high costs in the third trajectory group, these data were not available for analysis. Future studies should examine the reasons for high medical and long-term care costs.

In conclusion, the present prospective study identified five major trajectory patterns in cognitive function among a general population of community-dwelling older adults. The two lower-trajectory groups had higher risks for death from CVD, as

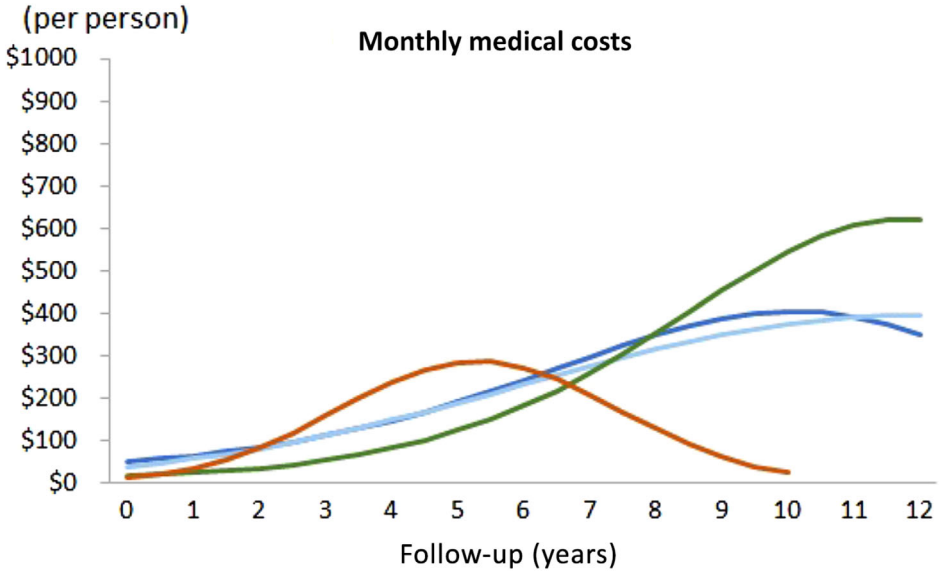

Figure 2 Cognitive function trajectory-specific trends in monthly medical costs. The solid lines are estimated values. (——), High group; (——) Second group; (——) Third group; (——) Fourth & low group.

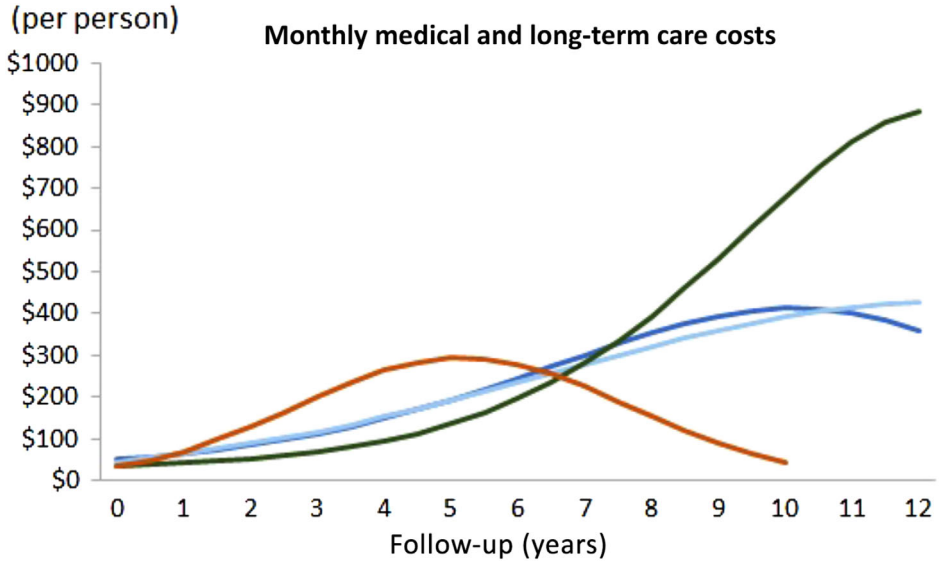

Figure 3 Cognitive function trajectory-specific trends in monthly medical and long-term care costs. The solid lines are estimated values. (——), High group; (——) Second group; (——) Third group; (——) Fourth & ——low group.

compared with the high trajectory group, and the participants in the third trajectory group had a higher risk for non-cancer death. The mean monthly healthcare costs were higher in the two lower-trajectory groups during the first 5 years of follow up. The third trajectory group had the highest healthcare costs after 8 years of follow up, perhaps because of hospitalizations attributable to gradual cognitive decline.

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Disclosure statement

The authors declare no conflict of interest.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Figure S1 Study flow to be eligible for the study

Figure S2 Cognitive function trajectory-specific probability of occurrence for hospitalization. The solid lines are estimated values.

File S1 Other variables in the study.

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