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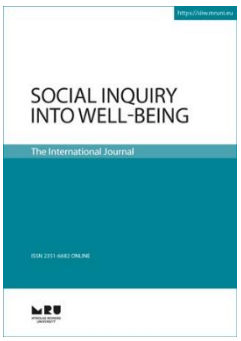

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Physical activity in maintaining cognitive functioning in older age – Mini-review of recent European studies

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Abstract

Physical activity earlier in life is considered one of the key determinants of an active and healthy older age. During the recent years, several population-based longitudinal studies with follow-up periods extending up to several decades have shown that a physically active lifestyle is associated with better older-age cognitive capacity and also decreased risk of dementia and Alzheimer's disease. Recent studies also show that increasing physical activity from mid- to late life have beneficial effects on later-life cognition, which indicates that the window of opportunity for preventive physical activity interventions may extend from midlife to old age. Among older people, the first randomized controlled trials aiming to prevent cognitive decline through physical activity and especially multidomain lifestyle-based interventions have been recently conducted, and promising results have been reported. This mini-review brings together information on life-long benefits of a physically active lifestyle, focusing on the favorable effects on brain health.

Keywords: physical activity; ageing; dementia; review

Introduction

Dementia is one of the leading causes of functional dependence and need for long-term care among the older population. Currently with constantly developing medical care in European countries, most chronic conditions can be prevented or at least treated. However, dementia and Alzheimer's disease are still diseases with no efficient prevention or cure. Along with population aging, dementia-related diseases will become even more common. It has been estimated that in year 2015 about 47 million people worldwide were living with dementia and it has been estimated that this number will almost double every 20 years, reaching almost 75 million in 2030 and over 130 million in 2050 (Alzheimer Disease International, Dementia statistics, http://www.alz.co.uk/research/statistics).

Previously, the common belief was that dementia-related illnesses are mainly caused by old age and genetic factors. This lead to relatively negative and fatalistic views and did not leave very much space for preventive interventions. However, currently there is increasing amount of evidence showing that several modifiable lifestyle factors have significant effects on dementia risk. Very recently, Satizabal and colleagues reported that the incidence of dementia has significantly declined over the course of previous three decades (Satizabal et al., 2016). Their study reported that the age- and sex-adjusted hazard rates for dementia have declined systematically from late 1970s to early 2010s. However, this decline together with improvements in cardiovascular health was observed only among persons who had at least high school diploma, indicating that the educational level may have a significant effect in delaying the onset of dementia. Similar declining trends have also observed in other studies (Matthews et al., 2013; Qiu, von Strauss, Backman, Winblad, & Fratiglioni, 2013; Rocca et al., 2011). It is possible that improvements in lifestyle and increased knowledge how to make positive changes have led to improvements in older age cognition.

In recent decades, especially research related to the association between modifiable life-style factors and

dementia risk has been emerging. Several large population-based datasets with follow-up periods extending up to several decades have provided sufficient evidence that a lot can be done by increasing knowledge on healthy life style and by adopting necessary changes. Physical activity and exercise have been among the widely studied methods to improve old-age cognitive functioning.

Methods of the mini-review

This mini-review gives a brief overview of population-based and intervention studies that have been carried out in Europe during the last decade (years 2006-2016). The additional inclusion criteria included a follow-up period more than five years in prospective population-based studies, baseline measure of physical activity (self-reported or objectively measured) and outcome measure of clinically assessed dementia, Alzheimer's disease, dementia-related structural brain changes or dementia-related mortality. European randomized controlled studies from years 2006-2016 including persons aged 60 years or older were also included. The literature search was conducted using the PubMed database.

Association between physically active lifestyle and dementia incidence – Evidence from prospective cohort studies

Several population-based cohort studies have shown strong associations between healthy lifestyle and lower risk of dementia. In order to be able to draw conclusions on causal pathways, prospective longitudinal studies with appropriate measures of physical activity and also detailed information on cognitive capacity and incident dementia in later life are needed. Also follow-up periods need to be long enough to diminish the possibility of reverse causality. In Europe and especially in Nordic countries there are long traditions in conducting large population-based cohort studies. Such studies have provided knowledge that by paying attention to individual lifestyle choices across the whole life course, it is possible to modify dementia risk and even delay the onset of the disease.

Strong evidence supporting the association between physically active lifestyle and lower dementia risk. Finland has been among the first countries in Europe where large prospective follow-up studies have been used to investigate the longitudinal associations between earlier life physical activity and older age cognitive functioning and dementia. One of the first studies was Finnish Cardiovascular risk factors, Aging and Dementia (CAIDE) study. Participants of the CAIDE study were randomly selected from previously conducted population-based studies, which had assessed cardiovascular risk factors in the Finnish population. For the CAIDE study, a random sample of persons aged 65-79 years was invited to take part. These persons were investigated previously at the mean age of 50 years. In the CAIDE study, earlier life physical activity as independent risk factor for old age dementia, Alzheimer's disease and dementia-related structural brain changes was investigated. Studies conducted by Rovio and colleagues showed that physical activity, especially physical activity during leisure time, is associated with lower risk of developing dementia and Alzheimer's disease almost two decades later (Rovio et al., 2005; Rovio et al., 2007). When investigating the possible mechanisms explaining the association between physically active lifestyle and dementia risk, the researchers found that physical activity in midlife was associated with larger gray matter volume in brains and also with larger total brain volume (Rovio et al., 2010). The authors hypothesize that physical activity may affect brain via vascular pathways, for example reducing cardiovascular risk factors (blood pressure, high cholesterol and by preventing from obesity). They also suggest that physical activity affects neurobiological mechanisms, for example activates molecular and cellular mechanisms that influence brain plasticity and maintain cognitive function during ageing (Rovio et al., 2010).

A few years later, Tolppanen et al. confirmed the results using the same CAIDE dataset with longer follow-up period (Tolppanen et al., 2015). When extending the follow-up from 21 to 28 years, this study confirmed the earlier results by showing that persons exercising a few times per year or less had 40 percent higher risk for incident dementia compared to persons who exercised two to three times per week or more. The association was more pronounced in men and persons who were overweight. More detailed analyses also showed that persons who increased their physical activity from midlife to late life, had significantly lower dementia risk compared to persons who stayed physically inactive. This finding clearly showed that becoming more active when getting older may contribute to lowering risk of cognitive decline (Tolppanen et al., 2015).

In Finland, further datasets have been used to analyze the longitudinal association between physical activity and dementia risk. Results from the large Finnish Twin Cohort including over 2,000 persons born in Finland before 1958 showed that being physically sedentary at the mean age of 52 years increases dementia risk more than two-fold over the 20-year follow-up (Virta et al., 2013). Also very recently, Iso-Markku et al. showed that in the same Finnish Twin Cohort with a 29-year follow-up period, vigorous physical activity (alternately jogging and walking, jogging or running) reduced the risk for dementia-related mortality by almost 40 percent (Iso-Markku, Waller, Kujala, & Kaprio, 2015).

Also studies from other European countries have provided evidence about the benefits of lifelong leisure-time physical activity. Andel et al. (2008) reported results from the Swedish Twin Registry, which consists of cohorts of twin pairs, with the oldest born in 1926. Their analyses consisted of altogether 3,134 individuals, whose physical activity was assessed at midlife (mean age of 48 years) and cognition was examined at the mean age of 80 years, thus the follow-up period being about 30 years. Their analyses showed that both light exercise (such as walking) and more straining exercise (regular sports) reduced future dementia risk. Regular exercise reduced the dementia risk for more than 60 percent even after controlling for other life style factors (Andel et al., 2008).

The type of physical activity seems to partly modify the associations between physical activity and dementia risk. Based on the findings by Rovio et al. (2007), work-related or commuting physical activity may not have similar beneficial effects (Rovio et al., 2007). However, this may be explained by the fact that persons who had physically straining work were less educated and thus may have had lower socioeconomic status, which in turn may increase their dementia risk. Since poor socioeconomic status is linked to increased risk for several chronic conditions, including dementia, this may partly explain the results. Another explanation may be that the intensity of commuting or work-related physical activity may not be intensive enough to provide the health-related effects (Rovio et al., 2007). It is possible that the beneficial effects of physical activity on cognition are modified by several other factors. For example a review by Dufouil et al. (2014) showed that the positive effects of physical activity was more pronounced among women (Dufouil, Seshadri, & Chene, 2014). However, conflicting results were reported by Tolppanen et al. 2015, who found stronger association in men. Also body weight and obesity may modify the relationship (Tolppanen et al., 2015)

Also conflicting results are reported. It should be noted that not all published results are consistent, and there are studies reporting non-significant associations between physically active lifestyle and lower dementia risk. The Rotterdam Study in the Netherlands with a mean follow-up period of nine years found only a borderline significant effect of physical activity on incident dementia. This study found that the association between higher physical activity and lower risk of incident dementia was significant with shorter follow-up (up to four years), but not with follow-up more than four years (de Bruijn et al., 2013). Therefore the authors hypothesized that the association between physical activity and better cognition may partly reflect reverse causality especially when the follow-up periods are not adequately long.

A Swedish study, Uppsala Longitudinal Study of Adult Men, which investigated men aged 49-51 years (n=2,293) in midlife and followed them up for four decades, showed that low work-time physical activity had a stronger association with better physical and cognitive function, but the association between leisure-time physical activity and older-age physical and cognitive function was not statistically significant (Franzon, Zethelius, Cederholm, & Kilander, 2015).

Also a meta-analysis by Batty and colleagues (2014) with pooled data from ten population-based UK cohort studies including over 100,000 men and women, with the mean follow-up period of eight years, investigated physical inactivity in relation to dementia-related mortality. Their study showed that in this extremely large sample, physical inactivity was not associated with increased risk for dementia-related mortality. The authors, however, state that it should be noted that all dementia-related illnesses were comprised in this analysis and it is possible that physical activity may have different effects for different dementia types. Also the outcome in this study was dementia-related mortality, not disease itself, which may have affected the results (Batty, Russ, Starr, Stamatakis, & Kivimaki, 2014).

As briefly described above, a physically active lifestyle seems to be one of the key determinants of maintaining good cognition in old age. However, it should be noted that also several other lifestyle factors do contribute to older-age cognition. Several prospective studies have reported how healthy diet including polyunsaturated fatty acids, vegetables, berries and rich in vitamins and antioxidants is associated with lower risk of dementia and cognitive decline (Barberger-Gateau et al., 2007; Eskelinen, Ngandu, Tuomilehto, Soininen, & Kivipelto, 2011; Orhan et al., 2015; Safouris, Tsivgoulis, Sergentanis, & Psaltopoulou, 2015). Similarly, social activities, including meeting friends and relatives and engaging in socially and mentally stimulating activities (Karp et al., 2006; Qiu, Xu, & Fratiglioni, 2010) have beneficial effects on older-age cognition and may prevent from dementing illnesses. For example, the study by Paillard-Borg et al. (2012) reported that mental, physical and social activities have relatively similar impact on increase in dementia risk. They also found that broad spectrum of participation in these activities reduced the dementia risk significantly more than one single activity alone (Paillard-Borg, Fratiglioni, Xu, Winblad, & Wang, 2012). A meta-analysis by Beydoun et al. (2014) showed that in prospective studies, physical activity is more consistently associated with lower dementia risk than any other life-style risk factor. In their meta-analyses, the pooled relative risks for dementia were 1.99 for low vs. higher educational attainment; 1.37 for smoking status (current or ever vs. never smokers; 0.58 for physical activity and 0.67 for high intake of n-3 fatty acids (Beydoun et al., 2014).

From cohort studies to interventions

Increasing evidence about the longitudinal associations between lifestyle factors and dementia incidence have resulted in the need for randomized controlled trials (RCT) in order to be able to test the real effects of lifestyle changes in dementia prevention. European RCTs investigating the effect of physical activity interventions on older-age cognition are still relatively scarce. However, a few studies have been conducted and are currently ongoing in Europe. Some of these studies specifically focus on increasing physical activity, and some studies have taken a multidomain approach.

Intervention studies focusing on increasing physical activity. Overall, interventions aiming at preventing dementia and Alzheimer's diseases via physical activity interventions have resulted in relatively modest results. Some studies have also included very specific population groups, especially persons with certain chronic conditions.

In 2010, Smith and colleagues performed a systematic literature review that summarized the randomized controlled trials examining the association between aerobic exercise training and neurocognitive performance among persons aged 18 years and older (Smith et al., 2010). Their review included studies with treatment duration for more than one month. Altogether 29 studies met their inclusion criteria, but only two of the reviewed studies were conducted in Europe

after 2005 and among persons aged 60 years or older. In the Netherlands, van Uffelen et al. (2008) examined community-dwelling older people aged 70-80 years with mild cognitive impairment and reported that intensive walking programme (aerobic exercise) was not effective in improving overall cognitive function within one year, however, it improved memory in men, and memory and attention in women with better adherence. In this study, the researchers used an outcome measure of cognitive function, measured with neuropsychological tests at baseline and after six and 12 months (van Uffelen, Chinapaw, van Mechelen, & Hopman-Rock, 2008). Also, Spanish researchers Munguía-Izquierdo and Legaz-Arrese (2008) investigated the effects of a 16-week exercise therapy (3 times a week) in a chest-high pool of warm water on cognitive functioning among women aged 18-60 years who had a diagnosis of fibromyalgia. Their study showed that a 16-week aquatic training program, including strength training, aerobic training, and relaxation exercises has beneficial effects on cognitive functioning (Munguia-Izquierdo & Legaz-Arrese, 2008). In 2013, Roig and colleagues performed another review including cardiovascular exercise intervention studies, which aimed at improving memory. Among a total of 39 reviewed studies, there were no studies conducted in the recent decade focusing on persons aged 60 years (Roig, Nordbrandt, Geertsen, & Nielsen, 2013).

Taken together, recent physical activity interventions aiming to prevent cognitive decline are scarce and have resulted in relatively modest findings. Since it is widely acknowledged that in addition to physical activity, several other life style factors have significant effects on cognition, interventions aiming to increase physical activity alone may not provide the most effective results.

Intervention studies with a multidomain approach. Although some randomized controlled trials have provided evidence that by increasing physical activity level, the onset of dementia-related illness could be postponed and cognitive capacity can be maintained or even improved, the effects of the interventions have been rather modest. This may be due to the above-mentioned fact that dementia and Alzheimer's disease are influenced by several lifestyle factors and modifying only one risk factor may not be enough. Therefore multidomain approaches most likely provide additional benefits.

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (Finger) study is the first multidomain intervention study in the world, which aims to maintain cognitive capacity among older people via multidomain lifestyle-based intervention with a multi-center randomized controlled trial. The aim of the Finger study is to provide evidence whether a multidomain lifestyle-based intervention could delay or prevent cognitive decline among older population (Kivipelto et al., 2013; Ngandu et al., 2014). First results from the Finger trial were published in 2015 (Ngandu et al., 2015). Finger trial included a multidomain intervention (diet, exercise, cognitive training, vascular risk monitoring, n=631), and a control group (n=628) that received general health advice. The outcome measure was a thorough cognitive assessment with standard neuropsychological tests, which were conducted by study psychologists. After the two-year intervention period, a significant beneficial effect of the intervention was seen for general cognitive capacity, executive functioning and processing speed. Improvement in executive functioning was 83% higher, and in processing speed 150% higher in the intervention group than in the control group (Ngandu et al., 2015). Finger study provides first evidence that among the general older population, modifying lifestyle may lead to significantly improved cognitive function. Results from the Finger trial have also received some criticisms. There have been discussions about the possible learning effect arising out of growing familiarity with the testing procedures possibly influencing cognitive testing, and also about the effect sizes for such an extensive intervention. These discussions indicate that additional research evidence is still required to fully understand the meaning of lifestyle in dementia prevention (Kivimaki, Batty, & Singh-Manoux, 2015; Kivipelto, Mangialasche, Solomon, & FINGER Study Group, 2015; Lampit & Valenzuela, 2015).

Currently, also other multidomain interventions studies are ongoing in Europe. For example in France, the Multidomain Alzheimer Preventive Trial (MAPT study) is investigating the efficacy of isolated supplementation of omega-3 fatty acid, an isolated multidomain intervention (nutritional counseling, physical exercise, cognitive stimulation) or a combination of the two interventions on cognitive functions in frail subjects aged 70 years and older (Vellas et al., 2014). Also in the Netherlands, a large cluster-randomized trial (Prevention of dementia by intensive vascular care (PreDIVA) investigates whether nurse-led intensive vascular care in primary care decreases the incidence of dementia and reduces disability during the 6-year follow-up in 3,700 subjects aged 70-78 years (Richard et al., 2009). Results from these studies will provide additional evidence about the benefits of multidomain interventions in dementia prevention.

Discussion and conclusions

As described in this mini-review, there is evidence that a physically active lifestyle may prevent dementia or postpone the onset of dementia-related diseases in old age. Evidence from prospective follow-up studies indicates that lifelong physical activity and also increasing physical activity after midlife have beneficial effect on brain health. Also first randomized controlled trials have suggested beneficial intervention effects.

However, dementia and Alzheimer's disease are known to be affected by several risk and protective factors. Based on several studies, a physically active lifestyle is one significant modifiable factor that most likely reduces the risk of dementia-related illnesses. It should also always be noted that physical activity alone may not be sufficient to prevent older-age cognitive decline. As reported in several population-based longitudinal studies and also in randomized controlled trials, further factors such as healthy diet (Valls-Pedret et al., 2015), prevention and good treatment of chronic conditions (Tolppanen, Solomon, Soininen, & Kivipelto, 2012), and also social activities (Karp et al., 2006) are associated with lower dementia

incidence. Therefore, healthy lifestyle, including proper nutrition, prevention and treatment of chronic conditions, social and mentally active lifestyle among with physical exercise are all key factors in cognitively healthy ageing. The multidomain approach in lifestyle-based intervention studies is most likely the most effective way to postpone the onset of dementia, Alzheimer's disease and other forms of cognitive decline in old age.

During the next few years, ongoing large clinical trials aiming to prevent cognitive decline will provide additional evidence about the lifestyle modifications, which could be considered as easy tools to prevent future burden of dementing illnesses in ageing population.

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