Physical activity and incident dementia in older Japanese adults:

The Okayama Study

Running title

Physical activity and incident dementia

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Data Availability Statement

The data that support the findings of this study are available from the Okayama City Public Health Center. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of Okayama City Public Health Center.

Abstract

Objective:

To evaluate the association between regular physical activity and the risk of incident dementia in older Japanese adults.

Methods:

This was a retrospective cohort study performed in Okayama City, Japan. Overall, 51,477 older Japanese adults were followed from 2008 to 2014. A health checkup questionnaire was used to assess regular physical activity. The Dementia Scale of long-term care insurance was used as a measure of incident dementia. Cox proportional hazard models were used to calculate adjusted hazard ratios, with their 95% confidence intervals, for the incidence of dementia across the categories of physical activity.

Results:

During a 7-year of follow-up, 13,816 subjects were considered as having incident dementia. Compared to participants who performed physical activity ≤ 1 time/week, the multivariate adjusted hazard ratio values (95% confidence intervals) for participants who performed physical activity ≥ 2 times/week but not every day and those who performed physical activity every day were 0.79 (0.75–0.84) and 0.94 (0.89–0.98), respectively. The interaction of physical activity and sex was statistically significant ($p < 0.01$). In subgroup analysis, the multivariate adjusted hazard ratio values (95% confidence intervals) remained low, at 0.76 (0.70–0.84) in males and 0.81 (0.76–0.87) in females who performed physical activity ≥ 2 times/week but not every day; they were 0.82 (0.76–0.89) in males and 1.01 (0.95–1.07) in females who performed physical activity every day.

Conclusions:

Regular physical activity could reduce the risk of incident dementia in older Japanese adults, except females who performed physical activity every day.

Keywords:

cohort study, dementia, elderly, Japanese, long-term care insurance, physical activity

Key-points:

1. Physical activity was defined as follows: sports, fitness, and other such activities–excluding working, housework, walking.
2. The Dementia Scale of long-term care insurance was used as a measure of incident dementia. And it had been shown to be well-correlated with the Hasegawa's Scale and Mini-Mental State Examination.
3. Regular physical activity could reduce the risk of incident dementia in older Japanese adults, except females who performed physical activity every day.

Introduction

Dementia is the leading cause of disability, dependence, and mortality in older adults worldwide.[1] The prevalence of dementia is increasing rapidly (from 4.6% in 1992 to 11.3% in 2012), and the burden of dementia has become a serious medical, social, and economic problem in Japan.[2] However, current drug-based treatments are not effective in reversing or improving the symptoms of dementia.[3] Therefore, it is necessary to identify modifiable risk factors of incident dementia to improve health policies aimed at preventing or delaying the onset of dementia.

Physical activity is considered a modifiable factor associated with incident dementia.[4] Several longitudinal studies[5,6] and meta-analyses[7,8] have suggested that physical activity could reduce the risk of incident dementia and that there is a dose-response relationship between them,[9,10] whereas other studies have not reported this protective effect.[11,12] Apart from inconsistent findings, there are other obvious limitations to the existing studies, such as a small sample size, short follow-up periods, and lack of quality investigations in Asia.[10]

Therefore, to better understand the relationship between physical activity and incident dementia in older Japanese adults, 18,053 males and 33,424 females were examined at baseline and followed up for seven years in Okayama City, Japan. We hypothesized that older adults who performed regular physical activity would have a lower risk of incident dementia.

Methods

Study subjects

The present study was part of the Okayama study, a longitudinal retrospective cohort study

conducted in Okayama city, Okayama prefecture, Japan. Okayama is a city encompassing a wide socioeconomic and urban-rural distribution. To identify modifiable risk factors of diseases in the elderly, it is important and valuable to use real-life data from regular health checkups in Japan. The aim of the Okayama study was to investigate the relationship between behaviors and certification for long-term care insurance (LTCI). The health checkup questionnaire of the present study included questions regarding socio-demographic status, behaviors, medical history, body function, and care information. The requirement for informed consent was waived as this was a retrospective study using anonymized data. The Ethics Committee of the Okayama University Graduate School of Medicine Dentistry and Pharmaceutical Sciences and Okayama University Hospital reviewed and approved the study (approval number K1703-037).

Figure 1 shows the flowchart of the study. From 2006 to 2007, a total of 109,757 elderly subjects who lived in Okayama City and completed the health check questionnaire from the Health Service of the municipal government of Okayama were enrolled. We excluded the following subjects: 41,979 who would be aged less than 65 years in late 2014; 11,878 subjects who received certification for LTCI before baseline; 12 subjects whose time of death was not known; and 4,411 subjects with missing data for physical activity at baseline. Finally, 51,477 subjects were included in our analysis. During the seven-year follow up period from 2008 to 2014, 3,679 subjects were lost to follow-up because of death or migration from the study area. This resulted in a follow-up rate of 92.9%. Among the 300,128.5 person-years, 13,816 subjects were regarded as having incident dementia, and the age-standardized prevalence was 11.4% in 2014.

Assessment of exposure

In the present study, physical activity was defined as follows: sports, fitness, and other such activities—excluding working, housework, or walking—and only exercise as described in Healthy Japan 21 (2nd series) from the Ministry of Health, Labour and Welfare.[13] Physical activity was assessed though the following two questions at baseline: "How many times do you engage in physical activity for more than 30 minutes in a week, and do you engage in physical activity every day?", and "Have you been engaging in physical activity for more than one year?". According to the answers of the self-reported questionnaire, the participants were allocated into the following three groups: physical activity ≤ 1 time per week; ≥ 2 times/week, but not every day; and every day.

Ascertainment of dementia

The LTCI is a national social insurance program in Japan that includes the assessment of physical and mental status and provides the long-term care for older Japanese adults. Briefly, anyone aged more than 65 years who has been paying premiums from the age of 40 years is eligible for application for certification from the municipal government. Subsequently, a care manager will conduct an interview at the elderly person's home to assess their physical and mental health status by using several scales developed by the Ministry of Health, Labour and Welfare. The care managers are licensed professionals with at least 5 years of experience, such as nurses, physicians, social workers, and physical therapists; all agreed to undertake a few days of training about the interview process. According to the results of the care manager's investigation and physician's opinion, the experts of the municipal certification committee for LTCI (who have experience or academic standing in the fields of health, medical treatment, and welfare) determined the certification and its level.[14]

The Dementia Scale of LTCI certification was used as a measure of incident dementia, a process that is objective, fair, and nationally standardized in Japan.[15] Dementia is classified into six ranks (0–IV and M) by the scale. Individuals without dementia are ranked as 0; individuals who had impairment with mild cognitive dysfunction, but who had no dementia-related symptoms or behavioral disturbance and were capable of living independently are ranked as I; and individuals ranked as ≥ II or M (rank M means that the individual has severe dementia-related symptoms and requires medical services) are regarded as having incident dementia.[16,17] In previous studies, the dementia scale of LTCI certification has been shown to be well-correlated with the Hasegawa's Dementia Scale (HDS-R) (Spearman's rank correlation coefficient $\rho = -0.732$) and Mini-Mental State Examination (MMSE) ($\rho = -0.736$),[18] and it has been applied as a measurement of incident dementia in older Japanese adults.[16,19] We obtained LTCI information from the Okayama City Public Health Center under the regulations of privacy protection.

Assessment of covariates

Covariates were assessed through a health checkup questionnaire at baseline in the present study and included the following variables: age (< 65, 65–70, 70–75, or ≥ 75 years), sex, body mass index (BMI, < 18.5, 18.5–23.0, 23.0–27.5, or ≥ 27.5 kg/m^2), current employment (yes/no), current disease (yes/no; including heart disease, hypertension, kidney disease, diabetes mellitus, liver disease, anemia, and hyperlipidemia), self-rated health (health/unhealthy), self-reported mental state (better or good/not good or worse), smoking status (non-smoker/currently), alcohol consumption (non-drinker, light to moderate, or heavy), and eating habits (health/unhealthy).

Statistical analysis

Participants contributed person-years from January 1, 2008 to the date of incident dementia, loss to follow-up (death or emigration from Okayama city), or the end of the follow-up period (December 31, 2014), whichever came first. The Schoenfeld residual test was used to check the proportional hazards assumption ($p = 0.49$). Therefore, Cox proportional hazard models were used to calculate adjusted hazard ratios (HRs) for incidence of dementia with 95% confidence intervals (CIs) across the categories of physical activity. On the basis of National Health and Nutrition Survey in Japan, individuals who performed physical activity of more than 30 minutes at a time and ≥ 2 times per week for more than one year were regarded as having regular physical activity;[20] subsequently, those who performed physical activity ≤ 1 time per week were categorized as references. To investigate the effect of daily physical activity, we also studied the association between daily physical activity and the risk of incident dementia. The following three adjustment models were developed: age and sex were adjusted for first (model 1), followed by adjustment for BMI, current employment, current disease, self-rated health, and self-reported mental state (model 2), and finally, smoking status, alcohol consumption, and eating habits were adjusted (model 3). Interactions between physical activity and each covariate were tested, and stratified models were developed only when the p value for the interaction term was < 0.05. To avoid overestimation of the protective effects as much as possible, we also used the competing-risk regression model (in which death was defined as the competing event) to examine the association between physical activity and incident dementia.

In addition, we performed two sensitivity analyses to test the robustness of our results. First, we excluded participants whose dementia event occurred in the first 2 years of follow-up. Second, we selected participants whose self-reported mental state was better or good at baseline.

All statistical analyses were performed using SPSS, version 25 (IBM Corp., Armonk, NY, USA) and the "cmprsk" package (version 2.2-7) of R, version 3.3.3. All p-values were two-sided and those less than 0.05 were considered statistically significant.

Results

Baseline characteristics

Among 51,477 participants, the mean [SD] age was 71.3 [7.5] years at baseline. Table 1 shows the characteristics of the participants according to the physical activity categories. Participants with higher frequency of physical activity were more likely to be males, self-rated their health status as healthy, and self-reported their mental state as better or good. Participants with lower frequency of physical activity were more likely to have jobs.

Association between physical activity and incident dementia

Table 2 shows the relationship between physical activity and incident dementia. The crude HR value (95% CI) for participants who performed physical activity ≥ 2 times per week but not every day was 0.69 (0.66–0.73), whereas for participants who performed physical activity every day, it was not significant (1.00 [0.96–1.04]). After the adjustment of age and sex in model 1, the HR value (95% CI) for participants who performed physical activity every day became significant, 0.91 (0.87–0.95). Even after multivariate adjustment for all potential confounders in model 3, the HR values (95% CI) remained significantly lower at 0.79 (0.75–0.84) for participants who performed physical activity ≥ 2 times per week but not every day and 0.94 (0.89–0.98) for participants who performed physical activity every day.

Association between physical activity and incident dementia by sex

The interaction of physical activity and sex was statistically significant ($p < 0.01$). To examine possible heterogeneity, we conducted subgroup analysis by sex (Table 3). The crude HR values (95% CI) for participants who performed physical activity ≥ 2 times per week but not every day were 0.73 (0.67–0.78) in males and 0.68 (0.64–0.72) in females, and the values for participants who performed physical activity everyday was 0.93 (0.87–0.99) in males, but no significant (1.07 [1.00–1.13]) association was observed in females. Even after multivariate adjustment for all potential confounders, the HR values (95% CI) remained lower at 0.76 (0.70–0.84) in males and 0.81 (0.76–0.87) in females who performed physical activity ≥ 2 times per week but not every day; they were 0.82 (0.76–0.89) in males and 1.01 (0.95–1.07) in females who performed physical activity every day.

Association between physical activity and incident dementia by competing-risk regression model

Table 4 shows the relationship between physical activity and incident dementia by competing-risk regression model. Even after considering the competing event of death and after multivariate adjustment of all potential confounders, HR values (95% CI) remained lower at 0.82 (0.78–0.86) (0.80 [0.73–0.86] in males and 0.83 [0.79–0.88] in females) among participants who performed physical activity ≥ 2 times per week but not every day; they were 0.95 (0.91–0.99) (0.88 [0.82–0.94] in males and 1.00 (0.95–1.05) in females who performed physical activity every day.

Sensitivity analysis

After excluding the participants whose dementia event occurred within the first 2 years of follow-up (Supplementary Table 1) and including the participants whose answers for the self-

reported mental state were better or good at baseline (Supplementary Table 2), the results of the sensitivity analysis were similar to those of the main analysis.

Discussion

During the 7 years of follow-up, and after adjustment for potential confounders, the results suggested that regular physical activity could reduce the risk of incident dementia among 51,477 older Japanese adults. However, there was no inverse association between performing physical activity every day and incident dementia in females on subgroup analysis.

Many epidemiological studies have shown that an inverse association may exist between physical activity and risk of incident dementia. For instance, in the Canadian Study of Health and Aging with 4,615 adults older than 65 years, Laurin et al.[9] found that there was a significant protective effect of regular physical activity (≥ 3 times per week with intensity greater than walking) against cognitive impairment, Alzheimer's disease, and dementia of any type, during the 5-year follow-up period. In a meta-analysis including five prospective studies, Xu et al.[10] reported that physical activity could play a major role in reducing dementia risk and that there is a dose-response relationship between them. Our results were similar to the results of these studies, and supported the recommendation (≥ 2 times per week) of regular physical activity by Healthy Japan 21 (2nd series).[13] However, we could not find a linear dose-response relationship between a single dimension of physical activity or general physical activity and incident dementia. This may be because we only measured the frequency and duration but not intensity or types of physical activity. In a study of 1,740 older adults, Larson et al.[5] reported that regular exercise (≥ 3 times/week) was associated with a delay in the onset of dementia during a mean

follow-up period of 6.2 years, but they also did not find a dose-response relationship by only dividing the exercise frequency into quartiles, which suggested that it was difficult to conduct the examination when the information of physical activity was insufficient.

Several other studies did not find an association between physical activity and reduced risk of incident dementia. For instance, in the Bronx Aging Study of 469 subjects older than 75 years, Verghese et al.[12] found that there was no association between physical activity and incident dementia during a mean follow-up period of 5.1 years. In the Whitehall II cohort study of 10,308 subjects aged 35–55 years at baseline, Sabia et al.[11] reported that physical activity had no protective effect against dementia during a mean follow-up period of 21.6 years. In a study of 567 older adults aged 70 years or older, Iwasa et al.[21] found that there was no significant protective effect of physical activity (yes/no, such as jogging, walking, Japanese croquet, hiking, dance, swimming and gymnastics) against the cognitive decline in Japanese people. These inconsistent results could be explained by methodological differences in physical activity definition and measurement, ascertainment of dementia, duration of follow-up, and adjusted confounding factors.[11]

Previous studies indicated some differences in the association between physical activity and incident dementia by sex. Laurin et al.[9] found that regular physical activity was associated with a reduced risk of incident dementia only in females. Yang et al.[22] found that physical activity of higher frequency decreased the risk of Alzheimer's disease only in males. In the present study, we also found that sex can modify the association between physical activity and incident dementia ($p < 0.01$). Physical activity ≥ 2 times per week but not every day had a protective effect against dementia for both males and females. However, this relationship

between physical activity every day and incident dementia was only found in males but not in females. The different effects against dementia between males and females may be due to the different types of physical activities that males and females were engaged in, and the different adaptation to physical activity though the difference in brain volume, which is associated with androgens and estrogens.[23,24]

Furthermore, we found that the protective effects of physical activity every day were lower than those of physical activity not every day, especially for older females, and there was no inverse association between physical activity and incident dementia. Based on the National Health and Nutrition Survey 2010 in Japan, only 41.9% (47.6% of males and 37.6% of females) of older adults were engaged in regular physical activity. In order to increase functional capability of daily living in older adults and longer healthy life expectancy, the government set the goal to increase participants by 10%. According to our results regarding daily physical activity, the recommendation of regular physical activity might be not be entirely appropriate; this should be considered in more detail.

If the decedents had both a higher frequency of physical activity at baseline and a high risk of incident dementia, the results may have been distorted. To avoid overestimation of the protective effects, we also used a competing-risk regression model, defining death as a competing event, to examine the relationship between physical activity and incident dementia. As the significant inverse relationships remain unchanged, the decedents may have little effect on our results.

Physical activity may influence the risk of incident dementia in several ways. First, physical activity has an impact on reducing brain atrophy in elderly adults, resulting in a better

attention span and memory.[25] Second, physical activity is associated with a reduction in the deposition of amyloid-β plaques in the form of oligomers which would result in cognitive decline.[26] Third, physical activity promotes positive neuroplasticity and neurogenesis by increasing the number of neurotrophins deriving from the brain (brain-derived neurotropic factor).[27] Finally, physical activity has beneficial effects on cardiovascular risk factors, which are associated with an increased risk of cognitive decline, including hypertension, diabetes mellitus, and obesity.[28]

The strengths of this study include its large sample size, a long follow-up period with a large number of incident dementia cases, a high follow-up rate, and consideration of many confounding factors. Additionally, the present study included the categories of physical activity performed not every day and every day, allowing for assessment of the persistent effects of physical activity. Our study also has several potential limitations. First, this was a retrospective study; thus, compared to other designs that allow for stricter control in prospective longitudinal epidemiological studies, the data used here were from archived records of checkup questionnaires and may be incomplete or inappropriate for research purposes. Second, as not all subjects who completed the health checkup questionnaire were included in our analysis, so that the study may not be free of selection bias. However, a previous study suggested that a proportion of missing data of less than 10% may not influence the results.[29] Third, physical activity was assessed by self-rating using relatively simple questions; thus, misclassifications cannot be ruled out. However, there would be non-differential misclassification or attenuate in the associations compared objective measures of physical activity.[30] Fourth, physical activity was assessed at baseline and we were unable to evaluate changes over the follow-up period for

the individuals under 65 years. However, behaviors have been shown to be relatively stable over time in older adults, except in those with a serious illness or those close to death.[31] Fifth, dementia states of participants were not confirmed at baseline; thus, reverse causation cannot be completely ruled out. However, the results of sensitivity analysis were consistent with those of our main analysis. In addition, a previous study has suggested that people with cognitive impairment, or dementia could also benefit from physical activity.[32] Sixth, we did not take into consideration the cause of dementia. A study reported that physical activity was associated with reduced risks of developing dementia of any type.[9] Whereas, in the Hisayama study, Yoshitake et al.[33] reported that physical activity was a significant preventive factor only for Alzheimer's disease but not for vascular dementia in Japan. Therefore, the relationship between physical activity and each subtype of dementia in Japan must be confirmed in a future study. Finally, although we modeled for numerous potential confounders, the results might have still been influenced by other factors such as education or socioeconomic status; however, the health inequalities (including income and education attainment) were relatively insignificant or absent in older Japanese adults,[34] and after adjusting for employment, the results were unchanged.

In conclusion, regular physical activity could reduce the risk of incident dementia in older Japanese adults, but not in females who were engaged in physical activity every day. Our finding suggests that physical activity may delay or prevent the onset of dementia in Japan.

Reference

1. Satizabal CL, Beiser AS, Chouraki V, Chene G, Dufouil C, Seshadri S. Incidence of Dementia over Three Decades in the Framingham Heart Study. The New England journal of medicine. 2016;374(6):523-532.
2. Ohara T, Hata J, Yoshida D, et al. Trends in dementia prevalence, incidence, and survival rate in a Japanese community. Neurology. 2017;88(20):1925-1932.
3. Casey DA, Antimisiaris D, O'Brien J. Drugs for Alzheimer's disease: are they effective? Pharmacy and Therapeutics. 2010;35(4):208.
4. Frankish H, Horton R. Prevention and management of dementia: a priority for public health. The Lancet. 2017;390(10113):2614-2615.
5. Larson EB, Wang L, Bowen JD, et al. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. Annals of internal medicine. 2006;144(2):73-81.
6. Llamas-Velasco S, Contador I, Villarejo-Galende A, Lora-Pablos D, Bermejo-Pareja F. Physical activity as protective factor against dementia: a prospective population-based study (NEDICES). Journal of the International Neuropsychological Society. 2015;21(10):861-867.
7. Blondell SJ, Hammersley-Mather R, Veerman JL. Does physical activity prevent cognitive decline and dementia?: A systematic review and meta-analysis of longitudinal studies. BMC public health. 2014;14(1):510.
8. Guure CB, Ibrahim NA, Adam MB, Said SM. Impact of physical activity on cognitive decline, dementia, and its subtypes: meta-analysis of prospective studies. BioMed

research international. 2017;2017.

9. Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. Archives of neurology. 2001;58(3):498-504.

10. Xu W, Wang HF, Wan Y, Tan C-C, Yu J-T, Tan L. Leisure time physical activity and dementia risk: a dose-response meta-analysis of prospective studies. BMJ open. 2017;7(10):e014706.

11. Sabia S, Dugravot A, Dartigues J-F, et al. Physical activity, cognitive decline, and risk of dementia: 28 year follow-up of Whitehall II cohort study. Bmj. 2017;357:j2709.

12. Verghese J, Lipton RB, Katz MJ, et al. Leisure activities and the risk of dementia in the elderly. New England Journal of Medicine. 2003;348(25):2508-2516.

13. Ministry of Health, Labour and Welfare. Health Japanese 21 (the second). https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/kenkou/kenkounippon21.html. Accessed September 4, 2018.

14. Olivares-Tirado P, Tamiya N. Trends and Factors in Japan's Long-Term Care Insurance System: Japan's 10-year Experience. Berlin: Springer Science & Business Media; 2013. 52P

15. Tsutsui T, Muramatsu N. Care-needs certification in the long-term care insurance system of Japan. Journal of the American geriatrics society. 2005;53(3):522-527.

16. Zhang S, Tomata Y, Sugiyama K, Sugawara Y, Tsuji I. Mushroom Consumption and Incident Dementia in Elderly Japanese: The Ohsaki Cohort 2006 Study. Journal of the American Geriatrics Society. 2017;65(7):1462-1469.

17. Ikeda A, Yamagishi K, Tanigawa T, et al. Cigarette smoking and risk of disabling dementia in a Japanese rural community: a nested case-control study. Cerebrovascular diseases. 2008;25(4):324-331.

18. Hisano S. The relationship between revised Hasegawa dementia scale (HDS-R), mini-mental state examination (MMSE) and bed-fast scale, dementia scale. Jpn J Geriatr Psychiatry. 2009;20:883-891.

19. Yamamoto T, Kondo K, Hirai H, Nakade M, Aida J, Hirata Y. Association between self-reported dental health status and onset of dementia: a 4-year prospective cohort study of older Japanese adults from the Aichi Gerontological Evaluation Study (AGES) Project. Psychosomatic medicine. 2012;74(3):241-248.

20. Ministry of Health, Labour and Welfare. National Health and Nutrition Survey. http://www.mhlw.go.jp/bunya/kenkou/kenkou_eiyou_chousa.html. Accessed June 9, 2018.

21. Iwasa H, Yoshida Y, Kai I, Suzuki T, Kim H, Yoshida H. Leisure activities and cognitive function in elderly community-dwelling individuals in Japan: a 5-year prospective cohort study. Journal of psychosomatic research. 2012;72(2):159-164.

22. Yang S-Y, Weng P-H, Chen J-H, et al. Leisure activities, apolipoprotein E e4 status, and the risk of dementia. Journal of the Formosan Medical Association. 2015;114(12):1216-1224.

23. Taki Y, Kinomura S, Sato K, Goto R, Kawashima R, Fukuda H. A longitudinal study of gray matter volume decline with age and modifying factors. Neurobiology of Aging. 2011;32(5):907-915.

410 24. Yuki A, Lee S, Kim H, Kozakai R, Ando F, Shimokata H. Relationship between
411 physical activity and brain atrophy progression. Medicine and science in sports and
412 exercise. 2012;44(12):2362-2368.
413 25. Erickson KI, Leckie RL, Weinstein AM. Physical activity, fitness, and gray matter
414 volume. Neurobiology of aging. 2014;35:S20-S28.
415 26. Adlard PA, Perreau VM, Pop V, Cotman CW. Voluntary exercise decreases amyloid
416 load in a transgenic model of Alzheimer's disease. Journal of Neuroscience.
417 2005;25(17):4217-4221.
418 27. Piepmeier AT, Etnier JL. Brain-derived neurotrophic factor (BDNF) as a potential
419 mechanism of the effects of acute exercise on cognitive performance. Journal of Sport
420 and Health Science. 2015;4(1):14-23.
421 28. Murtagh EM, Nichols L, Mohammed MA, Holder R, Nevill AM, Murphy MH. The
422 effect of walking on risk factors for cardiovascular disease: an updated systematic
423 review and meta-analysis of randomised control trials. Preventive medicine.
424 2015;72:34-43.
425 29. Hancock GR, Mueller RO, Stapleton LM. New York: The reviewer’s guide to
426 quantitative methods in the social sciences. Routledge; 2010. 439P
427 30. Middleton LE, Manini TM, Simonsick EM, et al. Activity energy expenditure and
428 incident cognitive impairment in older adults. Archives of internal medicine.
429 2011;171(14):1251-1257.
430 31. Artaud F, Dugravot A, Sabia S, Singh-Manoux A, Tzourio C, Elbaz A. Unhealthy
431 behaviours and disability in older adults: Three-City Dijon cohort study. Bmj.

2013;347:f4240.

32. Lam FM, Huang M-Z, Liao L-R, Chung RC, Kwok TC, Pang MY. Physical exercise improves strength, balance, mobility, and endurance in people with cognitive impairment and dementia: a systematic review. Journal of physiotherapy. 2018;64(1):4-15.

33. Yoshitake T, Kiyohara Y, Kato I, et al. Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population The Hisayama Study. Neurology. 1995;45(6):1161-1168.

34. Kondo K, Ashida T, Hirai H, Misawa J, Suzuki K. The relationship between socio-economic status and the loss of healthy aging, and relevant gender differences in the Japanese older population: AGES Project longitudinal study. Iryo To Syakai. 2012;22:19-30.

Table 1 Demographic characteristics of the participants at baseline

Characteristics	All	Physical activity		
		≤ 1 time/week	≥ 2 times/week	
			not every day	every day
No. of participants	51477	31038	9471	10968
Age, years, mean (SD)	71.3 ± 7.5	71.2 ± 7.8	70.3 ± 6.9	72.5 ± 7.0
Sex, n (%)				
Male	18053 (35.1)	9833 (31.7)	3367 (35.6)	4854 (44.3)
Female	33424 (64.9)	21205 (68.3)	6104 (64.4)	6114 (55.7)
Current employment, n (%)				
Yes	15651 (30.4)	10333 (33.3)	2514 (26.5)	2804 (25.6)
No	32654 (63.4)	18805 (60.6)	6488 (68.5)	7361 (67.1)
Missing category	3172 (6.2)	1900 (6.1)	469 (5.0)	803 (7.3)
Current diseases, n (%)				
Yes	29730 (57.8)	17583 (56.6)	5378 (56.8)	6769 (61.7)
No	20478 (39.8)	12667 (40.8)	3896 (41.1)	3915 (35.7)
Missing category	1269 (2.5)	788 (2.5)	197 (2.1)	284 (2.6)
Self-rated health, n (%)				
Healthy	45198 (87.8)	26695 (86.0)	8546 (90.2)	9957 (90.8)
Unhealthy	5019 (9.7)	3496 (11.3)	745 (7.9)	778 (7.1)
Missing category	1260 (2.4)	847 (2.7)	180 (1.9)	233 (2.1)
Self-reported mental state, n (%)				
Better, good	44324 (86.1)	26123 (84.2)	8423 (88.9)	9778 (89.2)
Not good, worse	4897 (9.5)	3414 (11.0)	717 (7.6)	766 (7.0)
Missing category	2256 (4.4)	1501 (4.8)	331 (3.5)	424 (3.9)
BMI (kg/m^2), n (%)				
Underweight (< 18.5)	3755 (7.3)	2433 (7.8)	543 (5.7)	779 (7.1)
Normal (18.5–23.0)	23083 (44.8)	13557 (43.7)	4494 (47.5)	5032 (45.9)
Overweight (23.0–27.5)	20262 (39.4)	12105 (39.5)	3756 (39.7)	4401 (40.1)
Obesity (≥ 27.5)	4336 (8.4)	2917 (9.4)	671 (7.1)	748 (6.8)
Missing category	41 (0.1)	26 (0.1)	7 (0.1)	8 (0.1)
Smoking status, n (%)				
Non-smoker	45734 (88.8)	27458 (88.5)	8628 (91.1)	9648 (88.0)
Currently	5495 (10.7)	3435 (11.1)	807 (8.5)	1253 (11.4)
Missing category	248 (0.5)	145 (0.5)	36 (0.4)	67 (0.6)
Alcohol consumption, n (%)				
Non-drinker	32548 (63.2)	20473 (66.0)	5513 (58.2)	6562 (59.8)
Light-to-moderate	14905 (29.0)	8171 (26.3)	3293 (34.8)	3441 (31.4)
Heavy	2767 (5.4)	1642 (5.3)	461 (4.9)	664 (6.1)
Missing category	1257 (2.4)	752 (2.4)	204 (2.2)	301 (2.7)

Eating habits, n (%)				
Healthy	46336 (90.0)	28664 (92.4)	8188 (86.5)	9484 (86.5)
Unhealthy	5140 (10.0)	2373 (7.6)	1283 (13.5)	1484 (13.5)
Missing category	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: BMI, Body mass index; SD, standard deviation

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Table 2 Hazard ratios for incidence of dementia associated with physical activity

	Physical activity		
	≤ 1 time/week	≥ 2 times/week	
		not every day	every day
No. of participants	31038	9471	10968
Person-years	178790.0	58119.5	63219.0
No. of events	8748	1968	3100
Crude HR (95% CI)	1.00 (reference)	0.69 (0.66–0.73) *	1.00 (0.96–1.04)
Adjusted Model 1[†]	1.00 (reference)	0.77 (0.74–0.81) *	0.91 (0.87–0.95) *
Adjusted Model 2[‡]	1.00 (reference)	0.78 (0.74–0.82) *	0.93 (0.87–0.97) *
Adjusted Model 3[§]	1.00 (reference)	0.79 (0.75–0.84) *	0.94 (0.89–0.98) *

Abbreviation: HR, hazard radio; CI, confidence interval; * $p < 0.05$; [†]Adjusted age (< 65, 65–70, 70–75 or ≥ 75 years) and sex; [‡]Adjusted model 1 plus current employment (yes, no, or missing), current disease (yes, no, or missing), self-rated health status (healthy, unhealthy, or missing), self-reported mental state (better or good, not good or worse, or missing), BMI (< 18.5, 18.5–23.0, 23.0–27.5, ≥ 27.5, or missing); [§]Adjusted model 2 plus smoking status (non-smoker, current, or missing), alcohol consumption (non-drinker, light-to-moderate, heavy, or missing), eating habits (healthy, unhealthy, or missing)

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Table 3 Hazard ratios for incidence of dementia associated with physical activity by sex

	Physical activity		
	≤ 1 time/week	≥ 2 times/week	
		not every day	every day
Male			
No. of participants	9833	3367	4854
Person-years	55399.5	20420.5	27960.0
No. of events	2613	697	1225
Crude HR (95% CI)	1.00 (reference)	0.73 (0.67–0.78) *	0.93 (0.87–0.99) *
Adjusted Model 1†	1.00 (reference)	0.73 (0.67–0.79) *	0.82 (0.77–0.88) *
Adjusted Model 2‡	1.00 (reference)	0.74 (0.68–0.81) *	0.81 (0.75–0.88) *
Adjusted Model 3§	1.00 (reference)	0.76 (0.70–0.84) *	0.82 (0.76–0.89) *
Female			
No. of participants	21205	6104	6114
Person-years	123390.5	37699.0	35259.0
No. of events	6135	1271	1875
Crude HR (95% CI)	1.00 (reference)	0.68 (0.64–0.72) *	1.07 (1.02–1.13)
Adjusted Model 1†	1.00 (reference)	0.80 (0.75–0.85) *	0.97 (0.92–1.02)
Adjusted Model 2‡	1.00 (reference)	0.80 (0.75–0.85) *	1.00 (0.95–1.06)
Adjusted Model 3§	1.00 (reference)	0.81 (0.76–0.87) *	1.01 (0.95–1.07)

Abbreviation: HR, hazard radio; CI, confidence interval; * $p < 0.05$; †Adjusted age (< 65, 65–70, 70–75, or ≥ 75 years); ‡Adjusted model 1 plus current employment (yes, no, or missing), current disease (yes, no, or missing), self-rated health (healthy, unhealthy, or missing), self-reported mental state (better or good, not good or worse, or missing), BMI (< 18.5, 18.5–23.0, 23.0–27.5, ≥ 27.5, or missing); §Adjusted model 2 plus smoking status (non-smoker, current, or missing), alcohol consumption (non-drinker, light-to-moderate, heavy, or missing), eating habits (healthy, unhealthy, or missing)

Table 4 Hazard ratios for incidence of dementia associated with physical activity by competing-risk regression model

	Physical activity		
	≤ 1 time/week	≥ 2 times/week	
		not every day	every day
No. of participants	31038	9471	10968
Person-years	178790.0	58119.5	63219.0
No. of events (dementia)	8748	2816	3100
Competing events (death)	1826	424	714
Crude HR (95% CI)	1.00 (reference)	0.70 (0.67-0.74) *	1.00 (0.96-1.04)
Adjusted Model 1†	1.00 (reference)	0.79 (0.75-0.83) *	0.92 (0.89-0.96) *
Adjusted Model 2‡	1.00 (reference)	0.80 (0.77-0.84) *	0.95 (0.91-0.98) *
Adjusted Model 3§	1.00 (reference)	0.82 (0.78-0.86) *	0.95 (0.91-0.99) *
Subgroups of sex¶			
Male	1.00 (reference)	0.80 (0.73-0.86) *	0.88 (0.82-0.94) *
Female	1.00 (reference)	0.83 (0.79-0.88) *	1.00 (0.95-1.05)

Abbreviation: HR, hazard radio; CI, confidence interval; *$p < 0.05$; †Adjusted age (< 65, 65–70, 70–75, or ≥ 75 years) and sex; ‡Adjusted model 1 plus current employment (yes, no, or missing), current disease (yes, no, or missing), self-rated health (healthy, unhealthy, or missing), self-reported mental state (better or good, not good or worse, or missing), BMI (< 18.5, 18.5–23.0, 23.0–27.5, ≥ 27.5, or missing); §Adjusted model 2 plus smoking status (non-smoker, current, or missing), alcohol consumption (non-drinker, light-to-moderate, heavy, or missing), eating habits (healthy, unhealthy, or missing); ¶Adjusted for the same covariates in Model 3 without sex

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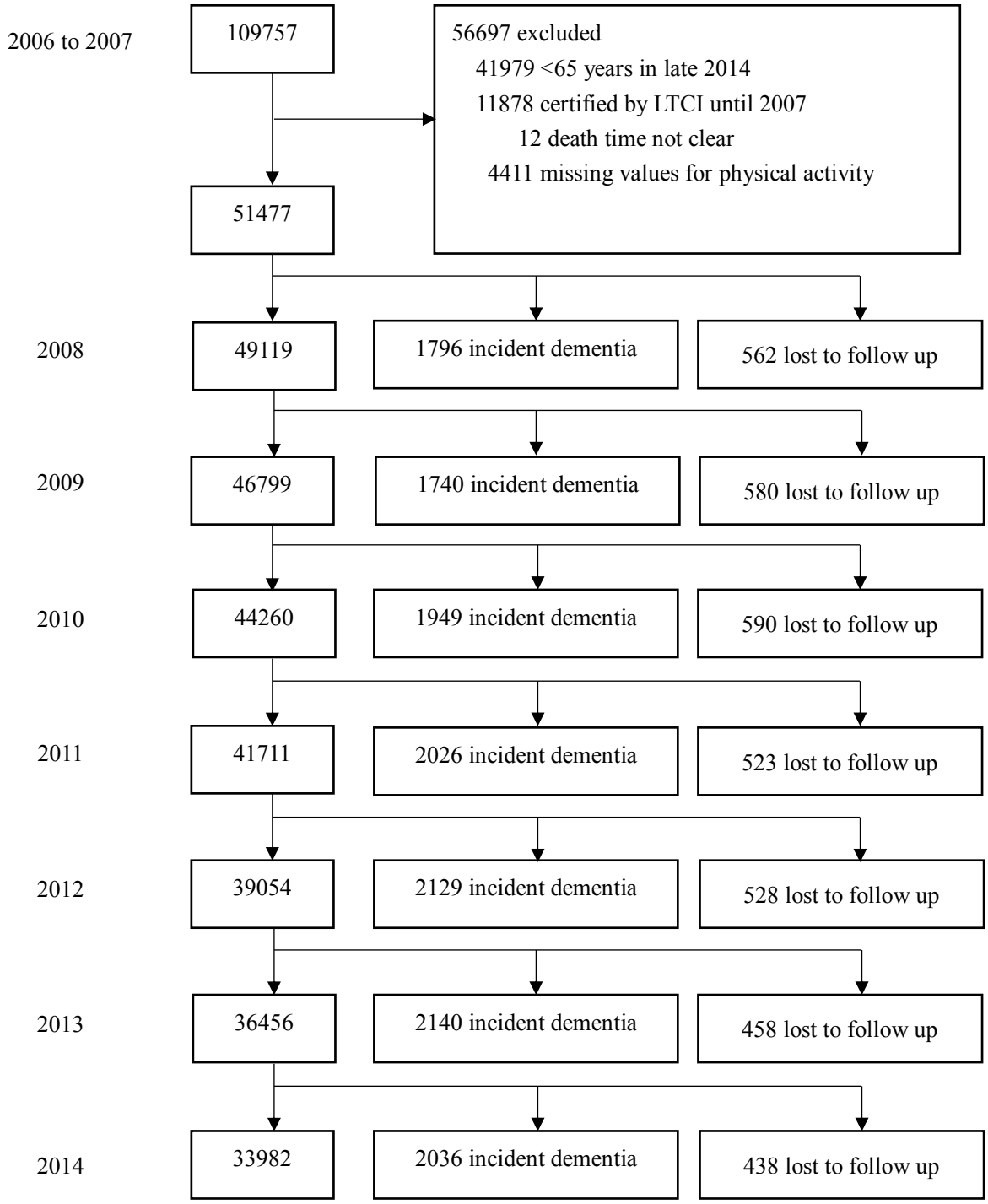

Figure 1. Flowchart of study participants

Abbreviation: LTCI, long-term care insurance

Lost to follow up: including death or migration