The Relationship Between Physical Activity and Dementia

A Systematic Review and Meta-Analysis of Prospective Cohort Studies

ABSTRACT

Physical activity may decrease the risk of dementia; however, conflicting findings exist. The purpose of the current meta-analysis was to investigate the relationship between physical activity and dementia risk based on physical activity type, amount, and intensity, and to propose an effective minimal physical activity amount for older adults. Forty-four studies were selected for the meta-analysis. Participation in high (a total of >2 hours of activity over the course of three sessions per week) and moderate (a total of >1 hour of activity over the course of two sessions per week) amounts of physical activity showed decreased dementia risks compared to physical inactivity. Vigorous exercise, regular exercise, leisure time physical activities, and gardening showed a positive effect toward lowering dementia risk, but walking was not associated with dementia risk. Physically inactive individuals had a higher dementia risk than those who participated in physical activity. Participation in physical activities produces a favorable effect toward lowering dementia risk. Participating in regular physical activity of >1 hour over the course of two sessions per week and avoiding physical inactivity are recommended for lowering dementia risk. [*Journal of Gerontological Nursing, 44*(10), 22-29.]

Junga Lee, PhD

Dementia is a brain illness that influences memory, thinking, behavior, and daily tasks (Christensen et al., 2013). Patients with dementia are mostly older adults, and dementia is an abnormal process of aging (Viswanathan, Rocca, & Tzourio, 2009). Forty-seven million older adults experienced dementia in 2017, and the estimated number of patients with dementia will approximately triple to 141 million by 2050 (Hebert, Weuve, Scherr, & Evans, 2013). The estimated worldwide economic cost of dementia was $818 billion in 2015, which is a massive burden for patients with dementia, their families, and the community (Wimo et al., 2017). Prevention of dementia in the aging society is important as there is no cure, only treatments to slow the progression of dementia after it occurs.

Physical activity is known to reduce the risk of dementia; however, controversial results have been reported. Some researchers have indicated that physical activity had no association

with dementia risk (Mehlig et al., 2014; Sabia et al., 2017), whereas other researchers have shown associations with reduced dementia risk (Heser et al., 2014; Llamas-Velasco, Contador, Villarejo-Galende, Lora-Pablos, & Bermejo-Pareja, 2015). Conflicting findings might be related to physical activity types, frequency, or intensity. Considering types of physical activity, a previous study found that older adults who participated in gardening had a 34% lower dementia risk than those who did no physical activity (McCallum, Simons, Simons, & Friedlander, 2007).

A recent meta-analysis reported an inverse association between leisure time physical activities and all-cause dementia and Alzheimer's disease (AD), but no association with vascular dementia (Xu et al., 2017). When a leisure time physical activity session was increased by 500 kcal or 10 Metabolic Equivalent of Task-hours, the risks of all-cause dementia and AD decreased by 10% and 13%, respectively (Xu et al., 2017). A limitation of the previous meta-analysis was that the study considered only caloric energy expended by physical activity.

Older adults incur a loss of physical strength and a reduction in physical function with aging. These factors might affect their ability to participate in physical activities, which may lead to lower amounts and intensity of physical activity compared to younger adults. To provide more practical guidelines regarding physical activity recommendations for older adults, the association between physical activity and dementia risk should consider factors such as physical activity types, activity session time periods, performance frequency, and intensity. Thus, the purpose of the current meta-analysis was to investigate the relationship between physical activity and all-cause dementia, AD, and vascular dementia based on physical activity type, amount, and intensity.

METHOD

Study Search

The current meta-analysis followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines in the selection process for identifying eligible studies (Liberati et al., 2009). Embase and Medline databases were used to search for eligible studies published in English from January 1990 to December 2017. Two researchers (J.L. and another) searched for relevant studies independently. Any procedural issues or conflicts discovered during the process were discussed and resolved to both researchers' satisfaction. Several search terms were used: *physical activity*, *exercise*, *dementia*, *Alzheimer's disease*, *vascular dementia*, and *risk*. All selected studies were evaluated by guidelines for the Meta-Analysis of Observational Studies in Epidemiology (Stroup et al., 2000). In addition, both researchers reviewed reference lists from the potentially relevant studies and the reviewed articles to find relevant studies. The Newcastle-Ottawa Quality Assessment Scale was used to evaluate the quality of the selected studies (Wells, 1948).

Eligibility Criteria and Data Extraction

The eligibility criteria required that a selected study must provide a prospective cohort study and include the relative risks (RRs) of dementia according to older adults' participation in physical activity. Basic information collected from the selected studies included: name of the first author, country in which the study took place, design of the study, publication year, sample size, years the study was conducted, follow-up years, dementia diagnosis criteria, measurements of physical activity (i.e., type, frequency, intensity, and time), RR with 95% confidence interval [CI], and adjustment factors. Disqualifying criteria were: any case-control, cross-sectional, meta-analysis, or review study; article not written in English; not within date range; and any study that did not provide RRs.

Statistical Analysis

Directly extracted RRs from each selected study were used to calculate a summary of RRs. The Q-statistic was used to determine the statistical heterogeneity within the sampled studies. In performing the Q-statistic analysis, if the p value was <0.05, a fixed-effect model was used; if the p value was ≥0.05, a random-effect model was used. Inconsistency across the sampled studies was determined by the I^2 statistic. If the p value from the I^2 statistic was >0.10, the summary was considered heterogeneous homogeneous. If the p value from the I^2 statistic was ≤0.10, the summary was considered homogeneous. Publication bias within the sampled studies was inspected visually using a funnel plot. Statistical significance was indicated when p was <0.05. The Comprehensive Meta-Analysis Version 1.25 software program was used to perform all statistical meta-analyses.

RESULTS

Literature Search

The process for selecting studies is presented in **Figure 1**. A total of 1,229 studies were identified from the initial keyword-based searching steps. Screening continued by reviewing titles and abstracts of the identified studies, reading the literature review, and confirming that the study met additional criteria for inclusion in a meta-analysis; from these steps, 1,104 studies were excluded. The full-text versions of the remaining 125 studies were carefully reviewed in their entirety to determine whether the studies fit all eligibility criteria for this study. Eighty-one studies were subsequently eliminated because they did not provide the RRs of dementia according to physical activity and were not prospective cohort studies. A total of 44 studies were selected for the meta-analysis (**Table A**, available in the online version of this article).

Study Characteristics

From the 44 studies selected for the meta-analysis, there was a total

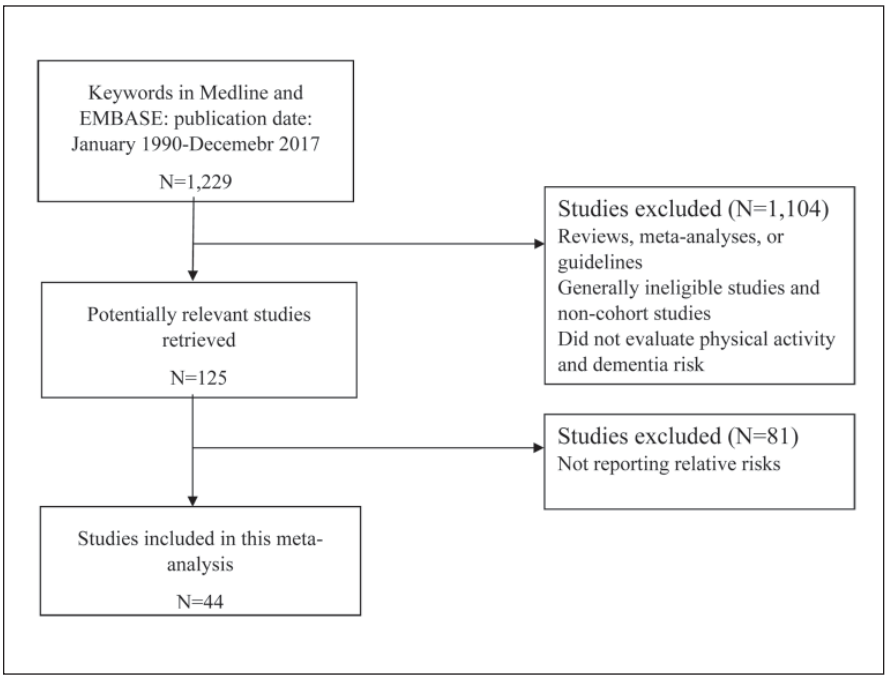


Figure 1. Process for selecting studies for the current meta-analysis.

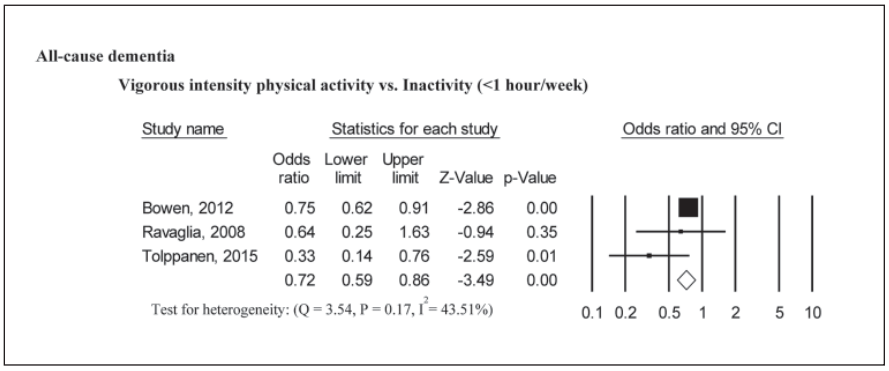


Figure 2. Physical activity intensity and all-cause dementia risk.

population of 258,138 participants. Thirty-six studies were conducted in America and Europe, seven studies were conducted in Asia, and one study was conducted in Africa. The average time for follow up was 9.51 years. Each study used a unique set of adjustments, with factors that included age, body mass index, and education. Older adults were divided into three groups depending on their physical activity levels. The first group, comprising older adults who rarely participated in physical activity or participated in physical activity for <1 hour per week, was the inactive group (Batty, Russ, Starr, Stamatakis, & Kivimaki, 2014; Bowen, 2012; Chang et al., 2010; de Bruijn et al., 2013; Elwood et al., 2013; Fabrigoule et al., 1995; Fenesi et al., 2017; Lee et al., 2015; Luck et al., 2014; McCallum et al., 2007; Mehlig et al., 2014; Morgan et al., 2014; Simons, Simons, McCallum, & Friedlander, 2006; Soni et al., 2017; Tolppanen et al., 2015; Tomata et al., 2017; Verghese et al., 2003; Yoshitake et al., 1995; Zhou, Fu, Hong, Wang, & Fang, 2017). The second group, the moderate physical activity group, participated in a total of >1 hour of physical activity over the course of two sessions per week (Abbott et al., 2004; Carlson et al., 2008; Karp et al., 2006; Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001; Llamas-Velasco et al., 2015; Sabia et al., 2017; Sumic, Michael, Carlson, Howieson, & Kaye, 2007; Wang, 2002). The third group comprised individuals who participated in a high amount of physical activity, participating in a total of >2 hours of physical activity over the course of three sessions per week (Akbaraly et al., 2009; Annweiler et al., 2012; Buchman et al., 2012; Gureje, Ogunniyi, Kola, & Abiona, 2011; Hebert et al., 2000; Heser et al., 2014; Hessler et al., 2016; Kishimoto et al., 2016; Larson et al., 2006; Lindsay et al., 2002; Neergaard et al., 2016; Podewils et al., 2005; Ravaglia et al., 2008; Rovio et al., 2005; Rovio et al., 2007; Scarmeas et al., 2009; Verdelho et al., 2012). Based on the types of physical activity identified in the selected studies, a summary of RRs for four types of physical activity was calculated: walking, gardening, leisure time physical activity, and regular exercise. Physical activity intensity, type, and amount were measured by physical activity questionnaires or by interview. Leisure time physical activity was a self-reported answer that included physical activities such as tennis, swimming, bicycling, team games, and walking for exercise.

Total Amount of Physical Activity and Dementia Risks

Older adults who participated in a high amount of physical activity experienced a 22% decrease in all-cause dementia risk (odds ratio [OR] = 0.78, 95% CI [0.74, 0.81], $p < 0.05$), a 28% decrease in AD risk (OR = 0.72, 95% CI [0.66, 0.80], $p < 0.05$), and a 46% decrease in vascular dementia risk (OR = 0.54, 95% CI [0.42, 0.69], $p < 0.05$) compared to older adults who did not participate in physical activity (**Figure A**, available in the online version of this article). In addition, the association between moderate amounts of physical activity and dementia risk had an inverse association with all-cause dementia (OR = 0.77, 95% CI [0.75, 0.79], $p < 0.05$), AD (OR = 0.68,

95% CI [0.60, 0.77], $p < 0.05$), and vascular dementia (OR = 0.72, 95% CI [0.54, 0.97], $p < 0.05$). There was no statistically significant heterogeneity across the sampled studies. No publication biases were revealed, as tested using a funnel plot and the trim and fill method.

Intensity of Physical Activity and Dementia Risks

Regarding the intensity of physical activity, the current meta-analysis was conducted only for vigorous physical activity in comparison to low-intensity physical activity for all-cause dementia risk due to the limited numbers of studies available, as shown in **Figure 2**. The vigorous intensity physical activity group had a 28% decreased association with all-cause dementia (OR = 0.72, 95% CI [0.59, 0.86], $p < 0.05$). No statistically significant heterogeneity among the sampled studies existed. There was no publication bias, as tested using a funnel plot and the trim and fill method.

Types of Physical Activity and Dementia Risks

An additional analysis was conducted in the current meta-analysis to examine physical activity types that included walking, gardening, leisure time physical activity, and regular exercise (**Figure 3**). Participation in gardening (OR = 0.59, 95% CI [0.50, 0.70], $p < 0.05$), leisure time physical activity (OR = 0.79, 95% CI [0.72, 0.88], $p < 0.05$), and regular exercise (OR = 0.58, 95% CI [0.47, 0.72], $p < 0.05$) each indicated a reduced association with all-cause dementia risks. However, that association was not found for individuals who participated in walking (OR = 0.86, 95% CI [0.72, 1.04], $p > 0.05$). Ten studies were used to analyze leisure time physical activity, seven for regular exercise, three for gardening, and four for walking. There was no statistically significant heterogeneity among the sampled studies. There was no publication bias, as tested using a funnel plot and the trim and fill method.

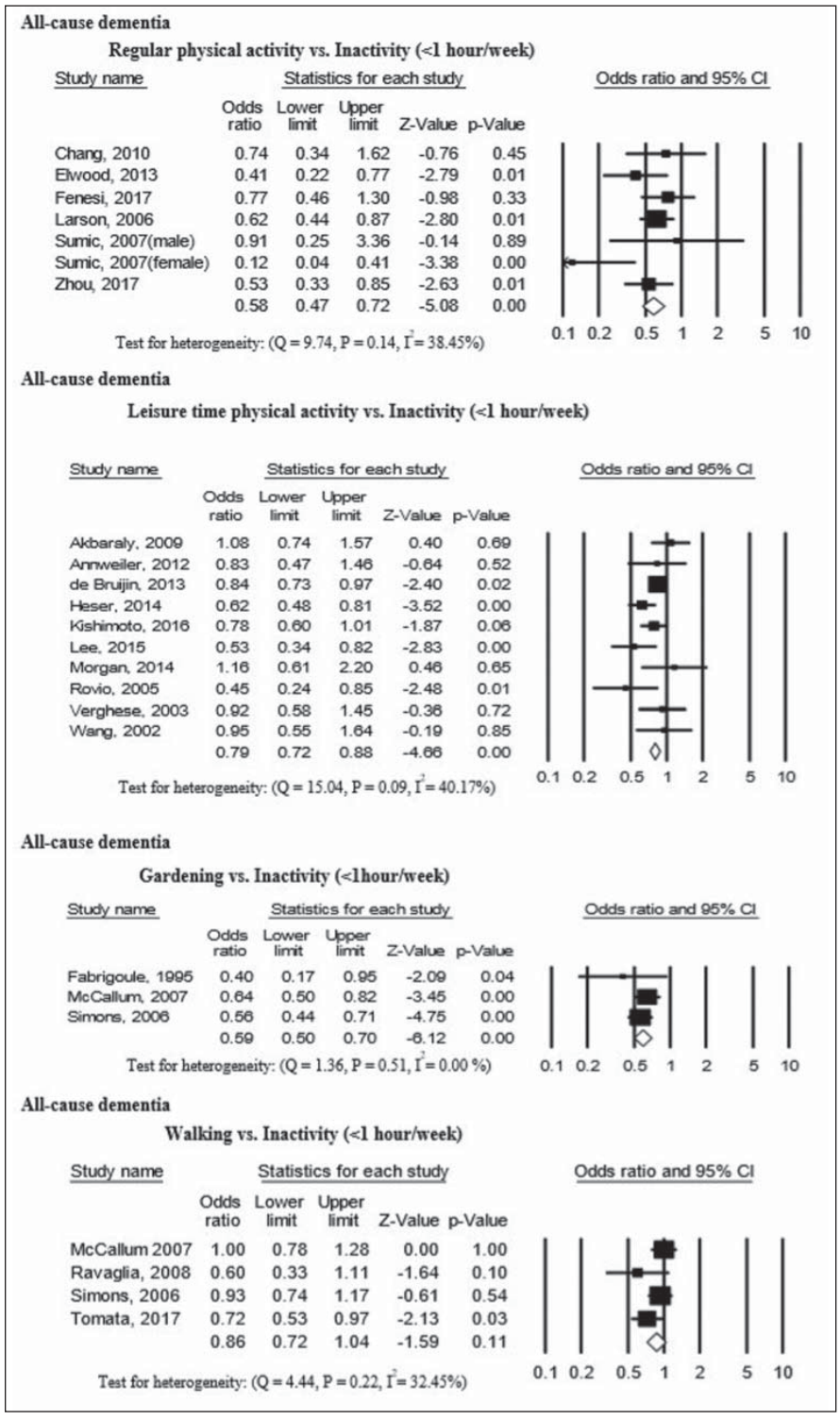


Figure 3. Physical activity types and all-cause dementia risk.

Physical Inactivity and Dementia Risks

Older adults who did not participate in physical activity had 1.51 times higher all-cause dementia risk (95% CI [1.27, 1.79], $p < 0.05$) compared to older adults who participated in a vigorous amount of physical activity, and a 1.32 times higher all-cause dementia risk (95% CI [1.10, 1.58], $p < 0.05$)

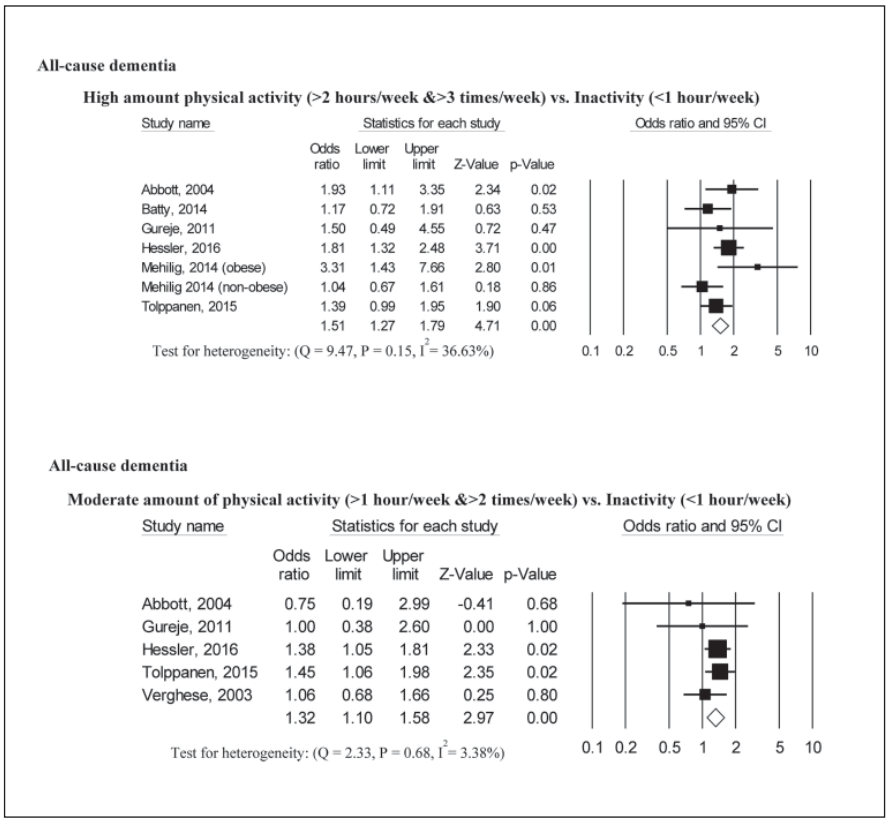


Figure 4. Physical inactivity and all-cause dementia risk.

compared to older adults who participated in a moderate amount of physical activity (**Figure 4**). No statistically significant heterogeneity among the sampled studies was found. There was no publication bias, as tested using a funnel plot and the trim and fill method.

DISCUSSION

A main finding of the current meta-analysis was the preventive effects of physical activity against dementia in older adults. Participation in physical activity, including high and moderate amounts of physical activity, was associated with decreases in all-cause dementia, AD, and vascular dementia in older adults. In addition, diverse physical activities including leisure time physical activity, regular exercise, and gardening showed a positive effect on dementia risk. However, physical inactivity may lead to an increase in dementia risk.

Older adults who participated in physical activities in high and moderate amounts had lower risks of all-cause dementia (22% and 23%, respectively), AD (28% and 32%, respectively), and vascular dementia (46% and 28%, respectively) compared to older adults who were physically inactive. These findings coincide with a previous meta-analysis that found an association between physical activity and dementia risk in older adults (Guure, Ibrahim, Adam, & Said, 2017). The greatest reduction (46%) was for vascular dementia in individuals with a high amount of physical activity. The larger reduction might be related to the impact of exercise on related risk factors that include diabetes mellitus, high blood pressure, high cholesterol, coronary heart disease, and peripheral artery disease, whereas AD risk factors are more likely associated with age, genetics, and general health (O'Brien & Markus, 2014).

Given the parameters of the source data regarding physical activity amounts, it is important to note that the cut-off for a high amount of physical activity in the current meta-analysis was a total of >2 hours of activity performed over the course of three sessions per week, and the cut-off for a moderate amount of physical activity was a total of >1 hour of activity performed over the course of two sessions per week. The minimum level of physical activity to have a positive effect against dementia is >1 hour per week performed over the course of two sessions per week. From these findings, the current meta-analysis suggests that participation in these amounts of physical activity helps prevent all-cause dementia, AD, and vascular disease.

A main finding of the current meta-analysis was that physical activity of vigorous intensity was inversely associated with all-cause dementia. That is, when older adults participated in vigorous intensity exercise, there was an associated 28% decrease in dementia risk, although only three studies were used in the meta-analysis to obtain this finding. An examination was not conducted for moderate intensity as associated with other subtypes of dementia, including AD and vascular dementia, as there was an insufficient amount of data to conduct a meta-analysis.

The sensitivity analysis of the current meta-analysis found that physical activity type influenced the risk of all-cause dementia. Gardening, which is considered more intense activity than moderate activity, was associated with a 41% decrease for all-cause dementia risk, but walking (likely of light intensity) did not have a statistically significant association with dementia risk. The current meta-analysis showed the importance of participation in regular exercise and leisure time physical activity against all-cause dementia risk. The association between intensity and types of physical activity and dementia needs further study. General comparisons to other similar studies (Kishimoto et al., 2016; Tomata et al., 2017) indicated that these findings were consistent in that moderate

intensity physical activity and regular exercise would be more beneficial than light intensity physical activity and walking to produce a protective effect against dementia.

The current meta-analysis found that physical inactivity was associated with increased all-cause dementia. Older adults who did not participate in physical activity had 1.51 times the dementia risk than older adults who performed a high amount of physical activity (a total of >2 hours of activity performed over the course of three sessions per week). In addition, inactive older participants had 1.32 times the dementia risk as older adults who participated in a moderate amount of physical activity (a total of >1 hour of activity performed over the course of two sessions per week). These results coincide with previous studies that found that physical inactivity was related to increased incidence of other chronic diseases, including cancer, cardiovascular diseases, and metabolic disorders (Biswas & Alter, 2015). The current meta-analysis used six studies to determine the association between physical inactivity and all-cause dementia risk. Findings support participation in physical activity as an important step toward lowering dementia risk.

Three prominent mechanisms may explain how physical activity leads to a favorable physiological effect in reducing dementia risk. First, physical activity causes an increase in brain-derived neurotrophic factor and insulin-like growth factor that stimulate neurotransmitter functions and neuroprotection in the brain (Cotman, Berchtold, & Christie, 2007). Second, exercise helps maintain flow of blood and supply of oxygen and nutrients, promoting cerebrovascular integrity (Querido & Sheel, 2007) and inhibiting atrophy of the hippocampus volume that preserves memory (Smith et al., 2014). Third, regular physical activity tends to decrease the amount of cortisol in the bloodstream, leading to a reduction in symptoms of stress (Kalmijn et al., 1998).

Participation in physical activity was associated with a decreased risk of dementia, whereas physical inactivity was associated with an increased risk.

LIMITATIONS

Several limitations of the current meta-analysis must be addressed. First, the amount and intensity of physical activity were heterogeneous. Measurements of physical activity amounts, intensity, and types were obtained by self-reported questionnaires. The current meta-analysis used the intensity categories directly from each original study to calculate a summary of RRs. Second, adjustment factors from each original study were unique to that study, and those unique differences could not be controlled. Third, the follow-up periods to determine the influence of exercise on dementia risk were different in each selected study.

CONCLUSION

Participation in physical activity was associated with a decreased risk of dementia, whereas physical inactivity was associated with an increased risk. Physical activity performed for at least 1 hour twice per week has been shown to reduce risk of dementia. Other amounts of regular exercise as well as gardening also help decrease dementia risk. The practical implication of the current meta-analysis is that participation in physical activity is an important factor in preventing dementia. The meta-analysis indicated that a total of 2 hours of exercise per week, performed three times per week, results in better outcomes for reducing dementia risk. Older adults would significantly benefit from participation in diverse activities such as leisure time physical activity, regular exercise, and gardening. Engaging in physical activity as a routine for older individuals should be recommended for preventing all-cause dementia, including AD and vascular dementia.

REFERENCES

Abbott, R.D., White, L.R., Ross, G.W., Masaki, K.H., Curb, J.D., & Petrovitch, H. (2004). Walking and dementia in physically capable elderly men. *JAMA, 292*, 1447-1453. doi:10.1001/jama.292.12.1447

Akbaraly, T.N., Portet, F., Fustinoni, S., Dartigues, J.F., Artero, S., Rouaud, O.,… Berr, C. (2009). Leisure activities and the risk of dementia in the elderly: Results from the Three-City Study. *Neurology, 73*, 854-861. doi:10.1212/WNL.0b013e3181b7849b

Annweiler, C., Rolland, Y., Schott, A.M., Blain, H., Vellas, B., Herrmann, F.R., & Beauchet, O. (2012). Higher vitamin D dietary intake is associated with lower risk of Alzheimer's disease: A 7-year follow-up. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 67*, 1205-1211. doi:10.1093/gerona/gls107

Batty, G.D., Russ, T.C., Starr, J.M., Stamatakis, E., & Kivimaki, M. (2014). Modifiable cardiovascular disease risk factors as predictors of dementia death: Pooling of ten general population-based cohort studies. *Journal of Negative Results in Biomedicine, 13*, 8. doi:10.1186/1477-5751-13-8

Biswas, A., & Alter, D.A. (2015). Sedentary time and risk for mortality. *Annals of Internal Medicine, 162*, 875-876. doi:10.7326/L15-5060-2

Bowen, M.E. (2012). A prospective examination of the relationship between physical activity and dementia risk in later life. *American Journal of Health Promotion, 26*, 333-340. doi:10.4278/ajhp.110311-QUAN-115

Buchman, A.S., Boyle, P.A., Yu, L., Shah, R.C., Wilson, R.S., & Bennett, D.A. (2012). Total daily physical activity and the risk of AD and cognitive decline in older adults.

Neurology, 78, 1323-1329. doi:10.1212/WNL.0b013e3182535d35

Carlson, M.C., Helms, M.J., Steffens, D.C., Burke, J.R., Potter, G.G., & Plassman, B.L. (2008). Midlife activity predicts risk of dementia in older male twin pairs. *Alzheimer's & Dementia, 4*, 324-331. doi:10.1016/j.jalz.2008.07.002

Chang, M., Jonsson, P.V., Snaedal, J., Bjornsson, S., Saczynski, J.S., Aspelund, T.,…Launer, L.J. (2010). The effect of midlife physical activity on cognitive function among older adults: AGES—Reykjavik Study. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 65*, 1369-1374. doi:10.1093/gerona/glq152

Christensen, K., Thinggaard, M., Oksuzyan, A., Steenstrup, T., Andersen-Ranberg, K., Jeune, B.,…Vaupel, J.W. (2013). Physical and cognitive functioning of people older than 90 years: A comparison of two Danish cohorts born 10 years apart. *Lancet, 382*, 1507-1513. doi:10.1016/S0140-6736(13)60777-1

Cotman, C.W., Berchtold, N.C., & Christie, L.A. (2007). Exercise builds brain health: Key roles of growth factor cascades and inflammation. *Trends in Neuroscience, 30,* 464-472. doi:10.1016/j.tins.2007.06.011

de Bruijn, R.F., Schrijvers, E.M., de Groot, K.A., Witteman, J.C., Hofman, A., Franco, O.H.,…Ikram, M.A. (2013). The association between physical activity and dementia in an elderly population: The Rotterdam Study. *European Journal of Epidemiology, 28*, 277-283. doi:10.1007/s10654-013-9773-3

Elwood, P., Galante, J., Pickering, J., Palmer, S., Bayer, A., Ben-Shlomo, Y.,…Gallacher, J. (2013). Healthy lifestyles reduce the incidence of chronic diseases and dementia: Evidence from the Caerphilly cohort study. *PLoS One, 8*, e81877. doi:10.1371/journal.pone.0081877

Fabrigoule, C., Letenneur, L., Dartigues, J.F., Zarrouk, M., Commenges, D., & Barberger-Gateau, P. (1995). Social and leisure activities and risk of dementia: A prospective longitudinal study. *Journal of the American Geriatrics Society, 43*, 485-490.

Fenesi, B., Fang, H., Kovacevic, A., Oremus, M., Raina, P., & Heisz, J.J. (2017). Physical exercise moderates the relationship of apolipoprotein E (APOE) genotype and dementia risk: A population-based study. *Journal of Alzheimer's Disease, 56*, 297-303. doi:10.3233/JAD-160424

Gureje, O., Ogunniyi, A., Kola, L., & Abiona, T. (2011). Incidence of and risk factors for dementia in the Ibadan study of aging. *Journal of the American Geriatrics Society, 59*, 869-874. doi:10.1111/j.1532-5415.2011.03374.x

Guure, C.B., Ibrahim, N.A., Adam, M.B., & Said, S.M. (2017). Impact of physical activity on cognitive decline, dementia, and its subtypes: Meta-analysis of prospective studies. *BioMed Research International, 2017*, 9016924. doi:10.1155/2017/9016924

Hebert, L.E., Weuve, J., Scherr, P.A., & Evans, D.A. (2013). Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. *Neurology, 80*, 1778-1783. doi:10.1212/WNL.0b013e31828726f5

Hebert, R., Lindsay, J., Verreault, R., Rockwood, K., Hill, G., & Dubois, M.F. (2000). Vascular dementia: Incidence and risk factors in the Canadian Study of Health and Aging. *Stroke, 31*, 1487-1493.

Heser, K., Wagner, M., Wiese, B., Prokein, J., Ernst, A., Konig, H.H.,…Eisele, M. (2014). Associations between dementia outcomes and depressive symptoms, leisure activities, and social support. *Dementia and Geriatric Cognitive Disorders Extra, 4*, 481-493. doi:10.1159/000368189

Hessler, J.B., Ander, K.H., Bronner, M., Etgen, T., Forstl, H., Poppert, H.,…Bickel, H. (2016). Predicting dementia in primary care patients with a cardiovascular health metric: A prospective population-based study. *BMC Neurology, 16*, 116. doi:10.1186/s12883-016-0646-8

Kalmijn, S., Launer, L.J., Stolk, R.P., de Jong, F.H., Pols, H.A., Hofman, A.,…Lamberts, S.W. (1998). A prospective study on cortisol, dehydroepiandrosterone sulfate, and cognitive function in the elderly. *Journal of Clinical Endocrinology and Metabolism, 83,* 3487-3492. doi:10.1210/jcem.83.10.5164

Karp, A., Paillard-Borg, S., Wang, H.X., Silverstein, M., Winblad, B., & Fratiglioni, L. (2006). Mental, physical and social components in leisure activities equally contribute to decrease dementia risk. *Dementia and Geriatric Cognitive Disorders, 21*, 65-73. doi:10.1159/000089919

Kishimoto, H., Ohara, T., Hata, J., Ninomiya, T., Yoshida, D., Mukai, N.,…Kiyohara, Y. (2016). The long-term association between physical activity and risk of dementia in the community: The Hisayama Study. *European Journal of Epidemiology, 31*, 267-274. doi:10.1007/s10654-016-0125-y

Larson, E.B., Wang, L., Bowen, J.D., McCormick, W.C., Teri, L., Crane, P., & Kukull, W. (2006). Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. *Annals of Internal Medicine, 144*, 73-81.

Laurin, D., Verreault, R., Lindsay, J., MacPherson, K., & Rockwood, K. (2001). Physical activity and risk of cognitive impairment and dementia in elderly persons. *Archives of Neurology, 58*, 498-504.

Lee, A.T., Richards, M., Chan, W.C., Chiu, H.F., Lee, R.S., & Lam, L.C. (2015). Intensity and types of physical exercise in relation to dementia risk reduction in community-living older adults. *Journal of the American Medical Directors Association, 16*, 899 e1-e7. doi:10.1016/j.jamda.2015.07.012

Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gotzsche, P.C., Ioannidis, J.P.,…Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *Journal of Clinical Epidemiology, 62*(10), e1-e34. doi:10.1016/j.jclinepi.2009.06.006

Lindsay, J., Laurin, D., Verreault, R., Hebert, R., Helliwell, B., Hill, G.B., & McDowell, I. (2002). Risk factors for Alzheimer's disease: A prospective analysis from the Canadian Study of Health and Aging. *American Journal of Epidemiology, 156*, 445-453.

Llamas-Velasco, S., Contador, I., Villarejo-Galende, A., Lora-Pablos, D., & Bermejo-Pareja, F. (2015). Physical activity as protective factor against dementia: A prospective population-based study (NEDICES). *Journal of the International Neuropsychological Society, 21*, 861-867. doi:10.1017/S1355617715000831

Luck, T., Riedel-Heller, S.G., Luppa, M., Wiese, B., Kohler, M., Jessen, F.,…Maier, W. (2014). Apolipoprotein E epsilon 4 genotype and a physically active lifestyle in late life: Analysis of gene-environment interaction for the risk of dementia and Alzheimer's disease dementia. *Psychological Medicine, 44*, 1319-1329. doi:10.1017/S0033291713001918

McCallum, J., Simons, L.A., Simons, J., & Friedlander, Y. (2007). Delaying dementia and nursing home placement: The Dubbo study of elderly Australians over a 14-year follow-up. *Annals of the New York Academy of Sciences, 1114*, 121-129. doi:10.1196/annals.1396.049

Mehlig, K., Skoog, I., Waern, M., Miao Jonasson, J., Lapidus, L., Bjorkelund, C.,… Lissner, L. (2014). Physical activity, weight status, diabetes and dementia: A 34-year follow-up of the population study of women in Gothenburg. *Neuroepidemiology, 42*, 252-259. doi:10.1159/000362201

Morgan, K.L., Rahman, M.A., Hill, R.A., Zhou, S.M., Bijlsma, G., Khanom, A.,… Brophy, S.T. (2014). Physical activity and excess weight in pregnancy have independent and unique effects on delivery and perinatal outcomes. *PLoS One, 9*, e94532. doi:10.1371/journal.pone.0094532

Neergaard, J.S., Dragsbaek, K., Hansen, H.B., Henriksen, K., Christiansen, C., & Karsdal, M.A. (2016). Late-life risk factors for all-cause dementia and differential dementia diagnoses in women: A prospective cohort study. *Medicine, 95*, e3112. doi:10.1097/MD.0000000000003112

O'Brien, J.T., & Markus, H.S. (2014). Vascular risk factors and Alzheimer's disease. *BMC Medicine, 12*, 218. doi:10.1186/s12916-014-0218-y

Podewils, L.J., Guallar, E., Kuller, L.H., Fried, L.P., Lopez, O.L., Carlson, M., & Lyketsos, C.G. (2005). Physical activity, APOE geno-

type, and dementia risk: Findings from the Cardiovascular Health Cognition Study. *American Journal of Epidemiology, 161*, 639-651. doi:10.1093/aje/kwi092

Querido, J.S., & Sheel, A.W. (2007). Regulation of cerebral blood flow during exercise. *Sports Medicine, 37*, 765-782.

Ravaglia, G., Forti, P., Lucicesare, A., Pisacane, N., Rietti, E., Bianchin, M., & Dalmonte, E. (2008). Physical activity and dementia risk in the elderly: Findings from a prospective Italian study. *Neurology, 70*, 1786-1794. doi:10.1212/01.wnl.0000296276.50595.86

Rovio, S., Kareholt, I., Helkala, E.L., Viitanen, M., Winblad, B.,… Kivipelto, M. (2005). Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. *Lancet Neurology, 4*, 705-711. doi:10.1016/S1474-4422(05)70198-8

Rovio, S., Kareholt, I., Viitanen, M., Winblad, B., Tuomilehto, J., Soininen, H.,...Kivipelto, M. (2007). Work-related physical activity and the risk of dementia and Alzheimer's disease. *International Journal of Geriatric Psychiatry, 22*, 874-882. doi:10.1002/gps.1755

Sabia, S., Dugravot, A., Dartigues, J.F., Abell, J., Elbaz, A., Kivimaki, M., & Singh-Manoux, A. (2017). Physical activity, cognitive decline, and risk of dementia: 28 year follow-up of Whitehall II cohort study. *BMJ, 357*, j2709. doi:10.1136/bmj.j2709

Scarmeas, N., Luchsinger, J.A., Schupf, N., Brickman, A.M., Cosentino, S., Tang, M.X., & Stern, Y. (2009). Physical activity, diet, and risk of Alzheimer disease. *JAMA, 302*, 627-637. doi:10.1001/jama.2009.1144

Simons, L.A., Simons, J., McCallum, J., & Friedlander, Y. (2006). Lifestyle factors and risk of dementia: Dubbo study of the elderly. *Medical Journal of Australia, 184*, 68-70.

Smith, J.C., Nielson, K.A., Woodard, J.L., Seidenberg, M., Durgerian, S., Hazlett, K.E.,…Rao, S.M. (2014). Physical activity reduces hippocampal atrophy in elders at genetic risk for Alzheimer's disease. *Frontiers in Aging Neuroscience, 6*, 61. doi:10.3389/fnagi.2014.00061

Soni, M., Orrell, M., Bandelow, S., Steptoe, A., Rafnsson, S., d'Orsi, E.,... Hogervorst, E. (2017). Physical activity pre- and post-dementia: English Longitudinal Study of Ageing. *Aging & Mental Health.* Advance online publication. doi:10.1080/13607863.2017.1390731

Stroup, D.F., Berlin, J.A., Morton, S.C., Olkin, I., Williamson, G.D., Rennie, D.,…Thacker, S.B. (2000). Meta-analysis of observational studies in epidemiology: A proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. *JAMA, 283*, 2008-2012.

Sumic, A., Michael, Y.L., Carlson, N.E., Howieson, D.B., & Kaye, J.A. (2007). Physical activity and the risk of dementia in oldest old. *Journal of Aging and Health, 19*, 242-259. doi:10.1177/0898264307299299

Tolppanen, A.M., Solomon, A., Kulmala, J., Kareholt, I., Ngandu, T., Rusanen, M.,… Kivipelto, M. (2015). Leisure-time physical activity from mid- to late life, body mass index, and risk of dementia. *Alzheimer's & Dementia, 11*, 434-443. doi:10.1016/j.jalz.2014.01.008

Tomata, Y., Zhang, S., Sugiyama, K., Kaiho, Y., Sugawara, Y., & Tsuji, I. (2017). Changes in time spent walking and the risk of incident dementia in older Japanese people: The Ohsaki Cohort 2006 Study. *Age and Ageing, 46*, 857-860. doi:10.1093/ageing/afx078

Verdelho, A., Madureira, S., Ferro, J.M., Baezner, H., Blahak, C., Poggesi, A.,… Inzitari, D. (2012). Physical activity prevents progression for cognitive impairment and vascular dementia: Results from the LADIS (Leukoaraiosis and Disability) study. *Stroke, 43*, 3331-3335. doi:10.1161/STROKEAHA.112.661793

Verghese, J., Lipton, R.B., Katz, M.J., Hall, C.B., Derby, C.A., Kuslansky, G.,… Buschke, H. (2003). Leisure activities and the risk of dementia in the elderly. *New England Journal of Medicine, 348*, 2508-2516. doi:10.1056/NEJMoa022252

Viswanathan, A., Rocca, W.A., & Tzourio, C. (2009). Vascular risk factors and dementia: How to move forward? *Neurology, 72*, 368-374. doi:10.1212/01.wnl.0000341271.90478.8e

Wang, S.Y. (2002). Weight loss and metabolic changes in dementia. *Journal of Nutrition, Health & Aging, 6*, 201-205.

Wells, K.F. (1948). Newcastle disease. *Canadian Journal of Comparative Medicine and Veterinary Science, 12*(4), 101-104.

Wimo, A., Guerchet, M., Ali, G.C., Wu, Y.T., Prina, A.M., Winblad, B.,…Prince, M. (2017). The worldwide costs of dementia 2015 and comparisons with 2010. *Alzheimer's & Dementia, 13*, 1-7. doi:10.1016/j.jalz.2016.07.150

Xu, W., Wang, H.F., Wan, Y., Tan, C.C., Yu, J.T., & Tan, L. (2017). Leisure time physical activity and dementia risk: A dose-response meta-analysis of prospective studies. *BMJ Open, 7*(10), e014706. doi:10.1136/bmjopen-2016-014706

Yoshitake, T., Kiyohara, Y., Kato, I., Ohmura, T., Iwamoto, H., Nakayama, K.,… Fujishima, M. (1995). Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: The Hisayama Study. *Neurology, 45*, 1161-1168.

Zhou, Z., Fu, J., Hong, Y.A., Wang, P., & Fang, Y. (2017). Association between exercise and the risk of dementia: Results from a nationwide longitudinal study in China. *BMJ Open, 7*(12), e017497. doi:10.1136/bmjopen-2017-017497

ABOUT THE AUTHOR

Dr. Lee is Assistant Professor, Sports Medicine and Science, KyungHee University, Gyeonggi-do, Republic of Korea.

The author has disclosed no potential conflicts of interest, financial or otherwise. The author thanks Dr. John Brobst for comments on a previous draft of this manuscript.

Address correspondence to Junga Lee, PhD, Assistant Professor, Sports Medicine and Science, KyungHee University, 1732 Deogyeong-daero, Giheung-gu, Yongin-si, Gyeonggi-do 17104, Republic of Korea; e-mail: junga613@gmail.com.

Received: January 5, 2018
Accepted: June 28, 2018
doi:10.3928/00989134-20180814-01

Table A. Characteristics of Selected Studies: Physical Activity, and Dementia Risk

First author (year), name of study, study design, country	Sample size study, recruitment period, age	Follow-up period (year)	Dementia assessment	Exercise assessment, exercise unites	RR (95% CI) Physical activity	Adjustments
Abbott (2004), a prospective cohort study, Japan (Abbott et al., 2004)	2,257 (1991-1999), 71-93 years	Average 25 years	Cognitive function	Physical activity interview, walking mile per day	**Walking (miles/day)** **All-cause Dementia** >2 1 2-1 1.33(0.73, 2.45) 0.5-1 1.75(1.03, 2.99) <0.25 1.93(1.11, 3.34) **Alzheimer Dementia** >2 1 2-1 1.88(0.87, 4.40) 0.5-1 1.86(0.91, 3.79) <0.25 2.21(1.06, 4.57) **Vascular Dementia** >2 1 2-1 0.16(0.02, 1.36) 0.5-1 1.21(0.45, 3.22) <0.25 1.17(0.42, 3.27) **Mixed & other Dementia** >2 1 2-1 2.00(0.36, 11.01) 0.5-1 2.84(0.62, 12.92) <0.25 2.83(0.59, 13.55)	Age, presence of apolipoprotein, baseline Cognitive Abilities Screening Instrument Score, decline in physical activity, education, body mass index, heart dieses, total cholesterol, prevalence coronary, diabetes, hypertension, HDLC
Akbaraly (2009), a prospective community study, France (Akbaraly et al., 2009)	5,698 (1991-2001), over 65 years old	4 years	DSM-IV	Physical Activity Questionnaire	**Leisure activates (tertile)** **All-cause Dementia: PA** Low 1 Mild 0.83(0.55, 1.25) High 1.08(0.74, 1.57) **Alzheimer Dementia** Low 1 Mild 0.87(0.52, 1.47) High 1.45(0.92, 2.28) **Mixed/Vascular Dementia** Low 1 Mild 0.76(0.34, 1.71) High 0.67(0.30, 1.53)	Vascular risk factors, depressive symptoms, physical functioning, other leisure activities
Annweiler (2012), a prospective multicenter cohort study, France (Annweiler et al., 2012)	7,598 (1992-1994), average 78 years old	7 years	Mini-Mental State Examination	Physical Activity Questionnaire	**Leisure PA (hours/week)** **All-cause Dementia** None 1 Light 0.83(0.47, 1.46) **Alzheimer Dementia** None 1	Age, body mass index, short portable mental state, high education level, disability, sun exposure at midday, chronic diseases, hypertension, depression, psychoactive drugs, dietary vitamin D intakes

					Light 0.79(0.44, 1.42)	
Batty (2014), a prospective cohort study, UK (Batty et al., 2014)	103,764 (2003-2008), average 47 years old	8 years	ICD-9 & 10	Physical Activity Questionnaire	**Inactivity (sessions/week)** **All-cause Dementia:** <5 1.17(0.72, 1.91) ≥5 1	Age, parity, age at menarche, menopausal status/postmenopausal hormone use, tubal ligation, smoking status
Bowen (2012), a prospective cohort study, U.S.A. (Bowen, 2012)	808 (1999-2005), average 71 years old	Medina 5 years	Cognitive Status interview	Physical Activity Questionnaire	**Vigorous PA** **All-cause Dementia (times/week)** None 1.17(0.72, 1.91) Vigorous 0.75(0.62, 0.92)	Smoking, drinking, body mass index, health condition
Buchman (2012), a prospective cohort study, U.S.A. (Buchman et al., 2012)	716 (1997-2005), average 81.6 years old	4 years	Stroke Alzheimer's Disease and Related Disorders Association	Actigraphs and daily physical activity questionnaire	**Daily PA (counts/day)** **Alzheimer Dementia** None 1 Active 0.47(0.27, 0.83)	Age, sex, education
Carlson (2008), a prospective study, U.S.A. (Carlson et al., 2008)	147 (1917-2005), over 70 years old	15 years	DSM-III-R	Physical Activity questionnaire	**Total PA (times/week)** **All-cause Dementia** None 1 Active 0.99(0.73, 1.33)	Age at date of activity assessment
Chang (2010), a longitudinal population-based study, Europe (Chang et al., 2010)	4,945 (1907-2002), 76 years old	26 years	Mini-Mental State Examination	Physical Activity Interview	**Sports & exercise (hours/week)** **All-cause Dementia** None 1 ≤5 0.59(0.40, 0.87) >5 0.74(0.34, 1.62)	Age, sex, education
de Bruijn (2013), a prospective cohort study, U.S.A. (de Bruijn et al., 2013)	4,406 (1997-1999), average 81.8 years old	4 years	Mini-Mental State Examination and Geriatric Mental Schedule	Zutphen Physical Activity Questionnaire	**All-cause Dementia: PA (hours/week)** Low 1 High 0.84(0.73, 0.97) **Alzheimer Dementia** Low 1 High 0.89(0.76, 1.03)	Age, sex, score on MMSE, low educational level, smoking, APOE carrier status, hypertension, body mass index, diabetes, total cholesterol, HDL-cholesterol
Elwood (2013), a prospective cohort study, U.K. (Elwood et al., 2013)	2,235 (1979-2004), over 70 years old	30 years	Clinical Dementia Rating	Physical activity Questionnaire	**Regular exercise (vigorous, miles/day)** **All-cause Dementia** Non 1 Exercise 0.41(0.22, 0.77)	Age, social class
Fabrigoule (1995), a prospective cohort study, France (Fabrigoule et al., 1995)	2,040 (1987-1990), at least 65 years old	3 years	Mini-Mental State Examination	Physical activity interview	**All-cause Dementia** **Sports** No 1 Yes 0.24(0.09, 0.64) **Gardening** No 1 Yes 0.26(0.14, 0.49)	Age

Fenesi (2017), a population-based study, Europe (Fenesi et al., 2017)	1,646 (1996-1997), ≥65 years old	5 years	Mini-Mental State Examination	Physical activity Questionnaire	**Exercise (times/week)** **All-cause Dementia** None 1 Exercise 0.77(0.46, 1.31)	Age, years of education
Gureje (2011), a prospective cohort study, Nigeria (Gureje et al., 2011)	1,408 (2003-2006), 65 years old	3 years	DSM-IV	International Physical activity questionnaire	**Total PA (scoring)** **All-cause Dementia** Vigorous 1 Middle 1.00(0.40, 2.70) Low 1.50(0.50, 4.60)	Age, sex, education
Heser (2014), a prospective multi-Centre study, German (Heser et al., 2014)	1,131 (2003-2008), over 75 years old	1.5-3years	Mini-Mental State Examination (MMSE)	Physical Activity Questionnaire	**Leisure (scoring)** **All-cause Dementia** Inactive 1 Active 0.62(0.47, 0.80) **Alzheimer Dementia** Inactive 1 Active 0.59(0.43, 0.82)	Age, sex, education, ApoE4, MMSE, Instrumental Activity of daily living (IADL)
Hebert (2000), a prospective case-control study, Canada (R. Hebert et al., 2000)	8,623 (1991-1996), over 65 years old	5 years	DSM-III-R, NINCDS-ADRDA, ICD-10	Questionnaires	**Regular exercise** **Vascular Dementia** **Men** Inactive 1 Active 1.24(0.57, 2.94) **Women** Inactive 1 Active 0.46(0.25, 0.82)	Age, region
Hessler (2016), a prospective cohort study, German (Hessler et al., 2016)	3,547 (2001-2008), over 55 years old	2.59 years	Mini-Mental State Examination	Physical activity questionnaire	**Vigorous PA (times/week)** **All-cause Dementia** Inactive 1.81(1.32, 2.47) 1-2 1.38(1.52, 1.81) ≥ 3 1	Age, sex, education
Karp (2006), a prospective cohort study, Sweden (Karp et al., 2006)	776 (1987-1996), 75 years old	6 years	Mini-Mental State Examination	Physical activity interview	**Total PA (scoring)** **All-cause Dementia** 0 1 1 0.55(0.34, 0.89) 2-3 0.61(0.38, 0.99) ≥4 0.51(0.26, 0.99) Higher 0.57(0.40, 0.81)	Age, sex, education, baseline MMSE score, comorbidity, physical functioning
Kishimoto (2016), a longitudinal population-based study, Japan (Kishimoto et al., 2016)	803 (1998-2005), over 65 years old	17 years	Diagnostic and Statistical manual of Mental Disorders	Physical activity questionnaire	**Leisure PA (times/week)** **All-cause Dementia** Inactive 1 Active 0.78(0.60, 1.01) **Alzheimer Dementia** Inactive 1 Active 0.59(0.41, 0.84) **Vascular Dementia**	Age, sex, low education level, systolic blood pressure, antihypertensive agents, diabetes, total cholesterol, body mass index, electrocardiogram abnormalities, history of stroke at entry, smoking habits, alcohol consumption

					Inactive 1 Active 0.74(0.47, 1.16) **Other Dementia** Inactive 1 Active 1.42(0.79, 2.56)	
Larson (2006), a prospective cohort study, U.S.A. (Larson et al., 2006)	1,740 (1994-2003), over 85 years old	6.2 years	DSM-IV & NINCD-ADRDA	Physical activity questionnaire	**Regular exercise (times/week)** **All-cause Dementia** Inactive 1 Active 0.62(0.44, 0.86) **Alzheimer Dementia** Inactive 1 Active 0.64(0.43, 0.96)	Age, sex
Laurin (2001), a prospective cohort study, Canada (Laurin et al., 2001)	6,434 (1991-1997), Medians 72 years old	11 years	Modified Mini-Mental State Examination	Physical activity questionnaire	**All-cause Dementia (scoring, times/week)** None 1 Low 0.64(0.41, 1.02) Moderate 0.69(0.51, 0.95) High 0.63(0.40, 0.98) **Alzheimer Dementia** None 1 Low 0.67 (0.39, 1.14) Moderate 0.67(0.46, 0.98) High 0.50(0.28, 0.90) **Vascular Dementia** None 1 Low 0.54(0.20, 1.44) Moderate 0.70(0.37, 1.31) High 0.63(0.27, 1.44)	Age, sex, education level
Lee (2015), a observational study, China (Lee et al., 2015)	15,589 (1994-2005), 65 years old	6 years	ICD-10	Physical activity questionnaire	**Leisure PA** **All-cause Dementia** No 1 Yes 0.53(0.34, 0.82)	Age, gender, other types of exercise, educational level, hypertension, diabetes, heart diseases, visual, hearing impairments, poor mobility, depression
Lindsay (2002), a prospective cohort study, Canada (Lindsay et al., 2002)	6,434 (1991-1997), 0ver 65 years old	5 years	Diagnostic and Statistical Manual of Mental Disorders	Physical activity questionnaire	**Total PA** **Alzheimer Dementia** No 1 Yes 0.69(0.50, 0.96)	Age, sex, education
Llamas-Velasco (2015), a prospective study, Spain (Llamas-Velasco et al., 2015)	5,278 (1994-1998), 65 years old	3 years	Diagnostic and Statistical Manual of Mental Disorders	Physical activity interview	**Total PA (classifying)** **Dementia** Inactive 1 Low 0.53(0.34, 0.82) Moderate 0.45(0.27, 0.76) High 0.29(0.16, 0.52)	Age, sex, education, alcohol consumption, stroke, hypertension, Charlson Index
Luck (2014), a longitudinal study,	6,619 (2003-2011), 81.1	1.5 years	Mini-Mental State Examination	Physical activity interview	**Total PA (times/week)** **Dementia**	Age, gender, education, alcohol consumption, smoking, MME score, mental activity, co-morbidity at follow-up

German (Luck et al., 2014)	years old				None 1
					Add 0.79(0.75, 0.90)
					Alzheimer Dementia
					None 1
					Add 0.81(0.69, 0.94)	

Mehlig (2014), a prospective population study, Swedish (Mehlig et al., 2014)	1,448 (1974-2002), 38-60 years old	5-34 year	Diagnostic and Statistical Manual of Mental disorders	Physical activity questionnaire	**Total Leisure time (hours/week)** **Dementia** Active 1 Inactive 1.04(0.67, 1.61) Obese active 0.98(0.51, 1.90) Obese inactive 3.31(1.43, 7.66)	Age, education, smoking, consumption of alcohol, triglycerides, hypertension, parental history of diabetes
McCallum (2007), a longitudinal study, Australia (McCallum et al., 2007)	1,805 (1988-2002), over 60 years old	14 years	ICD-9, ICD-10	Questionnaire	**All-cause Dementia** **Gardening (hours/week)** Rarely 1 Daily 0.64(0.50, 0.83) **Walking (hours/week)** Rarely 1 Daily 1.00(0.78, 1.28)	Marital status, education, prior history of stroke, activities of daily living
Morgan (2014), a prospective study, U.K. (R. J. Morgan, Jr., 2014)	2,959 (1979-2004), 45-59 years old	10 years	Cognitive Impairment not Dementia or Dementia	Physical activity questionnaire	**All-cause Dementia** **Work-related (tertiles)** Low 1 Moderate 0.70(0.36, 1.39) High 0.53(0.24, 1.19) **Leisure-time (tertiles)** Low 1 Moderate 0.57(0.28, 1.16) High 1.16(0.61, 2.19)	Age, social class, national adult reading test score, smoking status, marital status, self-reported history of vascular disease, alcohol consumption, body mass index, common mental disorder, Spielberg's State-Trait Anxiety Index score
Neergaard (2016), a prospective cohort study, Denmark (Neergaard et al., 2016)	5,855 (1999-2001), average 70 years old	Mean 11.9± 3.9 years	ICD-OD & AD	Physical activity questionnaire	**Total PA (times/week)** **All-cause Dementia** None 1 1 0.77(0.61, 0.96) 2 0.80(0.61, 1.04) 3+ 0.79(0.64, 0.97) **Alzheimer Dementia** None 1 1 0.84 (0.58, 1.20) 2 0.99(0.66, 1.47) 3+ 1.00(0.73, 1.37) **Vascular Dementia** None 1 1 0.55(0.24, 1.25) 2 0.46(0.16, 1.35)	Age, education, body mass index, smoking, alcohol, vascular factors, neural disorders

					3+ 0.42(0.19, 0.93) **Other Dementia** None 1 1 0.79(0.56, 1.04) 2 0.72(0.49, 1.05) 3+ 0.71(0.53, 0.95)	
Podewills (2005), a prospective cohort study, U.S.A. (Podewils et al., 2005)	3, 375 (1992–2000), ≥65 years or older	5.4 years	Modified mini-mental state examination	Minnesota Leisure Time Activity Questionnaire	**Total PA (scoring)** **All-cause Dementia** 0-1 1 2 0.90(0.69,1.18) 3 0.90(0.66,1.22) ≥4 0.58(0.41, 0.83) **Alzheimer Dementia** 0-1 1 2 0.73(0.49,1.08) 3 0.85(0.57,1.29) ≥4 0.55(0.34, 0.88) **Vascular Dementia** 0-1 1 2 1.09(0.74,1.60) 3 1.01(0.64,1.58) ≥4 0.65(0.39, 1.08)	Age, educational level, gender, ethnicity, apolipoprotein E genotype, baseline modified Mini-Mental State Examination Score, magnetic resonance imaging white-matter-grade score, activities of daily living impairment, instrumental activities of daily living impairment, Lubben Social Network Score, Social support score
Ravaglia (2008), a prospective population-based cohort, Italian (Ravaglia et al., 2008)	749 (1999-2003), over 65 years old	Over 3.9±0.7 years	DSM-IV	Physical activity questionnaire	**All-cause Dementia** **Walking (Kcal/week)** >209 1 209-417 0.67(0.37, 1,09) >417 0.60(0.33, 1.12) **Moderate (Kcal/week)** <3,455 1 3,455-6,749 0.51(0.28, 0.95) >6,749 0.86(0.52, 1.42) **Vigorous (Kcal/week)** No 1 Yes 0.64(0.25, 1.62) **Total activity (Kcal/week)** <4,774 1 4,774-8,090 0.63(0.38, 1.05) >8,090 0.52(0.29, 0.93) **Alzheimer Dementia** **Walking (Kcal/week)** >209 1 209-417 1.37(0.67, 2,83)	Cardiovascular disease, hypertension, hyperhomocysteinemia

					>417 0.60(0.45, 1.66) **Moderate (Kcal/week)** <3,455 1 3,455-6,749 1.53(0.79, 2.96) >6,749 0.81(0.36, 1.82) **Vigorous (Kcal/week)** No 1 Yes 0.93(0.25, 2.68) **Total activity (Kcal/week)** <4,774 1 4,774-8,090 0.94(0.50,1.77) >8,090 0.71(0.34, 1.49) **Vascular Dementia** **Walking (Kcal/week)** >209 1 209-417 0.27(0.12, 0,63) **Moderate (Kcal/week)** <3,455 1 3,455-6,749 0.29(0.12, 0.66) **Vigorous (Kcal/week)** No 1 Yes 0.36(0.05, 2.73) **Total activity (Kcal/week)** <4,774 1 4,774-8,090 0.24(0.11, 0.56)	
Rovio (2005), a population-based study, Sweden (Rovio et al., 2005)	1,449 (1972-1987), 65-70 years old	21 years	Modified mini-mental state examination	Physical activity questionnaire	**Leisure-time** **All-cause Dementia** Inactive 1 Active 0.45(0.24,0.85) **Alzheimer Dementia** Inactive 1 Active 0.34(0.15, 0.74)	Age, sex, education, follow=up time locomotors symptoms, main occupation during life, income leisure time commuting physical activity, ApoE genotype, body mass index, blood pressure, cholesterol, history of myocardial infarction
Rovio (2007), a population-based study, Sweden (Rovio et al., 2007)	1,449 (1972-1987), 65-70 years old	21 years	Modified mini-mental state examination	Physical activity questionnaire	**Occupational PA** **All-cause Dementia** None 1 Active 1.45(0.66, 3.17) **Alzheimer Dementia** None 1 Active 1.90(0.73, 4.95)	Age, sex, education, follow=up time locomotors symptoms, main occupation during life, income leisure time commuting physical activity, ApoE genotype, body mass index, blood pressure, cholesterol, history of myocardial infarction

Sabia (2017), Whitehall II prospective cohort study, U.S.A. (Sabia et al., 2017)	10,308 (1985-1993), 35-55 years old	27 years	International Classification of Diseases (ICD-10)	Physical activity questionnaire	**All-cause Dementia** **Total PA (hours/week)** ≤8 1 8-12 0.97(0.72, 1.29) ≥12 1.05(0.82, 1.36) ≥ per 1 0.99(0.98, 1.01) **Mild PA** <5 1 5-9 1.21(0.98, 1.58) ≥9 0.98(0.74, 1.30) ≥ per 1 1.00(0.98, 1.01) **Moderate to vigorous PA** ≤2 1 2-4 1.01(0.76, 1.35) ≥4 1.08(0.82, 1.41) ≥ per 1 0.99(0.97, 1.02) **PA recommendation (MVPA)** <2.5 1 ≥12 1.07(0.86, 1.35)	Age, sex, ethnicity, education, occupational position, marital status, smoking status, alcohol consumption, fruits and vegetable consumption, hypertension, diabetes, body mass index, general health questionnaire score, cardiovascular diseases, cardiovascular disease drugs
Scarmeas (2009), a prospective cohort study, U.S.A. (Scarmeas, Honig, et al., 2009)	1,908 (1992-2006), mean 77.2 years old	3.4 years	Diagnostic and Statistical Manual of Mental Disorders	Godin leisure time exercise questionnaire	**Total PA (MET)** **Alzheimer Dementia** No 1 Some 0.59(0.45, 0.78) Much 0.50(0.39, 0.67) Trend (1-3) 0.70(0.61, 0.82)	Age, sex, ethnicity, education, apolipoprotein, caloric intake, body mass index, smoking, depression, leisure activities, comorbidity index, baseline Clinical Dementia Rating score, time between first dietary, first physical activity assessment
Simons (2006), a prospective cohort study, Australian (Simons et al., 2006)	2,805 (1988-2004), 60 years old	16 years	ICD-9 & 10	Physical activity questionnaire	**All-cause Dementia (times/week)** **Gardening** None 1 Daily 0.56(0.44, 0.71) **Walking** None 1 Daily 0.93(0.74, 1.18)	Age, years of education
Soni (2017), a prospective cohort study, U.K. (Soni et al., 2017)	11,391 (2002-2013), over 50 years old	10 years	Informant Questionnaire on Cognitive Decline in the Elderly	Physical activity questionnaire	**All-cause Dementia (scoring)** Lower 1 Higher 0.82(0.72, 0.94)	Age, gender, education, wealth, cognitive function, physical function, smoking status, alcohol consumption, depression, mood problems, cardiovascular conditions, chronic disease
Sumic (2007), a prospective data, U.S.A. (Sumic et al., 2007)	66 (1989-19992), mean age 88.5	4.7 years	Mini Mental State Examination, Clinical Dementia Rating Scale	Physical activity questionnaire	**Exercise (hours/week)** **All-cause Dementia** **Women** ≤4 1 >4 0.12(0.03, 0.41) **Men** ≤4 1	Age, education, apolipoprotein allele 4 states, cognitive function

					>4 0.91(0.25, 3.40)	
Tomata (2017), a population-based cohort study, Japan (Tomata et al., 2017)	6,909 (1994-2006), over 65 years old	5.7 years	Long-term Care Insurance (LTCI)	Physical activity interview	**All-cause Dementia** **Walking (hours/day)** <0.5 1 0.5-1 0.80(0.59, 1.10) ≥1 0.72(0.53, 0.97)	Age, sex, body mass index, history of disease, education level, smoking, alcohol drinking, psychological distress score, pain, physical functioning level
Tolppanen (2015), population-based random sample stud, Finland (Tolppanen et al., 2015)	1,560 (1972–2000), average 78.8 years old	24.4 years	National Hospital Discharge Register, Special Reimbursement Register, Causes of Death Register	Physical activity survey	**Alzheimer Dementia** **Leisure-time PA(weekly MET-hours)** High 1 Moderate 1.45(1.06, 1.97) Low 1.39(0.99, 1.95) **Strenuous sports (hours/week)** Low(0) 1 Medium (<2) 1.02(0.92, 3.60) High (≥2) 0.33(0.14, 0.75) **Vigorous work (hours/week)** Low (0) 1 Medium (≤20) 0.88(0.53, 1.46) High (>20) 0.73(0.41, 1.31) **Moderate activity (hours/week)** Low (≤0) 1 Medium (11-30) 0.65(0.35, 1.20) High (≥31) 0.42(0.22, 0.81) **Activity-induced sweating** Low (0) 1 Medium (1-2) 0.59(0.31, 1.12) High (≥3) 0.57(0.37, 0.84)	Age, living area, education family income, body mass index, tobacco smoking, alcohol dirking, parity, duration of lactation, oral contraceptive and HRT use, previous hysterectomy, menstrual periods and reason for amenorrhea, smoking and energy from diet
Verdelho (2012), a prospective cohort study, Europe (Verdelho et al., 2012)	638 (1985-1992), 74.1 years	3 years	Mini-Mental State Examination	Interview physical activity	**Total PA (hours/week)** **All-cause Dementia** Inactive 1 Active 0.61(0.04, 0.38) **Alzheimer Dementia** <10 1 10-<30 1.93(0.82, 0.50) **Vascular dementia** Never 1 <1 0.42(0.22, 0.80)	Age, education, white matter change severity, medial temporal atrophy, previous and incident stroke, diabetes

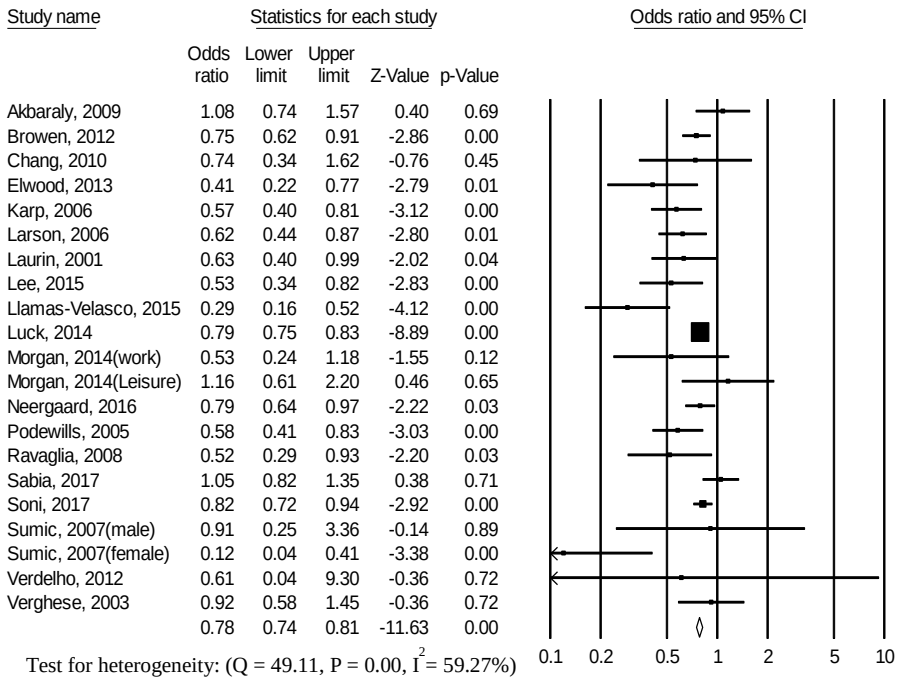
Verghese (2003), a prospective cohort study, U.S.A. (Verghese et al., 2003)	469 (1983-1989), older than 75 years of age	5.1 years	Diagnostic and Statistical Manual of Mental Disorders	Physical activity	**Leisure PA score (points)** **All-cause Dementia** <9 1 9-16 1.06(0.67, 1.65) >16 0.92(0.58, 1.45)	Age, sex, educational level, presence or absence of chronic medical lionesses
Wang (2002), a longitudinal population-based study, Sweden (W. Wang, Xie, Wan, & Wang, 2002)	1,473 (1987-1996), over 75 years old	6.4 years	Mini-Mental State Examination	Physical activity interview	**All-cause Dementia** **Total PA (times/week)** No 1 <7 0.97(0.42, 2.22) ≥7 0.41(0.13, 1.31) **Recreational PA** No 1 <7 1.06(0.42, 2.45) ≥7 0.95(0.55, 1.63)	Age, sex, education, baseline Mini-Mental State Examination Score, comorbidity, depressive symptoms, physical functioning
Yoshitake (1995), a prospective cohort study, Japan (Yoshitake et al., 1995)	828 (1985-1992), over 65 years old	7 years	NINDS-AIREN & NINCD-ADRDA	A standard questionnaire	**Total PA (scoring)** **Vascular Dementia** Inactive 1 Active 0.81(0.42, 1.57) **Alzheimer Dementia** <10 1 10-<30 0.18(0.06, 0.61)	Age
Zhou (2017), China, a nationwide longitudinal study, China (Y. L. Zhou, Liu, Yuan, & Lu, 2017)	7,501 (2002-2012), over 65 years old	9 years	Questionnaire	Physical activity questionnaire	**Exercise** **All-cause Dementia** Yes 1 No 0.53(0.33, 0.85)	Demographic characteristics, lifestyle variables, health status variables

Abbreviations: PA, Physical Activity; MVPA, Moderate to Vigorous Physical Activity

Figure A. High and moderate amounts of physical activity and dementia risk

All-cause dementia

High amount of physical activity (>2 hours/week &>3 times/week) vs. Inactivity (<1 hour/week)

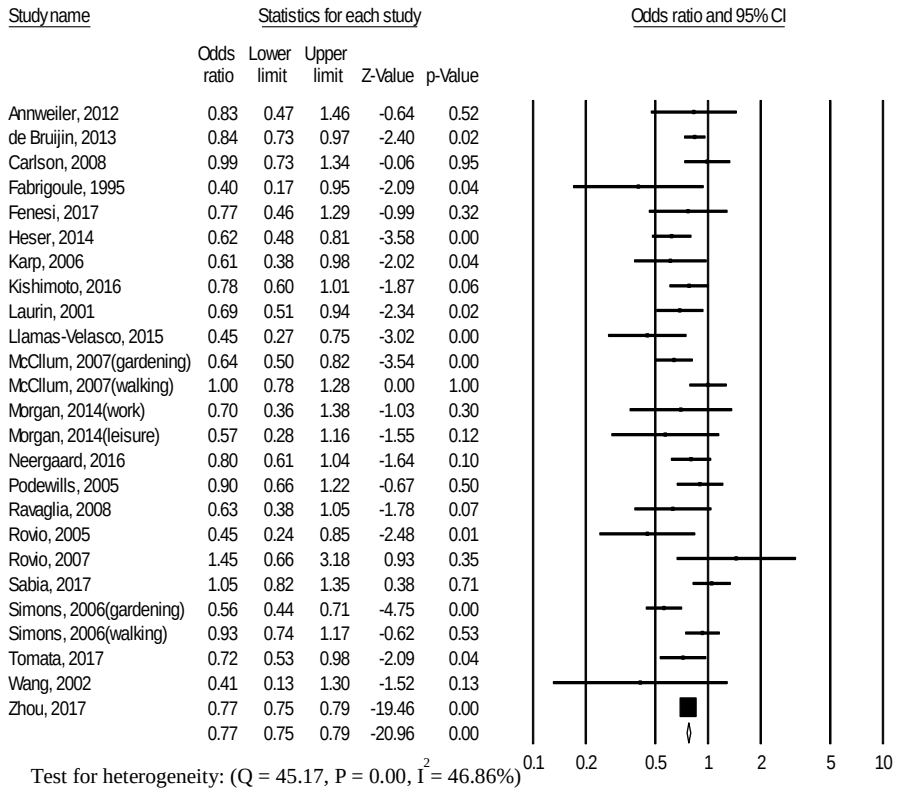


Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Akbaraly, 2009	1.08	0.74	1.57	0.40	0.69
Browen, 2012	0.75	0.62	0.91	-2.86	0.00
Chang, 2010	0.74	0.34	1.62	-0.76	0.45
Elwood, 2013	0.41	0.22	0.77	-2.79	0.01
Karp, 2006	0.57	0.40	0.81	-3.12	0.00
Larson, 2006	0.62	0.44	0.87	-2.80	0.01
Laurin, 2001	0.63	0.40	0.99	-2.02	0.04
Lee, 2015	0.53	0.34	0.82	-2.83	0.00
Llamas-Velasco, 2015	0.29	0.16	0.52	-4.12	0.00
Luck, 2014	0.79	0.75	0.83	-8.89	0.00
Morgan, 2014(work)	0.53	0.24	1.18	-1.55	0.12
Morgan, 2014(Leisure)	1.16	0.61	2.20	0.46	0.65
Neergaard, 2016	0.79	0.64	0.97	-2.22	0.03
Podewills, 2005	0.58	0.41	0.83	-3.03	0.00
Ravaglia, 2008	0.52	0.29	0.93	-2.20	0.03
Sabia, 2017	1.05	0.82	1.35	0.38	0.71
Soni, 2017	0.82	0.72	0.94	-2.92	0.00
Sumic, 2007(male)	0.91	0.25	3.36	-0.14	0.89
Sumic, 2007(female)	0.12	0.04	0.41	-3.38	0.00
Verdelho, 2012	0.61	0.04	9.30	-0.36	0.72
Verghese, 2003	0.92	0.58	1.45	-0.36	0.72
	0.78	0.74	0.81	-11.63	0.00

Test for heterogeneity: (Q = 49.11, P = 0.00, I^2 = 59.27%)

All-cause dementia

Moderate amount of physical activity (>1 hour/week &>2 times/week) vs. Inactivity (<1 hour/week)



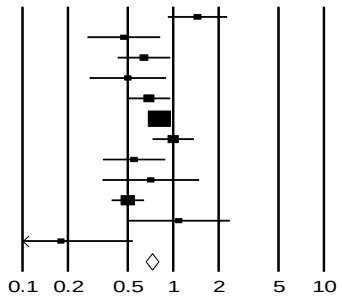
Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Annweiler, 2012	0.83	0.47	1.46	-0.64	0.52
de Bruijin, 2013	0.84	0.73	0.97	-2.40	0.02
Carlson, 2008	0.99	0.73	1.34	-0.06	0.95
Fabrigoule, 1995	0.40	0.17	0.95	-2.09	0.04
Fenesi, 2017	0.77	0.46	1.29	-0.99	0.32
Heser, 2014	0.62	0.48	0.81	-3.58	0.00
Karp, 2006	0.61	0.38	0.98	-2.02	0.04
Kishimoto, 2016	0.78	0.60	1.01	-1.87	0.06
Laurin, 2001	0.69	0.51	0.94	-2.34	0.02
Llamas-Velasco, 2015	0.45	0.27	0.75	-3.02	0.00
McCllum, 2007(gardening)	0.64	0.50	0.82	-3.54	0.00
McCllum, 2007(walking)	1.00	0.78	1.28	0.00	1.00
Morgan, 2014(work)	0.70	0.36	1.38	-1.03	0.30
Morgan, 2014(leisure)	0.57	0.28	1.16	-1.55	0.12
Neergaard, 2016	0.80	0.61	1.04	-1.64	0.10
Podewills, 2005	0.90	0.66	1.22	-0.67	0.50
Ravaglia, 2008	0.63	0.38	1.05	-1.78	0.07
Rovio, 2005	0.45	0.24	0.85	-2.48	0.01
Rovio, 2007	1.45	0.66	3.18	0.93	0.35
Sabia, 2017	1.05	0.82	1.35	0.38	0.71
Simons, 2006(gardening)	0.56	0.44	0.71	-4.75	0.00
Simons, 2006(walking)	0.93	0.74	1.17	-0.62	0.53
Tomata, 2017	0.72	0.53	0.98	-2.09	0.04
Wang, 2002	0.41	0.13	1.30	-1.52	0.13
Zhou, 2017	0.77	0.75	0.79	-19.46	0.00
	0.77	0.75	0.79	-20.96	0.00

Test for heterogeneity: (Q = 45.17, P = 0.00, I^2 = 46.86%)

Alzheimer diseases

High amount of physical activity (>2 hours/week &>3 times/week vs. Inactivity (<1 hour/week)

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Akbaraly, 2009	1.45	0.92	2.28	1.60	0.11
Buchman, 2012	0.47	0.27	0.82	-2.66	0.01
Larson, 2006	0.64	0.43	0.96	-2.18	0.03
Laurin, 2001	0.50	0.28	0.90	-2.33	0.02
Lindsay, 2002	0.69	0.50	0.96	-2.23	0.03
Luck, 2014	0.81	0.69	0.95	-2.67	0.01
Neergaard, 2016	1.00	0.73	1.37	0.00	1.00
Podewills, 2005	0.55	0.34	0.88	-2.46	0.01
Ravaglia, 2008	0.71	0.34	1.49	-0.91	0.36
Scrmeas, 2009	0.50	0.39	0.64	-5.47	0.00
Verdelho, 2012	1.09	0.50	2.37	0.22	0.83
Yoshitake, 1995	0.18	0.06	0.54	-3.06	0.00
	0.72	0.66	0.80	-6.46	0.00

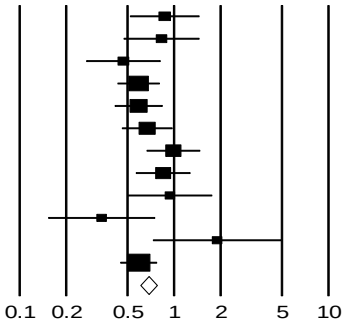


Test for heterogeneity: (Q = 36.42, P = 0.00, I^2 = 69.80%)

Alzheimer diseases

Moderate amount of physical activity (>1 hour/week &>2 times/week) vs. Inactivity (<1 hour/week)

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Akbaraly, 2009	0.87	0.52	1.46	-0.53	0.60
Annweiler, 2012	0.83	0.47	1.46	-0.64	0.52
Buchman, 2012	0.47	0.27	0.82	-2.66	0.01
Heser, 2014	0.59	0.43	0.81	-3.27	0.00
Kishimoto, 2016	0.59	0.41	0.84	-2.88	0.00
Laurin, 2001	0.67	0.46	0.98	-2.08	0.04
Neergaard, 2016	0.99	0.66	1.48	-0.05	0.96
Podewills, 2005	0.85	0.57	1.28	-0.78	0.44
Ravaglia, 2008	0.94	0.50	1.77	-0.19	0.85
Rovio, 2005	0.34	0.15	0.76	-2.65	0.01
Rovio, 2007	1.90	0.73	4.95	1.31	0.19
Scrmeas, 2009	0.59	0.45	0.78	-3.76	0.00
	0.68	0.60	0.77	-6.03	0.00

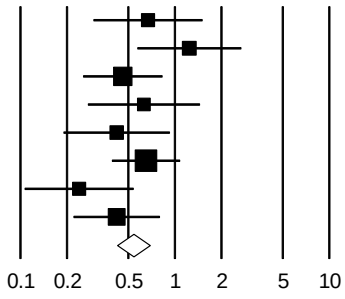


Test for heterogeneity: (Q =33.95, P = 0.00, I^2 = 67.60%)

Vascular dementia

High amount of physical activity (>2 hours/week &>3 times/week) vs. Inactivity (<1 hour/week)

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Akbaraly, 2009	0.67	0.30	1.51	-0.96	0.34
Hebert, 2000 (male)	1.24	0.57	2.70	0.54	0.59
Hebert, 2000 (female)	0.46	0.25	0.83	-2.56	0.01
Laurin, 2001	0.63	0.27	1.45	-1.08	0.28
Neergaard, 2016	0.42	0.19	0.93	-2.14	0.03
Podewills, 2005	0.65	0.39	1.08	-1.66	0.10
Ravaglia, 2008	0.24	0.11	0.54	-3.44	0.00
Verdelho, 2012	0.42	0.22	0.80	-2.63	0.01
	0.54	0.42	0.69	-4.97	0.00



Test for heterogeneity: (Q =10.37, P = 0.17, I^2 = 32.47%)

Vascular dementia

Moderate amount of physical activity (>1 hour/week &>2 times/week) vs. Inactivity (<1 hour/week)

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Akbaraly, 2009	0.76	0.34	1.70	-0.67	0.51
Laurin, 2001	0.70	0.37	1.32	-1.11	0.27
Neergaard, 2016	0.46	0.16	1.34	-1.43	0.15
Podewills, 2005	1.01	0.64	1.59	0.04	0.97
Ravaglia, 2008	0.29	0.12	0.68	-2.85	0.00
	0.72	0.54	0.97	-2.14	0.03

Test for heterogeneity: (Q = 7.23, P = 0.12, I^2 = 44.68%)