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Review

# Hard Physical Work and Alzheimer's Disease Risk

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**ABSTRACT**

Alzheimer's disease (AD) is the most common reason for dementia. Observable symptoms are unmissable, such as deteriorating memory, psychiatric disturbances, corruption of neurological functions. Factors that affect and create AD are commonly studied but rarely understood. However, indicators such as sleep, stress, eating habits, physical activity habits, and work environment (occupational physical activity) have been worked on and confirmed by scientific research. Tau protein and amyloid β-protein (Aβ) have been associated with the pathology of AD in the brain. Also, AQP4 polarization and AD relation are based upon the accumulation of unwanted structures such as tangle and plaque formations. On the other hand, the brain's clearance system, which is linked to bodily ailments such as cardiovascular problems and blood circulation, has been identified as a significant factor in brain health because any activity that affects circulation has the potential to link brain health, dementia, and AD. It has been observed that Leisure time physical activity (LTPA) such as planned physical activity (fitness, aerobic) is related to preventive factors for AD. Nevertheless, occupational physical activity (OPA) which is usually discussed as working time activity and hard physical work has been positioned in a negative field in the effects which are related to AD in past research. All research has been done in recent years. In this review, general factors that affect AD and the relational base of these factors will be discussed from the OPA and LTPA point of view.

**Keywords:** Alzheimer's disease, hard physical work, leisure-time physical activity, occupational physical activity

Alzheimer's disease (AD) is an important progressive neurodegenerative disorder. Every year AD is taking away numerous lives. AD has a lot of signs and symptoms. Nevertheless, pathological etiology and real reasons behind this condition still need to be searched to create certainty. AD as a subset of dementia is the most common type of the group with 60-70% case density.[1] AD symptoms might appear as lack of information processing, impaired reasoning, differences in language-behavioral circumstances, and most popular symptoms as deterioration of memory.[2]

Also, other symptoms are deficits in executive function (planning, insight, judgment) neuropsychiatric symptoms, depressive symptoms, and delusions. Symptoms of problems in the motor system are shown themselves in the final stages of the disease.[2] Protective factors (ex. educational status) and risk factors (ex. past physical experiences such as head injuries) may have an impact on building AD or preventing the disease.[3]

The genetic background of the disease has been defined within terms of beta-amyloid (Aβ) protein plagues which is an extracellular product of the amyloid precursor protein (APP), enzymatic complexes beta (β), and gamma (γ) secretase.[4,5]

On the other hand, intracellular factors of AD, such as hyperphosphorylated forms of the microtubule-associated protein tau (encoded by the MAPT gene) shown themselves as a form of neurofibrillary tangles in this disease.[6]

As a minority member of the AD family, Autosomal dominant Alzheimer's disease (ADAD) showed the three genes which are related to the underlying

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pathology of AD. These are APP, presenilin 1 (PSEN1), or presenilin 2 (PSEN2).[7-9]

General effects of mutations of APP have been observed as higher production and/or aggregation of amyloid-β, nevertheless type and localization of mutation creates differentiation on final mechanism.[8] Researches found a companionship between Aβ mutations execution and increase in plague load.[10]

Genetic risk factors for AD are diverse with a lot of indicators. Therewith, APP and the presenilins, common polymorphisms in the gene apolipoprotein E (APOE) have been stationed as the most stated factors.[8]

Alzheimer's disease is an enduring worldwide problem because of the lack of a stable cure. Preventing and curing still protects its mystery. However, better understanding will be obtainable with background analysis. Alzheimer's disease has various types of neurological indicators in the brain. This diversification makes this condition more complicated, on the other hand this type of variety is beneficial for the possibility of diverse curing methods.

One of the first requirements of the brain is clearance. However, Brain has no lymphatic circulation[9] which is related to bodily balance. In spite of the fact of the lack of lymphatic circulation, the brain still needs to be cleaned from extracellular proteins. For these reasons, there is another system for this cleaning process which is linked to the cerebrospinal fluid (CSF), interstitial fluid (ISF) and the water channel aquaporin-4 (AQP4) within the osteocytes.[11]

This related clearance system is called Paravascular Pathway (glymphatic pathway) which is portrayed as the waste clearance of the brain. Cerebrospinal fluid (CSF) is positioned in arteries of the brain while integrating and mixing with interstitial fluid (ISF) and solutes in parenchyma. Finally, it exits along paravascular spaces of draining veins. Past research cleared the importance of this pathway for possible cleaning options of neurodegenerative disease related proteins such as amyloid-β.[12]

Furthermore, AD etiology is mainly linked with Aβ and tau protein deposition.[13] Healthy brains consist of amyloid-β and Aβ associated with amyloid plaque burden. In need of cleaning, soluble Ab is possible with AQP4 dependent bulk flow.[11]

Aβ accumulation bring into the open a lot of situations which processes links with loss of a neuron such as death of cells, inflammatory response, tangle formation and lipid oxidation.[14]

Another important point for AD pathology is tau protein. The process of cleaning interstitial tau is related to AQP4 and the glymphatic system. In a research which includes AQP4 deficient mice has been found higher levels of tau which is a risk factor for neurodegenerative diseases.[15]

Additionally, there is research that shows the association of AQP4 depolarization and AD pathology.[16-18] AQP4 depolarization has an impact on clearance which causes inadequate CSF flow and intensified waste product accumulation.[11,19] The AQP4 and AD linkage is still unclear that loss of polarization is a consequence or a cause of Aβ accumulation.[16]

As a summary, accumulation of extracellular amyloid-β peptide (Aβ) in plagues which includes degenerating neurons (neuritic plaques), neurofibrillary tangles includes anomalously hyperphosphorylated tau protein and the deposition of it as intracellular changes. Also, neurons and neural connection's loss is additionally common[20] furthermore, past researches have been confirmed that Alzheimer's pathologic diagnosis includes neurotic plagues (consist of amyloid protein surrounded by astrocytes, microglia and dystrophic neurites) and neurofibrillary tangles (helical filaments of abnormally phosphorylated tau protein) in the brain.[2,21,22]

Arterial pulsatility is the key factor for CSF movement and pressure on surrounding fluid rises by arteries, in this way pressure creates the vessel wall's movement.[23] On the flipside, CSF movement has relation and connection with decreasing arterial pulsatility because of artery stiffening. Because of that kind of linkage, hypertension was found to have a negative impact on the glymphatic system.[24] Also, Greater cardiovascular fitness is positively related with better cognitive functions such as executive function and attention in older adults.[25,26]

Intercalary, the glymphatic system has other functions which are lately identified. CSF is a channel of nutrients such as glucose for neurons and astrocytes to intake.[15,27] On the other hand, CSF carries apolipoprotein E to brain's interstitium which is significant for synaptic plasticity and cholesterol transport.[15,28] Rapid

lipid transportation and glial signalling of brain occurs in the glymphatic system.[29]

Furthermore, research shows the significance of AQP4 on synaptic plasticity, neuroexcitation, astrocyte migration and cognitive functions such as memory and learning.[30] A laboratory study suggest that, AQP4 deficiency damages synaptic plasticity and related fear memory which is in the lateral amygdala.[31]

Plasticity is the key factor for understanding the effectiveness of environmental factors on the brain for instance learning process and memory formation. Specialties of the brain such as moldability, flexibility, changeability with environmental factors and everlasting noiseness bring out the concept of brain plasticity all along life. Plasticity gives us a lot of opportunity to expand our own limitations such as academic and cognitive performance. Also helps to reduce risks such as dementia.[32]

Hippocampal synaptic plasticity is undeniably important for hippocampus-dependent learning and memory. For instance, learnings which serve as fear conditioning (contextual fear conditioning) were investigated for understanding AQP4 role in memory formation. Results of this research shows that AQP4 deficiency is related with impairment of associative fear memory formation on mice.[33]

## DEMENTIA, PHYSICAL EXERCISE AND FITNESS

Physical exercise has been defined as any planned activities for improving physical fitness.[34] Past discoveries showing that long-term physical activity (PA) participation is linked with progressed cognition and useful changes to fundamental brain function.[32] Moreover, other clinical trials showed that, late adulthood PA participation, might make an enhancement or protection effect on the brain even in cognitively impaired individuals.[35]

The association between higher amounts of PA and greater gray matter volumes is related with reduction of cognitive impairment likewise past research. Also, greater fitness intensity post intervention is associated with higher white matter integrity.[36] Previous researches explored the relationship between aerobic fitness, white matter integrity and subcortical structures which are important for learning and memory processes. Briefly, gray matter volume and white matter integrity which are an important part of the brain structure are positively related with PA and fitness.[32]

As an example for this investigation, children were compared among their physical situations. Observations were clear that higher-fit children had greater gray matter volume in the hippocampus and basal ganglia rather than lower fit children. Moreover, physically higher-fit children display higher performance on tapped executive control and relational linked tasks.[37,38] Past research indicated that dementia has been related with brain atrophy, loss of volume and brain rust which are associated with age. Additionally, higher levels of aerobic fitness has been linked with greater gray matter volumes in elderly individuals at so many areas of brain such as frontal cortex,[39] hippocampus.[40] and caudate nucleus.[41]

Dose-response of physical activity (PA), applicational areas and molecular system behind that still requires later researches for understanding real cognitive effects of that.[32]

One of the following researches shown that Cognitive functions boosted in all the areas of cognition, but the most significant change observed in executive function while engaging in moderate intensity of PA.[42] Furthermore, observational studies approved that self-reported PA participation can decrease 40% risk of experiencing cognitive decline over long-term period.[43]

Results of the new researches have followed and confirmed the past route. Relationships between PA-exercise and decrease in the risk of getting caught to a cognitive regression and malfunction have been observed over again. In spite of that, there is still insufficient research based on dose-response of physical activity. Definitions of physical activities, types, molecular bases and effects of quantity of PA and relations with amount changes are still needed to be searched.

Relationships of late-life cognitive impairment and self-reported physical activity were investigated with 65 years old women. PA were questioned with a retrospective point of view in 4 periods of life-time of these aged people. Results indicated that PA at all of 4 lifetimes has been related with decreased risk of developing cognitive impairment.[44,45] On the other hand, controlled trials have been conducted on cognitively impaired participants. PA trial applied individuals showed improvements in global cognitive functioning compare to control group.[35]

PA which is defined as modest amounts is sufficient for better cognitive function and greater size and functions of the brain. For instance, higher amounts of PA have been related with decreased levels of Ab that is related with the reduction at risk of AD.[46]

Some past studies indicate that aerobic fitness and aerobic capacity (measured as maximal oxygen consumption during exercise, VO2 max) are positively related with the size of the brain, both in humans and other animals and also related with general cognitive abilities.[47,48] Studies on mice claim that exercise can increase hippocampal neurogenesis in aged mice.[49]

Most of the studies have focused on greater intensity exercise. Entire brain volume, gray matter volume, and greater white matter integrity has positively associated with moderate to vigorous intensity exercise and higher aerobic fitness.[50-52] However, even the little acts such as household physical activities were associated with greater brain volume, especially gray matter volume.[53]

As a general view point for setting a physical activity regimen at any age, moving as much as possible is the most significant matter. Past research indicates that there are four lifetime periods which have different requirements of PA for improving cognitive functional benefits.[54]

1. Preschool-aged children (3-5 years) ought to be physically active throughout the day.
2. Children and adolescents (6-17 years) should do 60 min or more per day of moderate-to-vigorous physical activity, 3 days per week.
3. Adults should do 50-300 min of moderate-intensity PA or 75-150 min of vigorous aerobic PA per week.
4. Old adults should do aerobic and muscle-strengthening activities as much as they can.[54,55]

N-acetylaspartate (NAA) concestural standard of neural viability and metabolism as a direct measure of the central nervous system. Higher aerobically fit individuals showed greater NAA levels which is also related with a better working memory.[56] In addition, NAA concentration decrease is age related which has also been linked with AD. Past research claims that PA can increase the size of memory formation related brain regions and functional activity. As a result of that, the relation between expectation of reduction of Ab levels and increase of NAA had been claimed. Few studies mentioned brain-derived neurotrophic factor (BDNF).[45]

In research, increased hippocampal volume with exercise was associated with increases in serum-derived BDNF.[57] Increased BDNF levels may have a relationship with cognitive benefits of PA[45] which is also related with AD.

Another exercise intensity related topic is heavy sports such as weight lifting. Weight lifting is commonly considered as a safe sport, however increasings of blood pressure while lifting can cause harmful situations such as injuries. On the other hand, consequences can be diverse as brain stem ischemia[58] and subarachnoid hemorrhage.[59]

There are some other factors and indicators which affect brain health, especially dementia and AD. Education, smoking, mid-life obesity, hypertension, diabetes, depression, and physical inactivity are mutable risk factors of AD and even small decrease of these factors might create huge differences.[45]

Additionally, another concept which is related to AD is eating. Eating habits are important because of obesity and AD, the relationship between malnutrition and psychological and physical problems. For instance, hard workers generally consume larger amounts of protein than sedentary workers.[60] Larger protein consumption might increase the performance of work and demonstrate a larger increase of muscle power. Because of that , lack of sufficient protein intake might create unhealthy results. Hard physical training including hard muscular activities may cause sports anemia. However, this situation can be prevented by taking a high qualified protein diet.[61]

A study on rodents has shown that dietary delimitations are beneficial for general health and lifespan. Especially advantageous for brain health by increasing the prevention of neuron degeneration chance.[62] Diets that are advantageous or at least harmless for AD are beneficial for other health related problems such as cardiovascular disease. Recommendations should have been considered on basis of these representatives.[63]

Under these circumstances, considering all these findings, evaluation of results under the perspective of the relationship of AD and cardiovascular health shows that quality and healthy nutrition intake and brain health ought to have a relationship (especially with dementia).

Age is an important factor for the entire body and especially for the brain. Past findings indicated that AQP4 polarization is impaired in the aged brain.[64] Aging brain has requirements to protect brain plasticity which is significant to preserve cognitive functioning. For instance physical activity, healthy eating habits, education, healthy psychological state, having a non-risky genetic background.

## OCCUPATIONAL PHYSICAL ACTIVITY AND HARD PHYSICAL WORK

In this review, generally hard work will be mentioned as occupational physical activity (OPA).

In previous research, heavy physical work and heavy conditions have been evaluated and worked with in terms of factors such as "effort variables," i.e., performances, physiological measurements, age and perceptual responses".[65]

Leisure-time physical activity (LTPA) contains high intensity and low duration and includes dynamic postures followed by sufficient recovery. On the other hand, occupational physical activity (OPA) is usually of low to moderate intensity and long duration with static postures and insufficient recovery. OPA generally includes delayed and long term standing, heavy lifting, or repetitive and cumbersome working conditions.[66] Besides all these definitions, knowledge of necessary dose of PA in the context of duration, frequency, or intensity is still unclear and insufficient.[67]

Nabe-Nielsen et al.[66] had studied OPA and dementia relationships. First data of the research was started to be taken in the 1970-71 period. Research was based on self-report evaluations. Assessments were settled up on profound questions. ("Is your current work…?" with the response options: *(i)* Sedentary (reference group), *(ii)* Light physical work, and *(iii)* Heavy physical work).[66]

There were alternative assessment (CMS) answer options. *(i)* Mainly sedentary (reference group), *(ii)*Quite a bit of walking without carrying heavy loads, *(iii)* Mostly walking, stair climbing and often carrying loads, and *(iv)* Heavy physical work load).[66]

Consequently, high levels of OPA has related with greater risk of cardiovascular disease and mortality opposed to LTPA.[68,69] Additionally, cerebrovascular dysfunction is associated with dementia in past findings, because of that OPA and dementia and AD might have a relationship.[70] Opposition between OPA and LTPA even shows itself in the mental health area. LTPA has positive association with mental health, however OPA was associated negatively with mental health (even the poor side of the spectrum of mental health).[71,72] On the other hand, poor psychological health such as depression[73] and stress[74] has been linked to greater risk of dementia.

Past studies claims that, greater amount of PA is associated with decreased levels of developmenting dementia.[75,76] However, generally people are not prone to meet the minimal need amount of PA on a weekly basis.[77,78] Future studies should focus on the effect of OPA on dementia and AD for better understanding and preventing these conditions.[66,79]

Also, gender differences in effects of OPA on general health are still needed to be studied. Prefound sex differences in evaluation of OPA and dementia relationship makes harder to generalization of the results.[72,80]

Heavy work with a steady position may have a negative impact on blood circulation. Possible underlying basis of results are claimed to be negative effects of OPA on the cardiovascular system.[66]

PA has been affected by a lot of factors. Age,[81,82] educational attainment,[81-83] income and urbanization.[84,85]

One of the most effective types of PA is Occupational Physical activity which is defined and evaluated as differently in research. Past research on OPA indicates the importance of cultural background, country, habits and immigration. As an example for previous research PA were examined with leisure, occupational and commuting activities. Also, evaluation of cultural differences studied with different countries have been observed. Past research shows that leisure-time PA has been related with socioeconomic status in developed countries.[86] However, the same pattern has not been observed by researchers in developing countries.[87]

As an evaluation which is consistent with past findings, low income and low education indicated higher levels of occupational activity and active commuting.[87] Differences among countries based on PA levels should be evaluated with individual, contextual, cultural, economical and environmental factors for better understanding.[87]

For a healthy lifestyle, people between the ages of 19-64 should participate in at least 30 min of moderate-to-vigorous physical activity on at least five days a week and lower sedentary times based on UK guidelines.[88]

In a study which researches sedentary occupational activity, OPA has been explained as habitual behavior. Activities such as climbing stairs have been related with higher activity and lower sedentary behavior in the office environment.[89-91] In laboratory-controlled research based on 8 hours period times, dividing sitting time as 20 min sitting-2 min walking (light-intensity or moderate-intensity) has been linked with lower postprandial glucose and insulin levels in overweight/obese adults.[92] Research claims that increasing shifts between sit and walk positions may have beneficial effects on metabolic health.[93]

For another point of view, in past research, LTPA has been defined as exercise and non-regular occupational activity while NLTPA has been defined as walking or cycling for transportation. Finally, occupational activity has been shown as work activity, including housework.[94]

Understanding PA has not been sufficient with LTPA so the distinction between LTPA AND NLTPA is necessary to collect data on PA of women and minorities.[94-96] PA has not been showing itself in the form of LTPA for Korean American and immigrant women. PA has been hidden in their daily routine.[97] Researchers have claimed that NLTPA and OPA are beneficial for fitness and lowering mortality.[98]

Differences among meeting of NLTPA recommended levels has been observed between Asian American women aged 40 to 59 years and US-born non-Asian women aged 40-59 years. However, the same differentiation has not been observed between Asian American and US-born non-Asian men. The Study found that generally Asian American men and women are less prone to meeting recommendation standards.[94]

Education and income levels have been associated with higher LTPA and lower recommended NLTPA for men. However, increasing income has been sharing the same patterns while higher education has been only related with higher recommended LTPA and lower OPA. Also, recent Asian American immigrants have been least likely to meet recommended PA levels. As a summary of this situation, immigration time and years that passed at the country that people had immigrated to are important factors to understand the inactivity levels and sedentary life. The increase of time that has passed (more than 10 years) has related to higher activity levels.[99,100]

Moreover, we need to mention people with special needs as a part of minority groups. Individuals with intellectual disabilities (IDs) generally live a sedentary lifestyle. However, this lifestyle is not beneficial for their health. Cardiovascular diseases, diabetes, obesity and depression may occur with that lifestyle. Games and developed apps are beneficial for creating motivation for PA on people with special needs.[101]

Another less mentioned group is women in the paid labor market. Factors such as long working hours, double work burden and stress have been linked with noncommunicable diseases (NCDs) which are coronary heart diseases, hypertension, diabetes, obesity, cancer and mental health issues. NCDs based on the death rates of women are especially higher in low-middle income countries. Risk factors of NCD have been defined as obesity, low physical activity, unhealthy diet, dyslipidemia. Intervention programs should be based on these criteria.[102]

Another past research has examined heavy and light work classification which was studied for hospital cleaning service. Gender differences at assigning these tasks were clearly made. Women are more likely to be assigned to cleaning toilets, which leads to nosocomial infections. Also, other negative health impacts of heavy work have been observed as musculoskeletal symptoms of respiratory and cardiovascular health. Gender discrimination created differences in impacts of this job on women and men.[103]

It is important to add another point on effective factors on AD. This factor is anent with job security. Decrease of stress and high job control has been associated with lower cardiovascular disease and dementia rates.[66,104-107]

## DISCUSSION

Alzheimer's disease is a common neurodegenerative disease which affects all over the world. A great number of factors affect the AD pathology. Mentioning reasons to shed light on the etiological basis such as genetic differences, eating habit differences, cardiovascular problems, physical activity, intensity of PA, cultural differences of PA and

eating habits, hard work environment, stress and psychological factors, education, socioeconomic differences creates the differentiation of AD pathology.

Physical activity is linked with brain and body health. PA has been considered as a decreasing factor for AD. However, occupational physical activity which is defined as hard physical activity is considered as harmful for developing AD. Cardiovascular effects of OPA on AD and health based effects have been researched and confirmed. Because of this confirmation, hard physical work, AD and cardiovascular problems have been linked with each other.

Moreover, cultural generalization is not possible with these findings. Gender and culture are important topics with different variables and features for AD. The Styles of OPA and PA are intertwined in most of the Asian countries. Women are generally prone to participate in PA, OPA and housework more than men, especially in high socioeconomic sections. This situation creates a confusion for separation of OPA and PA in Asian women. On the other hand, cultural differences are significant for this area. The reason behind that is cultural eating habits, definition of work environment and style of living differences.

Furthermore, there is no certain definition of OPA and PA which have been formed by scientific authorities because that self-report style has been used in studies which decreases measurability and generalizability of research. Descriptions of healthy OPA and PA are in insufficient amounts. Measuring and reality adaptation of OPA needs to be searched in clinical settings for more trustworthy results.

Research variety is limited for job occupation range whereupon generalizability and definitions affected by these limited circumstances.

Generally, salary and earnings of physically hard working people are not adequate for providing a healthy and sufficient diet, so their diets are less qualified to set up a healthy cardiovascular base which is linked to AD. Also, eating habits have been affected by cultural background and general economical facilities. Countries which are commonly related with high obesity rates are in danger of getting caught AD because of less proclivity of PA, unhealthy eating habits, predisposition to cardiovascular problems. All of the socioeconomic differences and cultural background diversities, shows that generalization ought to be searched in further research.

On the other hand, stress is an important factor for AD. Relation between less stressful working environments and lower cardiovascular disease and dementia rates has created another important field which needs to be studied more. Security of physically heavy working people and consequences of psychological health which are related to dementia and AD have had an important impact on these circumstances. Stress is also related to vita experiences of a human being. Poverty, living difficulties, general long work hours of heavy workers, lack of sufficient sleep and nutrition, unquality living standards such as past traumatic experiences and lower socioeconomic status have been interacting with a lot of factors which are related to AD. Absence of consideration of these factors creates a biased foundation. Consequently, providing information for AD and OPA is possible with creating a setup which purifies from other etiological factors as much.

Treatment sufficiency is another pinpoint of AD. Inasmuch as growing numbers of populations with risk of AD are needed to meet with prevention programs rapidly because of lack of certain curing methods.

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