Title: The impact of various intensities and frequencies of non-occupational physical activity on the risk of dementia among physically independent older adults: The Japan Gerontological Evaluation Study

Running title: Physical activity and dementia

Authors: Ahmed Arafa[a,b], Ehab S. Eshak[a,c], Kokoro Shirai[a], Dorina Cadar[d], Hiroyasu Iso[a], Taishi Tsuji[e], Satoru Kanamori[f,g], Katsunori Kondo[h,i]

[a] Public Health, Department of Social Medicine, Osaka University Graduate School of Medicine, Osaka, Japan

[b] Department of Public Health, Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt

[c] Department of Public Health, Faculty of Medicine, Minia University, El-Minia, Egypt

[d] Department of Behavioral Science and Health, University College London, London, UK

[e] Faculty of Health and Sport Sciences, University of Tsukuba, Tokyo, Japan

[f] Teikyo University Graduate School of Public Health, Tokyo, Japan

[g] Department of Preventive Medicine and Public Health, Tokyo Medical University, Tokyo, Japan

[h] Department of Social Preventive Medical Sciences, Center for Preventive Medical Sciences, Chiba University, Chiba, Japan.

[i] Center for Gerontology and Social Science, National Center for Geriatrics and Gerontology, Aichi, Japan

Correspondence: Hiroyasu Iso, MD, Ph.D., MPH, Professor of Public Health, Department of Social Medicine, Osaka University Graduate School of Medicine, Suita-shi, Osaka 565-0871, Japan. Phone: +81-6-6879-3911; Fax: +81-6-6879-3919; E-mail: iso@pbhel.med.osaka-u.ac.jp

Text word count: 2575

Tables: 5, **Figures:** 1, **Supplementary files:** 1

1

Abstract

Objectives: To investigate the association between different intensities and frequencies of non-occupational physical activity (PA) and the risk of dementia among Japanese older adults.

Study design: This was a prospective cohort study.

Methods: A total of 2194 participants aged ≥ 65 years from the Japan Gerontological Evaluation Study were followed up between 2010 and 2016. The standardized dementia scale of the long-term care insurance system was used to identify incident dementia while non-occupational PA (< or ≥ 2 times/week on each intensity: light, moderate, and vigorous) was assessed using a questionnaire. The Cox regression was used to compute the hazard ratios (HRs) and 95% confidence intervals (CIs) for incident dementia.

Results: After adjustment for sociodemographic and medical characteristics, various frequencies and intensities of non-occupational PA, compared with no non-occupational PA at all, were associated with reduced risk of dementia: [(light PA: ≥ 2 times/week: HR= 0.61, 95% CI: 0.38-0.97), (moderate PA: < 2 times/week: HR= 0.46, 95% CI: 0.28-0.76 and ≥ 2 times/week: HR= 0.57, 95% CI: 0.36-0.91), and (vigorous PA: < 2 times/week: HR= 0.40, 95% CI: 0.21-0.74 and ≥ 2 times/week: HR= 0.29, 95% CI: 0.15-0.57)]. In the sex-specific analysis, moderate PA< 2 times/week and vigorous PA ≥ 2 times/week were associated with the reduced risk of dementia in men while light and moderate PA ≥ 2 times/week and all frequencies of vigorous PA were associated with the reduced risk of dementia in women.

Conclusion: Practicing non-occupational PA was associated with a reduced risk of dementia among Japanese older adults.

Keywords: Older adults; physical activity; dementia; cohort study

Highlights

- Non-occupational physical activity, even light intensity, was associated with a reduced risk of dementia among older adults.
- Older women gained more protective benefits against dementia from light and moderate physical activity than older men.

Introduction

Along with the aging population in Japan, the prevalence and burden of dementia have been increasing rapidly making it a serious public health concern. Throughout the past decade, the number of patients with dementia in the country has more than doubled (0.42 million in 2002 versus 1.05 million in 2014). The total social burden has witnessed a similar rise (184 to 242 billion US$ in 2002 versus 379 to 551 billion US$ in 2014). [1]

Several modifiable lifestyle factors such as social isolation, stress, and unhealthy diets are associated with the risk of dementia. [2-4] However, behavioral interventions in the form of social engagement, stress relief, and healthy dietary changes can reduce this risk. [5-7] Thus, identifying other modifiable lifestyle risk factors for dementia, to implement risk-prevention approaches and health initiatives, should be prioritized.

One of these factors; physical activity (PA) carries significant benefits for many chronic diseases related to dementia such as coronary artery ischemia, stroke, dyslipidemia, hypertension, and insulin resistance. [8] Indeed, PA improves cerebral health via enhancing blood flow in the neural circuits involved in cognitive functioning. [9] It can also induce brain expression of neurotrophic factors such as brain-derived neurotrophic factors that induce synaptic function and promote the survival of neurons affected by neurodegenerative diseases. [10,11]

Although the favorable impacts of PA on cognitive functions have been documented in clinical settings [12], there are significant inconsistencies among the epidemiological studies regarding its protective role against the development of dementia. For example, previous

cohort studies conducted on older adults in the US [13], Spain [14], and China [5] showed that PA was associated with minimized risk of dementia whereas other cohort studies conducted on older adults in Australia [15], Nigeria [16], and the Netherlands [17] did not reach the same conclusion. Besides, the question of whether PA intensity and frequency can modify this protective role is still without a clear-cut answer. [18,19] We, therefore, used the data of the Japan Gerontological Evaluation Study (JAGES) to investigate the prospective association between different intensities and frequencies of non-occupational PA and the risk of dementia among older adults in Japan.

Participants and Methods

Study population and baseline questionnaire

The protocol and baseline self-administered questionnaire of the JAGES were described elsewhere. [20,21] Briefly, the JAGES 2010 is a population-based study covering 31 municipalities in 12 prefectures and focusing on the social determinants of several health conditions among the physically independent older adults (≥ 65 years) in Japan. Physically independent older adults were defined as older adults who could bathe without assistance. A randomly selected subsample (almost 20%) of older adults in two municipalities (Kashiwa and Nagoya) included in the JAGES 2010 received, in addition to the regular JAGES questionnaire, another questionnaire assessing their non-occupational PA. A convenience sampling approach was used to select the two municipalities based on their cooperation. Kashiwa is a city located in Chiba Prefecture with 433,436 people and Nagoya is the Capital of Aichi Prefecture with 2,327,557 people. Among the older adults who received non-occupational PA questionnaires, a response rate of 62.6% was detected. Since we had no data on non-respondents, we were not able to detect the differences, if any, between respondents and non-respondents. Besides, questionnaires lacking data on age, sex, and non-occupational PA were excluded. Also, older adults who did not meet our eligibility criteria for physical

independence and those who were not linked to the dementia records were excluded. Eventually, a total of 2194 older adults were followed up between 2010 and 2016 and included in the analysis (Figure 1).

Exposure

Three intensities of non-occupational PA (vigorous, moderate, and light) were assessed using the following questions in the JAGES baseline questionnaire: "*Without including activities at work, I would like to ask about your regular PA (exercise, sports, activities, housework, etc.)*."; Light PA: "*Do you practice the same level of activity as in stretching, bowling, walking, shopping, or going out, etc.*?"; Moderate PA: "*Do you practice the same level of activity as in jogging, dancing, farming and garden work, or gymnastics, etc.*?"; Vigorous PA: "*Do you practice the same level of activity as in running, swimming, cycling, tennis, or mountain climbing, etc.*?". Subjects were asked to pick one of the following four choices for each of the three questions: "*Never, 1 to 3 times/month, about once/week, or ≥ 2 times/week*". The same exposure with the same question format was used in a previous study from the JAGES. [22]

Outcome

We used the standardized dementia scale (0 to IV) to evaluate incident dementia. This scale was used in the public long-term care insurance (LTCI) system [23] and its validity and reliability were documented elsewhere. [24,25] In the present study, the diagnosis of dementia was set when the participant manifested symptoms, behaviors, or communication difficulties hindering daily activities and equating to ≥ level II on the LTCI dementia scale. This cut-off was documented in a nationwide survey to be sensitive for disabling dementia. [26] The same diagnosis was used in previous studies from the JAGES. [27-30]

Statistical analyses

The frequencies of 1 to 3 times/month and about once/week were merged into one category (< 2 times/week) to obtain statistical power. Subjects who selected the response "*never*" for light, moderate, and vigorous non-occupational PA were considered inactive. The Chi-squared test was used to detect the baseline differences between active and inactive subjects per PA intensity. The Cox proportional hazards models were used to calculate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for incident dementia among the active versus the inactive older adults per PA intensity with and without their frequencies over the follow-up period. Person-years of follow-up were censored at the date of dementia diagnosis, death, or end of the study, whichever came first. Based on prior literature [31], the following covariates were included in the regression models as potential confounders: age (65-75 or ≥ 75 years), sex (men or women), the municipality (Kashiwa or Nagoya), body mass index (BMI) (< 23 or ≥ 23 kg/m^2), marital status (currently married or others), annual income (< 3 or ≥ 3 million yen/year), years of education (< 10 or ≥ 10 years), smoking behavior (current smoker or current non-smoker), alcohol intake (current alcohol consumer or current alcohol non-consumer), and histories of hypertension, diabetes, and hyperlipidemia (yes or no). Interactions with sex (men versus women) and age category (65-75 versus ≥ 75 years) were calculated in stratified analyses. Missing data were treated using a dummy-variable adjustment approach. Later, we conducted sensitivity analyses by excluding older adults who were censored during the first couple of years of follow-up, whether due to loss to follow-up or developing dementia, to guard against the possibility of reverse causation. The software, Statistical Package for Social Science (SPSS) Released in 2013, IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp was used for data analysis.

Results

This study included 2194 older adults with a mean age ± standard deviation of 73.6 ± 5.4 years, 51.3% were men, 37.8% were aged ≥ 75 years, and 73% were currently married. The majority of older adults reported practicing different intensities of non-occupational PA: light PA (22.3%), moderate (38.7%), and vigorous PA (23.7%) (Table 1).

Throughout a median follow-up period of 5.2 years, 194 (8.8%) of older adults developed dementia. In general, the more vigorous PA intensities, regardless of frequency, were positively associated with a more protective effect against dementia in the overall, sex-stratified, and age-stratified analyses (p-values for trend < 0.05) (Table 2).

Older adults who practiced light PA ≥ 2 times/week or any frequency of moderate or vigorous PA were less likely to develop dementia compared with those who did not practice non-occupational PA at all in the models adjusted for age, sex, and area. The incidence of dementia was as follows: no non-occupational PA at all 17.0%, < 2 times/week light PA 14.2%, ≥ 2 times/week light PA 9.9%, < 2 times/week moderate PA 6.1%, ≥ 2 times/week moderate PA 7.5%, < 2 times/week vigorous PA 5.4%, and ≥ 2 times/week vigorous PA 4.2%. After further adjustment for BMI, marriage, education, annual income, smoking, alcohol intake, hypertension, diabetes, and hyperlipidemia, all frequencies of PA, but one (light PA: < 2 times/week: HR= 0.90, 95% CI: 0.51-1.58), were associated with lower dementia risk than those who did not practice non-occupational PA at all: [(light PA: ≥ 2 times/week: HR= 0.61, 95% CI: 0.38-0.97), (moderate PA: < 2 times/week: HR= 0.46, 95% CI: 0.28-0.76 and ≥ 2 times/week: HR= 0.57, 95% CI: 0.36-0.91), and (vigorous PA: < 2 times/week: HR= 0.40, 95% CI: 0.21-0.74 and ≥ 2 times/week: HR= 0.29, 95% CI: 0.15-0.57)] (Table 3). Sensitivity analyses after excluding 133 older adults who were censored during the first couple of years of follow-up did not materially change the incidence of dementia and the HRs (95% CIs) of the associations between different intensities of PA and the risk of dementia (Supplementary Table 1).

Among men, light and frequent moderate PA were not significantly associated with a reduced risk of dementia while vigorous PA ≥ 2 times/week was associated with the reduced risk of dementia (HR= 0.21, 95% CI: 0.07-0.62). Among women frequent light and moderate PA and vigorous PA regardless of frequency were associated with the reduced risk of dementia [(light PA ≥ 2 times/week: HR= 0.50, 95% CI: 0.27-0.95), (moderate PA ≥ 2 times/week: HR= 0.35, 95% CI: 0.16-0.76), (vigorous PA < 2 times/week: HR= 0.24, 95% CI: 0.08-0.72), and (vigorous PA ≥ 2 times/week: HR= 0.22, 95% CI: 0.08-0.63)]. However, we did not find a significant sex interaction with a p-value for interaction > 0.10 (Table 4).

Older adults aged ≥ 75 years who practiced vigorous PA showed reduced risk of dementia [(vigorous PA < 2 times/week: HR= 0.37, 95% CI: 0.17-0.83) and (vigorous PA ≥ 2 times/week: HR= 0.40, 95% CI: 0.18-0.90)]. The p-value for interaction with age-category was > 0.10 (Table 5).

Discussion

This study indicated that practicing different intensities of non-occupational PA was associated with reduced risk of dementia among the physically independent Japanese older adults aged ≥ 65 years. Overall, engaging in vigorous intensities of PA showed more protective effects than lighter intensities, and higher frequencies of light and vigorous PA were superior to lower frequencies in terms of dementia prevention. Among men, moderate PA< 2 times/week and vigorous PA ≥ 2 times/week were associated with the reduced risk of dementia while light and moderate PA ≥ 2 times/week and any frequency of vigorous PA was associated with the reduced risk of dementia among women. The protective effect of vigorous PA remained evident among older adults aged ≥ 75 years. Excluding older adults who were censored during the first two years of follow-up did not alter the results. Our findings support the "*Active Guide*" published by the Japanese Ministry of Health, Labor, and Welfare calling on older adults to perform moderate to vigorous PA daily. [32]

Of note, the dose-response relationship between PA and dementia is controversial. Our results showed a more protective effect among vigorous intensities and high frequencies of PA. A meta-analysis of a limited number of studies showed that every 500 kcal of non-occupational PA increase per week was associated with a 10% decrease in the risk of dementia. [33] In contrast, a meta-analysis of 17 prospective cohort studies showed a slight difference in the reduction of dementia risk between moderate and vigorous PA; 24% and 21%, respectively, however, it revealed a significant difference in the reduction of cognitive decline risk between both intensities; 33% for vigorous PA and 26% for moderate PA. Still, this meta-analysis was limited by the heterogenous categorizations of PA across studies. [34] Unexpectedly, older men, not women, who reported moderate PA < 2 times/week in our study developed fewer incident dementia than those who reported the same intensity of PA but ≥ 2 times/week; 5.6% versus 9.5% which adds to the complexity of the dose-response relationship between PA and dementia. On the other hand, older women, not men, who practiced light or moderate PA ≥ 2 times/week showed a reduced risk of dementia while vigorous PA ≥ 2 times/week was associated with the reduced risk of dementia in both sexes. Therefore, it could be concluded, in general, that higher intensities and frequencies of PA would be more protective than lower ones.

There are several sex-specific differences in dementia genetic, cardiovascular, hormonal, inflammatory, and social risk factors [35], and we also noticed in this study that women gained more protective benefits from light and moderate PA, which equates to walking and jogging, than men. A previous study that investigated the sex-specific relationship between walking and the risk of cognitive declines measured by hippocampal structure, detected a significant association between walking and larger hippocampal volumes among older women but not among older men, indicating more cognitive improvement after walking in older women only. [36] However, our results showed that the

protective effect of vigorous PA against dementia did not differ significantly across sexes which agreed with a previous meta-analysis: [(men: HR= 0.77, 95% CI: 0.68-0.86) versus (women: HR= 0.78, 95% CI: 0.64-0.91)]. [34]

We could also notice that despite older adults ≥ 75 years constituted 37.8% of our study population, they constituted 49.1% of older adults not practicing non-occupational PA at all. However, when we stratified our results by age category, vigorous PA whether < or ≥ 2 times/week was associated with the reduced risk of dementia in the age category ≥ 75 years.

It was suggested that PA could protect from dementia by reducing the risk of cardiovascular diseases, a known risk factor for dementia. [37] Yet, when we controlled for numerous cardiovascular risk factors, PA remained significantly associated with the decreased risk of dementia, suggesting that PA has an independent protective effect against dementia.

Although this study described the association between different intensities and frequencies of non-occupational PA and the risk of dementia among physically independent older adults using a prospective design and adjusted for most confounders, several limitations should be addressed. First, Kashiwa and Nagoya are two urban municipalities, therefore, generalizing our results to rural areas should be done cautiously. Second, whereas different types of dementia have various pathogenesis factors, we defined our outcome as all-cause dementia. [38] However, a previous meta-analysis showed that PA was associated with a reduced risk of different types of dementia. [39] Third, engaging in non-occupational PA was subjectively evaluated by self-report making the exposure vulnerable to recall, misclassification, and social desirability forms of bias. Fourth, we had no information on the duration of practicing non-occupational PA, thus, a precise dose-response could not be calculated. Fifth, baseline characteristics of our study population showed that older adults who reported moderate and vigorous PA were significantly younger, more educated, with

higher income, but with a higher prevalence of hypertension, diabetes, and hyperlipidemia than older adults who reported light PA. Despite our risk models adjusted for these covariates, the possibility of residuals could not be omitted. Sixth, because of the limited number of the study population, many associations did not reach statistical significance when results were stratified by sex or by age. Also, the wide confidence intervals in the stratified analyses made it difficult to precisely detect the preventive effect of different PA intensities and frequencies. These associations might have been solidified if we had a larger sample size which highlights the potential difference between the statistical and the clinical significance.

Furthermore, it could be argued that the follow-up period of this study is not lengthy, and since PA is reduced in the preclinical phase of dementia, the possibility of reverse causation bias cannot be entirely excluded. In their meta-analysis, Kivimäki and colleagues showed that PA reduced the risk of dementia when PA was only assessed < 10 years before dementia diagnosis while studies that assessed PA ≥ 10 years before dementia diagnosis did not show a difference in dementia risk. [40] However, this meta-analysis was limited by confining the analysis to studies that performed separate analyses for incident dementia during the first 10 years of follow-up and incident dementia from year 10 onwards in those without a dementia diagnosis at year 10. On the other hand, an earlier, however more comprehensive, meta-analysis of studies with prospective cohort design by Guure and colleagues showed that the protective effect of PA against dementia in studies with a follow-up period of ≤ 5 years was almost the same as those with a follow-up period of > 5 years. [34] Also, sensitivity analyses of our study by removing older adults who were censored during the first couple of years of follow-up did not affect the results. Besides, reverse causality cannot explain the substantial cognitive improvements attributed to PA in short-term randomized controlled trials. [41,42]

In conclusion, non-occupational PA was shown to reduce the risk of dementia among Japanese older adults aged ≥ 65 years, and practicing moderate or vigorous PA carried additional protective merits than light PA. Engaging in frequent light and vigorous PA showed higher preventive effects than less frequent PA of the corresponding intensities. Women gained more protective benefits than men from practicing frequent light and moderate PA and infrequent vigorous PA. The protective effect of vigorous PA remained significant among older adults aged ≥ 75 years. Thus, awareness programs aiming to encourage older adults to practice higher intensities and frequencies of PA are warranted. Future studies should recruit a larger number of populations and adopt a more reliable method to assess PA intensity and frequency.

Author contributions

Conceptualization: AA, EE, KS, DC, HI, TT, SK, and KK

Methodology: AA, EE, KS, DC, HI, TT, SK, and KK

Project administration and funding acquisition: KS, HI, and KK

Draft preparation and statistical analyses: AA and EE

Review and editing: KS, DC, HI, TT, SK, and KK

Acknowledgments

This study used data from the Japan Gerontological Evaluation Study (JAGES), conducted by the Center for Wellbeing and Society, Nihon Fukushi University. We thank the members of the JAGES Project for their sincere efforts to conduct the survey.

Ethical approval

The Ethics Committees at Nihon Fukushi University, Chiba University, and the National Center for Geriatrics and Gerontology gave their approval to the JAGES which was conducted per the principles of the Declaration of Helsinki. Informed consent was obtained from all participants.

Funding

The JAGES was supported by the Health Labour Sciences Research Grant, Comprehensive Research on Aging and Health (H22-Choju-Shitei-008, H24-Junkanki(Syosyu)-Ippan-007, H24-Chikyukibo-Ippan-009, H24-Choju-Wakate-009, H25-Kenki-Wakate-015, H25-Choju-Ippan-003, H26-Irryo-Shitei-003(Fukkou), H26-Choju-Ippan-006, H30-Junkankitou-Ippan-004) from the Ministry of Health, Labour and Welfare, Japan; Grant-in-Aid for Scientific Research (KAKENHI) (22330172, 22390400, 23243070, 23590786, 23790710, 24390469, 24530698, 24683018, 25253052, 25870573, 25870881, 20H00557) from the Japan Society for the Promotion of Science; a grant from National Center for Geriatrics and Gerontology, Japan (20-19, 24-17, 24-23, J09KF00804); and Japan Agency for Medical Research and Development (JP20dk0110034).

Competing interests

The authors declare no competing interests.

References

1. Hanaoka S, Matsumoto K, Kitazawa T, Fujita S, Seto K, Hasegawa T. Comprehensive cost of illness of dementia in Japan: a time trend analysis based on Japanese official statistics. Int J Qual Health Care. 2019; 31:231–7.
2. Evans I, Llewellyn D, Matthews E, Woods R, Brayne C, Clare L; CFAS-Wales research team. Social isolation, cognitive reserve, and cognition in healthy older people. PLoS One. 2018; 13:e0201008.
3. Wang H, Wahlberg M, Karp A, Winblad B, Fratiglioni L. Psychosocial stress at work is associated with increased dementia risk in late life. Alzheimers Dement. 2012; 8:114–20.
4. Morris M. Nutrition and risk of dementia: overview and methodological issues. Ann N Y Acad Sci. 2016; 1367:31–7.
5. Zhou Z, Wang P, Fang Y. Social engagement and its change are associated with dementia risk among Chinese older adults: a longitudinal study. Sci Rep. 2017; 8:1551.

6. Rakesh G, Szabo S, Alexopoulos G, Zannas A. Strategies for dementia prevention: latest evidence and implications. Ther Adv Chronic Dis. 2017; 8:121–36.
7. Sindi S, Kåreholt I, Eskelinen M, et al. Healthy dietary changes in midlife are associated with reduced dementia risk later in life. Nutrients. 2018; 10:1649.
8. Nystoriak M, Bhatnagar A. Cardiovascular effects and benefits of exercise. Front Cardiovasc Med. 2018; 5:135.
9. Mandolesi L, Gelfo F, Serra L, et al. Environmental factors promoting neural plasticity: insights from animal and human studies. Neural Plast. 2017; 2017:7219461.
10. Erickson K, Miller D, Roecklein K. The aging hippocampus: interactions between exercise, depression, and BNDF. Neuroscientist. 2012; 18:82–97.
11. Leckie R, Oberlin L, Voss M, et al. BDNF mediates improvements in executive function following a 1-year exercise intervention. Front Hum Neurosci. 2014; 8:985.
12. Shen Y, Li R. What do we know from clinical trials on exercise and Alzheimer's disease? J Sport Health Sci. 2016; 5:397–9.
13. Larson E, Wang L, Bowen J, et al. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. Ann Intern Med. 2006; 144:73–81.
14. 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). J Int Neuropsychol Soc. 2015; 21:861–7.
15. McCallum J, Simons L, Simons J, Friedlander Y. Delaying dementia and nursing home placement: the Dubbo study of elderly Australians over a 14-year follow-up. Ann N Y Acad Sci. 2007; 1114:121–9.
16. Gureje O, Ogunniyi A, Kola L, Abiona T. Incidence of and risk factors for dementia in the Ibadan study of aging. J Am Geriatr Soc. 2011; 59:869–74.
17. de Bruijn R, Schrijvers E, de Groot K, et al. The association between physical activity and dementia in an elderly population: the Rotterdam Study. Eur J Epidemiol. 2013; 28:277–83.
18. Herold F, Müller P, Gronwald T, Müller N. Dose-response matters! - A perspective on the exercise prescription in exercise-cognition research. Front Psychol. 2019; 10:2338.

19. Sanders L, Hortobágyi T, la Bastide-van Gemert S, van der Zee E, van Heuvelen M. Dose-response relationship between exercise and cognitive function in older adults with and without cognitive impairment: A systematic review and meta-analysis. PLoS One. 2019; 14:e0210036.
20. Kondo K. Progress in aging epidemiology in Japan: The JAGES project. J Epidemiol. 2016; 26:331–6.
21. Kondo K, Rosenberg M, World Health Organization. Advancing universal health coverage through knowledge translation for healthy ageing: lessons learnt from the Japan gerontological evaluation study. World Health Organization. https://apps.who.int/iris/handle/10665/279010. 2018.
22. Kanamori S, Takamiya T, Inoue S, Kai Y, Tsuji T, Kondo K. Frequency and pattern of exercise and depression after two years in older Japanese adults: the JAGES longitudinal study. Sci Rep. 2018; 8:11224.
23. Tamiya N, Noguchi H, Nishi A, et al. Population ageing and wellbeing: lessons from Japan's long-term care insurance policy. Lancet. 2011; 378:1183–92.
24. Hisano S. The relationship between Revised Hasegawa Dementia Scale (HDS-R), Mini-Mental State Examination (MMSE) and Bed-fast Scale, dementia scale. Japanese J Geriatr Psychiatry. 2009; 20:883–91.
25. Meguro K, Tanaka N, Kasai M, et al. Prevalence of dementia and dementing diseases in the old-old population in Japan: The Kurihara project. Implications for long-term care insurance data. Psychogeriatrics. 2012; 12:226–34.
26. Asada T. Prevalence of dementia in urban areas and functional disability in dementia for FY2011–2012. Ministry of Health, Labour and Welfare, Tokyo, 2013. www.tsukuba-psychiatry.com/wp-content/uploads/2013/06/H24Report_Part1.pdf Accessed on 1/3/2020.
27. Saito T, Murata C, Saito M, Takeda T, Kondo K. Influence of social relationship domains and their combinations on incident dementia: a prospective cohort study. J Epidemiol Community Health. 2018; 72:7–12.
28. Tani Y, Suzuki N, Fujiwara T, Hanazato M, Kondo K. Neighborhood food environment and dementia incidence: the Japan Gerontological Evaluation Study Cohort Survey. Am J Prev Med. 2019; 56:383–92.
29. Murata C, Saito T, Saito M, Kondo K. The association between social support and incident dementia: A10-year follow-up study in Japan. Int J Environ Res Public Health. 2019; 16:239.

30. Tsuji T, Kanamori S, Miyaguni Y, Hanazato M, Kondo K. Community-level sports group participation and the risk of cognitive impairment. Med Sci Sports Exerc. 2019; 51:2217–23.
31. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. Lancet. 2017; 390:2673–734.
32. Miyachi M, Tripette J, Kawakami R, Murakami H. "+10 min of physical activity per day": Japan is looking for efficient but feasible recommendations for its population. J Nutr Sci Vitaminol. 2015; 61:S7–S9.
33. Xu W, Wang HF, Wan Y, Tan C, Yu J, Tan L. Non-occupational time physical activity and dementia risk: a dose-response meta-analysis of prospective studies. BMJ Open. 2017; 7:e014706.
34. Guure C, Ibrahim N, Adam M, Said S. Impact of physical activity on cognitive decline, dementia, and its subtypes: Meta-analysis of prospective studies. Biomed Res Int. 2017; 2017:9016924.
35. Barha C, Liu-Ambrose T. Exercise and the aging brain: Considerations for sex differences. Brain Plast. 2018; 4:53–63.
36. Varma V, Tang X, Carlson M. Hippocampal sub-regional shape and physical activity in older adults. Hippocampus. 2016; 26:1051–60.
37. Gallaway P, Miyake H, Buchowski M, et al. Physical activity: a viable way to reduce the risks of mild cognitive impairment, Alzheimer's disease, and vascular dementia in older adults. Brain Sci. 2017; 7:22.
38. Elahi F, Miller B. A clinicopathological approach to the diagnosis of dementia. Nat Rev Neurol. 2017; 13:457–76.
39. Lee J. The Relationship between physical activity and dementia: A systematic review and meta-analysis of prospective cohort studies. J Gerontol Nurs. 2018; 44:22–9.
40. Kivimäki M, Singh-Manoux A, Pentti J, et al. Physical inactivity, cardiometabolic disease, and risk of dementia: an individual-participant meta-analysis. BMJ. 2019; 365:l1495.
41. Heyn P, Abreu B, Ottenbacher K. The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis. Arch Phys Med Rehabil. 2004; 85:1694–704

42. Jia R, Liang J, Xu Y, Wang Y. Effects of physical activity and exercise on the cognitive function of patients with Alzheimer disease: a meta-analysis. BMC Geriatr. 2019; 19:181.

Table 1: Baseline characteristics of the study population according to their non-occupational physical activity

Characteristics	Overall	No PA	Light PA	Moderate PA	Vigorous PA	P-value
Frequency	2194	336	489	849	520	---
Age ≥ 75 years, %	37.8	49.1	43.4	34.6	30.4	<0.001
Men, %	51.3	61.3	38.2	54.7	51.5	<0.001
BMI ≥ 23 kg/m^2, %	43.6	42.1	42.9	44.8	43.2	0.816
Currently married, %	73.0	72.3	64.3	76.0	76.8	0.004
Education < 10 years, %	31.2	43.8	37.9	26.6	24.3	<0.001
Annual income < 3 million yen, %	44.6	48.4	50.7	39.9	44.4	0.001
Current smoking, %	12.6	10.8	13.3	13.4	11.5	0.014
Current alcohol intake, %	41.1	37.2	33.7	43.8	45.9	<0.001
History of hypertension, %	49.3	43.4	47.5	51.3	52.2	0.090
History of diabetes, %	15.8	20.0	13.6	16.6	13.8	0.096
History of hyperlipidemia, %	15.3	9.4	13.9	17.4	17.6	0.011

Table 2: Hazard ratios and confidence intervals for incident dementia according to different intensities of non-occupational physical activity regardless of frequency

Non-occupational physical activity	Number	Dementia incidence (%)	Model I	Model II
(Overall)				
Never	336	17.0	1	1
Light	489	11.0	0.66 (0.45-0.96)	0.74 (0.49-1.10)
Moderate	849	6.8	0.43 (0.30-0.62)	0.53 (0.36-0.77)
Vigorous	520	4.8	0.32 (0.20-0.51)	0.38 (0.23-0.63)
P-value for trend			0.001	0.002
(Men)				
Never	206	16.5	1	1
Light	187	12.3	0.73 (0.43-1.24)	0.95 (0.54-1.70)
Moderate	464	7.5	0.46 (0.29-0.75)	0.64 (0.38-1.07)
Vigorous	268	4.5	0.28 (0.14-0.54)	0.37 (0.18-0.73)
P-value for trend			0.012	0.010
(Women)				
Never	130	17.7	1	1
Light	302	10.3	0.59 (0.35-1.02)	0.55 (0.31-0.99)
Moderate	385	6.0	0.39 (0.22-0.70)	0.41 (0.22-0.76)
Vigorous	252	5.2	0.36 (0.18-0.72)	0.36 (0.18-0.75)
P-value for trend			0.041	0.088
(65-74 years)				
Never	171	8.2	1	1
Light	277	4.3	0.58 (0.26-1.27)	0.62 (0.27-1.43)
Moderate	555	2.2	0.27 (0.12-0.58)	0.27 (0.12-0.62)
Vigorous	362	1.9	0.24 (0.10-0.59)	0.24 (0.10-0.63)
P-value for trend			0.048	0.093
(≥75 years)				
Never	165	26.1	1	1
Light	212	19.8	0.68 (0.44-1.05)	0.78 (0.49-1.25)
Moderate	294	15.6	0.50 (0.33-0.76)	0.64 (0.41-1.01)
Vigorous	158	11.4	0.35 (0.20-0.61)	0.45 (0.25-0.81)
P-value for trend			0.011	0.015

Model I: Adjusted for age, sex, and area

Model II: Further adjusted for BMI, marriage, education, annual income, smoking, alcohol intake, hypertension, diabetes, and hyperlipidemia

The p-value for sex interaction= 0.701, The p-value for age-category interaction= 0.451

Table 3: Hazard ratios and confidence intervals for incident dementia according to different frequencies of non-occupational physical activity

Non-occupational physical activity	Number	Dementia incidence (%)	Model I	Model II
Never	336	17.0	1	1
Light				
< 2 times/week	127	14.2	0.78 (0.46-1.32)	0.90 (0.51-1.58)
≥ 2 times/week	362	9.9	0.60 (0.39-0.92)	0.61 (0.38-0.97)
P-value for trend			0.019	0.039
Moderate				
< 2 times/week	408	6.1	0.38 (0.24-0.60)	0.46 (0.28-0.76)
≥ 2 times/week	441	7.5	0.49 (0.32-0.76)	0.57 (0.36-0.91)
P-value for trend			0.001	0.014
Vigorous				
< 2 times/week	257	5.4	0.35 (0.19-0.62)	0.40 (0.21-0.74)
≥ 2 times/week	263	4.2	0.27 (0.14-0.52)	0.29 (0.15-0.57)
P-value for trend			<0.001	<0.001

Model I: Adjusted for age, sex, and area

Model II: Further adjusted for BMI, marriage, education, annual income, smoking, alcohol intake, hypertension, diabetes, and hyperlipidemia

Table 4: Sex-specific hazard ratios and confidence intervals for incident dementia according to different frequencies of non-occupational physical activity

Non-occupational physical activity	Number	Dementia incidence (%)	Model I	Model II
(Men)				
Never	206	16.5	1	1
Light				
< 2 times/week	74	16.2	0.92 (0.48-1.77)	1.17 (0.57-2.39)
≥ 2 times/week	113	9.7	0.59 (0.30-1.17)	0.59 (0.28-1.27)
P-value for trend			0.141	0.231
Moderate				
< 2 times/week	232	5.6	0.35 (0.18-0.66)	0.47 (0.24-0.95)
≥ 2 times/week	232	9.5	0.59 (0.34-1.02)	0.85 (0.46-1.56)
P-value for trend			0.037	0.524
Vigorous				
< 2 times/week	138	5.8	0.37 (0.17-0.81)	0.49 (0.21-1.16)
≥ 2 times/week	130	3.1	0.18 (0.06-0.50)	0.21 (0.07-0.62)
P-value for trend			<0.001	0.002
(Women)				
Never	130	17.7	1	1
Light				
< 2 times/week	53	11.3	0.60 (0.26-1.49)	0.59 (0.22-1.62)
≥ 2 times/week	249	10.0	0.59 (0.34-1.04)	0.50 (0.27-0.95)
P-value for trend			0.076	0.038
Moderate				
< 2 times/week	176	6.8	0.40 (0.20-0.81)	0.46 (0.21-1.00)
≥ 2 times/week	209	5.3	0.38 (0.18-0.78)	0.35 (0.16-0.76)
P-value for trend			0.005	0.006
Vigorous				
< 2 times/week	119	5.0	0.32 (0.13-0.80)	0.24 (0.08-0.72)
≥ 2 times/week	133	5.3	0.44 (0.19-1.03)	0.22 (0.08-0.63)
P-value for trend			0.022	0.004

Model I: Adjusted for age and area

Model II: Further adjusted for BMI, marriage, education, annual income, smoking, alcohol intake, hypertension, diabetes, and hyperlipidemia

Table 5: Age-specific stratified hazard ratios and confidence intervals for incident dementia activity according to different frequencies of non-occupational physical

Non-occupational physical activity	Number	Dementia incidence (%)	Model I	Model II
(65-74 years)				
Never	171	8.2	1	1
Light				
< 2 times/week	63	4.8	0.60 (0.17-2.10)	0.61 (0.14-2.56)
≥ 2 times/week	214	4.2	0.57 (0.24-1.37)	0.60 (0.22-1.68)
P-value for trend			0.200	0.327
Moderate				
< 2 times/week	263	2.3	0.27 (0.11-0.71)	0.34 (0.12-0.99)
≥ 2 times/week	292	2.1	0.27 (0.10-0.72)	0.32 (0.11-0.92)
P-value for trend			0.005	0.027
Vigorous				
< 2 times/week	178	2.8	0.35 (0.12-0.97)	0.37 (0.12-1.17)
≥ 2 times/week	184	1.1	0.14 (0.03-0.62)	0.13 (0.03-0.64)
P-value for trend			0.003	0.006
(≥75 years)				
Never	165	26.1	1	1
Light				
< 2 times/week	64	23.4	0.85 (0.47-1.52)	0.96 (0.50-1.84)
≥ 2 times/week	148	18.2	0.61 (0.37-1.01)	0.63 (0.36-1.09)
P-value for trend			0.055	0.103
Moderate				
< 2 times/week	145	13.1	0.42 (0.24-0.71)	0.53 (0.29-0.96)
≥ 2 times/week	149	18.1	0.59 (0.36-0.96)	0.71 (0.42-1.21)
P-value for trend			0.019	0.176
Vigorous				
< 2 times/week	79	11.4	0.34 (0.17-0.71)	0.37 (0.17-0.83)
≥ 2 times/week	79	11.4	0.36 (0.17-0.73)	0.40 (0.18-0.90)
P-value for trend			0.001	0.010

Model I: Adjusted for sex and area

Model II: Further adjusted for BMI, marriage, education, annual income, smoking, alcohol intake, hypertension, diabetes, and hyperlipidemia

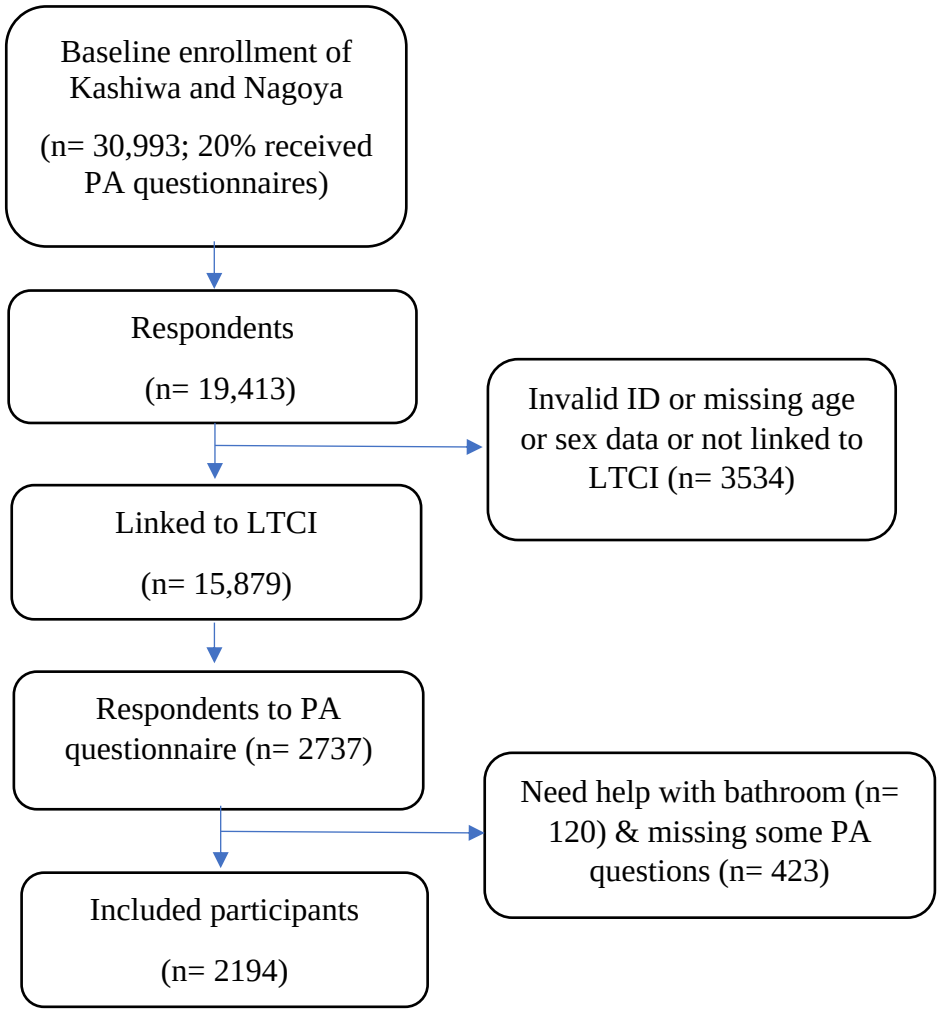

Figure 1: Flowchart of the included participants

Supplementary Table 1: Hazard ratios and confidence intervals for incident dementia according to different frequencies of non-occupational physical activity after excluding older adults censored during the first two years of follow-up

Non-occupational physical activity	Number	Dementia incidence (%)	Model I	Model II
Never	316	16.8	1	1
Light				
< 2 times/week	117	14.5	0.81 (0.47-1.40)	0.88 (0.49-1.58)
≥ 2 times/week	336	9.5	0.58 (0.37-0.92)	0.56 (0.34-0.92)
P-value for trend			0.019	0.022
Moderate				
< 2 times/week	395	6.3	0.39 (0.24-0.62)	0.47 (0.28-0.77)
≥ 2 times/week	407	7.9	0.52 (0.33-0.81)	0.60 (0.37-0.96)
P-value for trend			0.002	0.026
Vigorous				
< 2 times/week	241	5.0	0.31 (0.17-0.59)	0.35 (0.18-0.68)
≥ 2 times/week	249	4.4	0.28 (0.15-0.54)	0.28 (0.14-0.56)
P-value for trend			<0.001	<0.001

Model I: Adjusted for age, sex, and area

Model II: Further adjusted for BMI, marriage, education, annual income, smoking, alcohol intake, hypertension, diabetes, and hyperlipidemia