Psychiatria Danubina, 2021; Vol. 33, Suppl. 4 (part IV), pp 1267-1273 *Conference paper*

Review

COULD MENTAL AND PHYSICAL EXERCISE ALLEVIATE ALZHEIMER'S DISEASE?

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SUMMARY

The aim of this review is to emphasize the importance of mental activity and aerobic physical exercise as one of the most important health-related activities which may delay the onset or slow down the progression of Alzheimer's dementia. Studies have shown that the elderly who regularly engage in mental and physical activities have a lower risk of dementia development. Performing mental and physical activities regularly has a synergistic effect on the improvement of cognitive functions. Complex mental activity during life is associated with a reduction in the hippocampal atrophy rate, which is a sensitive early-stage biomarker of dementia while regular physical exercise can slow down the progressive reduction of the cortical brain volume which occurs during aging. Mental activity increases a person's "cognitive reserve" and promotes the formation of new communications between brain cells. Since it is not possible to influence genetic components of Alzheimer's dementia, preventative interventions such as encouraging regular engagement in mental and physical activities are extremely important. Activities need to be safe, moderate, comfortable, and adapted as to type, duration, and especially the health and functional status of the patient. In the near future, it is expected that genome analysis in personalized medicine will guide us in the right direction on certain types of physical and mental exercise.

Key words: *Alzheimer's dementia - mental activity -physical activity - personalized medicine*

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INTRODUCTION

According to the WHO, Alzheimer's and other dementias are one of the top ten causes of death and a major cause of disability among older people worldwide (WHO 2018). In developed countries, Alzheimer's disease is the 3rd most frequent cause of mortality, with a rate of over 60 deaths per 100,000 (WHO 2018). There are no national studies on this issue for Croatia, but taking into account the data published by the Croatian Institute of Public Health and the number of deaths for 2018, we came to these data shown in Table 1.

With the increase in the percentage of older people who make up the fastest-growing part of the population in developed countries, the prevalence of chronic diseases, among which Alzheimer's dementia is one of the most common, is increasing. In Croatia, over 17.62% of the population is aged over 65, and more than 24% of the population is older than 60 years. The number of patients with Alzheimer's disease in Croatia is around 80,000 (Mimica et al. 2017), while globally almost 47 million people suffer from dementia. It is estimated that the number of people with dementia will reach 75 million by 2030 and that the number will exceed 130 million by 2050 (Prince et al. 2015). It should be emphasized that the number of studies on dementia in this part of Europe is relatively small compared to research in Western Europe (number of studies /10 mil population: Western Europe 6.6, Central Europe 2.2 and Eastern Europe 0.2) (Alzheimer's Disease International 2019).

Table 1. List of selected causes of death in 2018 in Croatia (data obtained from Croatian Institute of Public Health) (Stevanović et al. 2019)

Cause of death	Gender	Number of deaths	Percentage of total deaths	Deaths per 100.000
All causes of death	Total	51794		1274.07
	Male	25352		1286.46
	Female	26442		1262.41
Dementia	Total	615	1.19	15.13
	Male	160	0.63	8.12
	Female	455	1.72	21.72
Alzheimer's disease	Total	439	0.85	10.80
	Male	148	0.58	7.49
	Female	291	1.10	13.89

Dementia is a disease of the central nervous system with a consequent reduction in cognitive ability and impaired nerve function. Alzheimer's dementia is the most common disease in people aged over 65 (WHO 2018) and it accounts for 60 to 80 percent of the dementia cases in this age-group (Radić et al. 2019). Frequently, dementia is associated with vascular cognitive disorders. The risk factors for the development of vascular dementia are older age, post-cerebrovascular injury, arterial hypertension, hyperlipoproteinemia, elevated serum LDL levels, elevated total cholesterol levels, reduced HDL cholesterol, and elevated triglyceride levels, type 2 diabetes, and smoking (Viswanathan et al. 2009).

PREVENTION OF ALZHEIMER'S DISEASE

Due to the World Alzheimer Report 2019 (Alzheimer's Disease International 2019), 95% of the public think they will develop dementia in their lifetime and 1 in 4 people think that there is nothing you can do about that because dementia is caused by normal ageing. But, is it really true that lifestyle changes have no impact in the risk of developing AD?

Studies have shown that the elderly who regularly engage in mental and physical activities have a lower risk of cognitive impairment and dementia development (Larson et al. 2006; Barnes et al. 2013). Barnes and Yaffe (Barnes & Yaffe 2011) estimated that 54% of AD risk factors might be preventable. Performing mental and physical activities regularly and frequently contributes to the improvement of cognitive functions and reduces the risk of dementia (Larson et al. 2006). Barnes and colleagues pointed to a synergistic effect of mental and physical activity. In a controlled 12-week trial, they showed improved cognitive function in inactive elderly individuals who had symptoms of short-term memory loss, with the combined use of mental and body activity, indicating a greater effect of the amount than the type of activity (Barnes et al. 2013). Furthermore, Lipnicki et al. showed that higher levels of education and vigorous physical activity were associated with better performance ($p<0.01$ for both) (Lipnicki 2019).

MENTAL ACTIVITY IN THE PREVENTION OF ALZHEIMER'S DISEASE

Research suggests a neuroprotective and neuroregenerative effect of performing complex mental activities such as education, artistic creation, reading, writing, and social activities. Complex mental activity during life is associated with a reduction in the hippocampal atrophy rate, which is a sensitive early-stage biomarker of dementia (Valenzuela et al. 2008). The neuroprotective effect in the medial temporal lobe is considered to be responsible for the association between complex mental activity during life and lower rates of dementia in population research (Valenzuela et al. 2008). Mental activity can be maintained so that the brain is permanently activated, which not only increases a person's "cognitive reserve", but also enables the creation of new connections between cells (Verghese et al. 2003). To preserve mental activity, it is useful to read, solve crossword or other types of puzzles and similar tasks, as well as to encourage socializing and engaging in social activities, developing different interests, and engaging in hobbies. Up to date, for various leisure activities, a protective effect on the development of dementia has been shown. Verghese and colleagues showed that reading, playing board games, playing musical instruments, and dancing are associated with a lower risk of dementia (Verghese et al. 2003). Fabrigoule et al. showed that knitting, gardening, and traveling reduced the risk of dementia (Fabrigoule et al. 1995). It has been shown that low levels of brain activity (e.g., individuals of lower education) are more often associated with the development of Alzheimer's disease, while a higher level of education is associated with a later onset of the disease (Zschucke et al. 2013, Hamer et al. 2009, Daviglus et al. 2010, Rot et al. 2009). Additionally, any other known way to improve memory, like learning a foreign language, playing with grandchildren, or learning to play a musical instrument, may be of value. In those who have already started to develop Alzheimer's disease, increased involvement in mental activity can contribute to a milder course of the disease as well as slower progression, compared to those who do not engage in such activities (Zschucke et al. 2013, Hamer et al. 2009, Daviglus et al. 2010, Rot et al. 2009).

PHYSICAL ACTIVITY IN THE PREVENTION OF ALZHEIMER'S DISEASE

Regular moderate exercise is one of the requirements for a healthy life and preventing certain chronic diseases such as dementia, atherosclerosis, and malignant diseases (breast cancer, colon cancer). Physical activity is also important in regulating body mass, blood pressure, and glucose levels. Cardiorespiratory capacity associated with muscular abilities is significantly related to a lower risk of developing chronic diseases and a better quality of life, especially in the elderly. A study on the effects of physical activity on health showed antioxidative and anti-inflammatory effects of moderate physical activity, which were manifested as a reduction of inflammatory markers (Hs-CRP, interleukin-6, TNF-α) and an increase of anti-inflammatory factor concentrations (Mišigoj-Duraković et al. 2012). The anti-

inflammatory effects of exercise are of particular importance given that numerous inflammatory factors are involved in the pathogenesis of many chronic diseases. Several prospective clinical studies have found that high-intensity physical activity could slow or delay the onset of dementia (Daviglus et al. 2010), and the strongest correlation is shown for endurance training (Hamer et al. 2009). In patients with Alzheimer's disease, physical exercise can help improve communication skills. Results of several studies have shown improved verbal expression and cognitive symptoms in those patients who engage in physical activity, which had not been shown in previous studies (Zschucke et al. 2013).

Regular exercise can slow down the progressive reduction of cortical brain volume which occurs during aging. In elderly persons who engage in regular physical activities, a higher volume of cortical and hippocampal gray matter has been recorded compared to physically inactive individuals (Erickson et al. 2011). Cotman and Berchtold showed an increase of gray and white matter volume in the prefrontal cortex due to aerobic exercise training (Cotman and Berchtold 2002) and Erickson showed an increase in hippocampal volume by 2% due to exercise training, effectively reversing age-related loss in volume by 1 to 2 y (Erickson et al. 2011). Due to physical exercise, numerous positive physiological and biochemical changes occur in the human body, as well as changes in the way of thinking and understanding of oneself and the environment, with a consequent improvement of the mental state. Physical exercise has been shown to improve the mental state by reducing the effects of stress as well as creating feelings of satisfaction (Zhu et al. 2016). Physical exercise not only improves mood, general personal adjustment, self-esteem, attitude towards one's body, self-confidence, cognitive and perceptual processing, but also alleviates some mental disorders (Da Silva et al. 2012). It has a relaxing effect, reduces somatic, cognitive, and muscular tension, negative thoughts, and reduces signs of depression and anxiety (Da Silva et al. 2012). It also reduces psychopathological changes in terms of reducing their intensity; it improves general functions in terms of oscillation during some daily life activities and allows one to accept situations that had previously been experienced as disruptive. Physical exercise can be an additional tool in the treatment of depressive and anxiety disorders. In the United States, more than half of the practitioners recommend physical exercise to their patients suffering from anxiety: walking (at least 5 km a day, continually or divided into 2 or 4 segments), swimming, cycling, and running are all very beneficial (Carek et al. 2011). Thus, for example, in the treatment of diabetes or mild arterial hypertension (systolic blood pressure 140-159, diastolic blood pressure 90-99 mmHg), exercise is very useful and prescribed in most cases (Mišigoj-Duraković et al. 2012). For elderly dementia patients, besides being important for maintaining the ability to move, exercise also has a social significance, which contributes to an improvement of the mental state. If physical exercise is not engaged in permanently, there is a relatively rapid loss of beneficial effects (Zelinski et al. 2011). Although the question of the effect of physical activity on the development of dementia is still considered controversial and with an ambiguous answer, data from meta-analyses that have addressed this question point to the unquestionable impact of physical activity in dementia prevention (Table 2).

There are several different explanations of how physical exercise contributes to psychological well-being. One of those hypotheses' states distraction as a major factor because a person practicing physical activity is excluded from everyday life difficulties (Peluso and de Andrade 2005). Another hypothesis claims that improving physical fitness during and after physical exercise increases the sense of competence and self-efficacy (Craft 2005). Also, the more pleasure and satisfaction a person experiences in exercise, it will have more beneficial effects on the mental state. That being said, it is important to emphasize that the choice of physical activity should be in agreement with the patient depending on his or her preferences. Most commonly, aerobic exercise is recommended in combination with moderate muscular endurance exercises which contribute to the maintenance of muscle and bone mass. Coordination and flexibility exercises are also important in the elderly and contribute to preventing falls and injuries. To achieve positive mental changes in patients with dementia, the optimal exercise frequency should be on daily basis or at least three times a week. Exercise intensity should be low to moderate, depending on the patient's mental and somatic characteristics. The duration should also be individually adjusted - a total of 30 minutes, which can be divided into several 10-15-minute segments, is recommended. If exercise is for some reason not possible, the patient should be encouraged to walk as much as possible, alone or with the assistance of a caregiver. Physical activity needs to be safe, moderate, comfortable and adapted as to type, duration, and especially the health and functional status of the patient.

PERSONALIZED MEDICINE IN THE SELECTION OF PHYSICAL EXERCISE IN ALZHEIMER'S DISEASE

The term "Personalized Medicine" has been increasingly used since 2005. It is based on the use of genetic features of an individual for the detection, treatment, and prevention of disease. Access to more detailed information about a person's genome is enabled by the development of new advanced methods. Personalized medicine is based on individually adjusted diagnostic and therapeutic procedures, considering the presumed risks of a particular disease (Mimica et al. 2017). By

Table 2. Overview of the findings from ten meta-analysis published in the last five years on the impact of physical activities on cognitive functions

Study	Number of Subjects	Protocol type	Main findings
Du et al. 2018	13 RCTs 869 patients diagnosed with AD	meta-analysis of RCT	PA might improve the cognitive function of AD or slow down the decline of cognition Eight studies demonstrated that PA improves cognitive function for individuals with AD while five studies did not display a beneficial effect.
Jia et al. 2019	13 RCTs 673 patients diagnosed with AD	meta-analysis of RCT	PA can improve cognition of older adults with AD. They showed no difference in concomitant effects on cognition functions of high frequency interventions and low frequency interventions.
Santos-Lozano 2016	Ten studies 23,345 participants Follow-up 3.9 to 31 years	meta-analysis of prospective observational cohort studies	Regular PA performed by elderly people might play a certain protective role against AD. The pooled odds ratio for development of AD in participants who were active vs those who were inactive was 0.60 (95% CI, 0.51-0.71; P<.001; limitations of self-reported PA
Kivimäki et al. 2019	19 studies 404 840 participants who were initially free of dementia	meta-analysis of prospective cohort studies. Exposure was physical inactivity	When measured <10 years before dementia diagnosis, physical inactivity was associated with increased incidence of ACD (hazard ratio 1.40, 95% CI 1.23 to 1.71) and AD (1.36, 1.12 to 1.65). When PA was initiated ≥10 years before dementia onset, no difference in dementia risk between physically active and inactive participants was observed.
Guure et al. 2017	117410 participants highest follow-up of 28 years	meta-analysis of prospective studies (≥ 12 months)	The study showed a protective effect for high PA on ACD, odds ratio of 0.79, 95% CI (0.69, 0.88), a higher and better protective effect for AD, and a nonprotective effect for VD.
Xu et al. 2017	16 studies (15 for ACD, 8 for AD and 4 for VD) for the primary analysis five studies for the dose–response analysis (4 for ACD and 4 for AD).	dose-response relationship	The study reported a dose-response relationship between leisure time PA and dementia, They showed that for every 500 kcal PA increase per week, there was, on average, 10% and 13% decrease in the risk of ACD and AD, respectively.
Panza et al. 2018	19 studies 1,145 subjects	Controlled studies (exercise-only intervention vs nondiet, nonexercise control group)	There was a modest favorable effect of PA on cognitive function (d_+ = 0.47, 95% confidence interval (CI) = 0.26-0.68). Aerobic exercise had a moderate favorable effect on cognitive function (d_{+w} = 0.65, 95% CI = 0.35-0.95), but other exercise types did not (d_{+w} = 0.19, 95% CI = -0.06-0.43).
Cammisuli et al. 2018	NR	meta-analysis of RCT	The included studies reported only positive effects for patients'global cognition after intervention. It is not certain whether the benefits of exercise are evident in all stages of AD pathology.
Lipnicki et al. 2019	20 cohorts from 15 countries 48,522 individuals without dementia at baseline. 2-15 years of follow-up.	Meta-analysis of population-based cohorts	Their results suggest that education, smoking, PA, diabetes, and stroke are all modifiable factors associated with cognitive decline
Chai et al. 2017	35 studies 3,113 participants	Meta-analysis of randomized controlled trials	The study revealed a positive overall random effect of PA on cognitive function in patients with chronic diseases.

ACD - all-cause dementia; AD - Alzheimer's disease; NR - not reported; PA - physical activity; RCT - randomized controlled trials; VD - vascular dementia

studying the genome, it is possible to find out what genetic predisposition the patient has for some diseases, how he metabolizes food, how he responds to treatment, etc. Personalized medicine involves the use of genetic information about a particular patient, which should enable detection of the underlying mechanisms of the disease. Based on the information obtained, the main objective is to provide targeted action at the level of disrupted underlying mechanisms that cause the disease. Worldwide, personalized medicine is rapidly evolving and involves molecular diagnostics as well as cell and gene therapy targeted and adjusted to each individual (Buford et al. 2013). Analysis of the genome could be useful in the selection of exercise in patients suffering from Alzheimer's and other dementias. It is expected that this will include individual evaluation of the patient´s response to the training and adjustment in training dosage so that the patient has the highest benefit and the least discomfort.

DISCUSSION

In Croatia, around 14% of patients aged over 65 suffer from dementia, and approximately 10% are diagnosed with Alzheimer's dementia (about 80,000) (Mimica et al. 2017). Alzheimer's dementia is becoming the most significant public health, social, and economic problem in the elderly. The aetiology of the disease is still not fully elucidated. Studies showed a variety of environmental and genetic factors that could affect the course of this disease. It has been shown that mental activity contributes to the preservation of a better cognitive status at an older age, which has so far been shown by image studies of the cerebral cortex and hippocampus (Valenzuela et al. 2008). Mental activity reduces anxiety, improves mood, and acts to preserve cognitive health. It increases the quality of life, especially in the elderly, preventing the progression of Alzheimer's disease (Rot et al. 2009; Daviglus et al. 2010; Mochcovitch et al. 2016).

Physical exercise has numerous benefits on physical and mental functions. It reduces blood pressure in normotensive individuals and those with mild and moderate arterial hypertension. It helps in body mass regulation and enables maintaining an optimal body composition in terms of bone and muscle mass preservation, thus preventing sarcopenia and osteoporosis, reducing insulin resistance, decreasing levels of elevated serum LDL and VLDL levels, elevating HDL levels and having an anti-inflammatory effect (Larson et al. 2006, Newsom et al. 2016, Angulo et al. 2016, Wood et al. 2016, Kim et al. 2016, Zaleski et al. 2016). However, to achieve maximum benefit and to avoid unwanted side effects, physical exercise should be adjusted to the health and functional status of the patient. There are still questions about the optimal duration and form of exercise.

Today, it is considered that Alzheimer's disease is a result of a complex interplay of many genetic and environmental factors. The main genetic risk factors are amyloid precursor protein (APP) gene mutations on chromosome 2, mutations of the presenilin-1 gene on chromosome 14, and the presenilin-2 gene on chromosome 1. These gene mutations are associated with the accumulation of amyloid-beta (Aβ) peptide 42 proteins, which may suggest an amyloid hypothesis in the onset of Alzheimer's disease. Mutations of the presenilin-1 gene on chromosome 14 and the presenilin-2 gene on chromosome 1 are being associated with the hereditary form of Alzheimer's disease. The late onset of this disease is linked to the APOE ε4 allele on chromosome 19. But the finding of this allele does not necessarily mean that a person will develop Alzheimer's disease. Therefore, preventative interventions are extremely important. The disease is more common in older adults of low education levels, in those who have experienced central nervous system trauma, in females, and in people experiencing prolonged stress. Preventive and therapeutic measures should be focused on habits and somatic illnesses that can exacerbate dementia such as smoking, obesity, dyslipoproteinemia, arterial hypertension, diabetes, and other chronic diseases (Kim et al. 2016, Zaleski et al. 2016). Increasing mental and physical exercise is important in the effort to delay dementia. If dementia has been diagnosed, efforts should be made to enable the patient to perform everyday activities, from dressing to social activities, independently. In the future, genome analysis in personalized medicine will hopefully suggest individually adjusted physical and mental exercises to prevent or slow down the development of dementia.

CONCLUSION

Regular engagement in mental and physical activities lowers the risk of cognitive impairment and dementia development. Mental activity increases a person's "cognitive reserve" and promotes the formation of new communications between brain cells. Physcal exercise in patients with dementia improves mood, general adaptation, self-confidence, cognitive and perceptual processing, in addition to alleviating some mental disorders. It has a relaxing effect, reduces somatic and cognitive tension, decreases muscle tension, wards off negative thoughts, and relieves depression and anxiety. Elderly individuals participating in regular aerobic exercise have a lesser degree of cortical and hippocampal mass reduction. By analysing the genome and specific mutations, personalized medicine could be useful in suggesting specific exercises precisely adjusted for the individual patient suffering from Alzheimer's disease.

Acknowledgements: None.

Conflict of interest: None to declare.

Contribution of individual authors:

All authors contributed to the study conception and design.

Borislav Radić, Antonela Blažeković & Din Duraković performed the literature search and data analysis.

Borislav Radić & Antonela Blažeković were major contributors in writing the manuscript.

Ervina Bilić & Fran Borovečki wrote the final opinion and critically revised the work.

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