Which type of exercise, Cardiovascular exercise or Resistance exercise is more effective for the prevention of development of Alzheimer's disease?

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1. Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder that causes memory loss and impairs cognitive functioning. The disease has a progressive character in which the loss of neuronal structure and functioning increases over time. AD is characterized by the presence of amyloid plaques and neurofibrillary tangles in the brain. Furthermore, AD is the most common cause of dementia in elderly individuals and places a significant burden on society. A curative therapy has not yet been found for the disease. Therefore, treatments for AD are now composed of multidomain interventions targeting risk factors of the disease, thereby alleviating symptoms and slowing further progression. A lack of physical exercise is one of the risk factors of AD, therefore physical exercise therapy is used to treat AD. The aim of this literary review is to investigate which form of exercise is the most effective to treat AD. This is done by reviewing the pathological characteristics of AD and subsequently comparing the effects of cardiovascular exercise and resistance exercise on these pathological characteristics. This review found cardiovascular exercise to have greater benefits than resistance exercise, but a combination of both types of exercise seems to provide the greatest benefits. Increasing the understanding of treatments of AD, will lead to more efficient therapies and thereby decrease the burden of the disease on both patients and society.

2. Introduction

As a result of improved global health, living standards, economic growth and development on many more domains, the demographic composition of the worlds population is shifting. Population aging is a clearly visible and irreversible global trend, resulting from an increase in life expectancy and decrease in birth rate. The increase of the number of older adults has been accompanied by an increase in rates of acute and chronic conditions. (United Nations Department of Economic and Social Affairs, 2023). Dementia is one of these chronic conditions, of which more than 55 million people suffer worldwide, and this number is predicted to increase to more than 130 million people in 2050. Furthermore dementia is the seventh leading cause of death according to the WHO (2023), the condition is a major cause of disability and dependency among aging individuals, and it imposes the largest treatment costs on healthcare systems worldwide.

Alzheimer's disease (AD) is the most commonly observed form of dementia, contributing to 60-70% of all cases (WHO, 2023). The disease can be subdivided into two categories, early-onset Alzheimer's disease (EOAD) and late-onset Alzheimer's disease (LOAD), which comprises about 90% of all cases (Bertram & Tanzi, 2004). Furthermore AD is a neurodegenerative disorder, characterized by a progressive loss of neuronal structure and function (Braak & Braak, 1991).

Various risk factors are associated with AD including non-modifiable risk factors like sex, age, and genetics. However, research has also established the presence of many modifiable risk factors. (Edwards et al., 2019). Curative treatments for AD have not yet been found, so prevention of further cognitive decline of people diagnosed with AD, is of great importance (Cummings & Fox, 2017) Decreasing the risk factors is a useful strategy for this, which can be achieved by a multidomain intervention. Multidomain interventions target factors including diet, social engagement, cognitive activity and cardiovascular risk management (Coley et al., 2008). Physical activity is also often included in these multidomain interventions, as many studies have established the positive effects of physical exercise on cognition (Mandolesi et al., 2018).

The aim of this literary review is to investigate which form of exercise, is most beneficial for the prevention of cognitive decline and limiting or even restoring pathological alterations of the brain in Alzheimer's disease, focusing on LOAD. The effects of both cardiovascular exercise (CE) and resistance exercise (RE) are compared in this review, to answer this question. It is hypothesized that CE will have greater beneficial effects than RE, but that a combination of both will lead to the greatest improvements on cognitive functioning and AD development.

3. Background

To understand how both cardiovascular exercise and resistance exercise can possibly affect the development of Alzheimer's disease, it is important to gain an understanding in the basic mechanisms, pathology, progressive character and risk factors underlying Alzheimer's disease. This will contribute to a better understanding of how exercise can prevent AD or slow down AD development.

3.1. Neuropathology of Alzheimer's disease

3.1.1. Macroscopic level

On the macroscopic level a few changes are visible in the brains of AD patients however, none of these features or combinations of multiple features are specifically associated with AD, although they are highly suggestive (DeTure & Dickson, 2019b). Firstly cortical atrophy is visible in many AD brains. Due to the atrophy ventricles often enlarge (Apostolova et al., 2012). Cerebrovascular impairments are also often visible in AD brains, causing cortical microinfarcts and lacunar infarct in basal ganglia (Braak & Del Tredici, 2011).

3.1.2. Microscopic level

Alzheimer's disease is characterized by the occurrence of positive lesions and negative lesions in the brain (Perl, 2010).
Amyloid beta (Aβ) is a protein released from the amyloid precursor protein (APP), which is produced by neurons, through 2 proteolytic cleavages (Masters et al., 1985). The Aβ proteins form the main component of the positive lesion, the neocortical neuritic plaques (Cras et al., 1991). An increase in dense-core plaques is one of the hallmarks of AD (Kidd, 1964).
Neurofibrillary tangles (NFTs) are another positive lesion found in AD patients. These tangles are mostly composed of microtubule-associated tau proteins that are misfolded and hyperphosphorylated, causing them to lose their ability to bind and stabilize microtubules, eventually leading to increased aggregation (Alonso et al., 1994). Neurofibrillary tangles show different morphological stages, progressing in severity. (Bancher et al., 1989).
The neurofibrillary tangles are accompanied by neuropil threads (NTs). Neuropil threads also contain hyperphosphorylated tau protein (Perry et al., 1991).
The Aβ protein not only causes the formation of amyloid plaques, the protein also accumulates in vessel walls causing cerebral amyloid angiopathy (CAA). CAA can lead to impaired blood flow, can cause ischemic lesions and small artifacts and in severe cases cause haemorrhages (Vonsattel et al., 1991)
Microglial cells play a multifaceted role in AD. They are involved in the innate immune response as phagocytes in the brain of AD patients, but they can also contribute to inflammation and neurodegeneration. (Serrano-Pozo et al., 2011). In the early stages of AD the phagocytic function of microglial cells is used to clear Aβ peptides from the brain and to protect the brain by removing pathogens, cellular debris and by producing pro- and anti-inflammatory cytokines to ensure homeostasis in the brain (Mangialasche et al., 2010; Gelman et al., 2016). In later stages of AD however, chronic microglial activation in response to accumulation of pathological factors may become harmful (Jardanhazi-Kurutz et al., 2010). At this stage the brain is not sufficiently capable of producing cytokines, phagocytosis and Aβ clearance anymore (Hickman et al., 2018).
Reactive astrocytes are important mediators of the second inflammatory response, in which they are thought to react to cytokines, and act as neuroprotective agents of damaged neurons (Liddelow et al., 2017).

Besides the positive lesions, negative lesions including neuronal and synaptic loss also occur (Terry et al., 1991; Gómez-Isla et al., 1997). Neuronal death is often linked to the accumulation of pathological proteins including previously mentioned Aβ and NFTs (Chakrabarti et al., 2015). Regulation of neuronal cell death happens through multiple different pathways. (Green & Llambi, 2015). A switch in neuronal metabolism from oxidative phosphorylation to glycolysis is also suggested to induce apoptosis (Herrero-Méndez et al., 2009; Kole et al., 2013).
Synaptic loss and a reduction in dendritic spine density are viewed as important mediators of cognitive decline in AD (Terry et al., 1991; Spires et al., 2005). Amyloid plaques and the accumulation of hyperphosphorylated tau mediate these losses (Meyer-Luehmann et al., 2008; Bittner et al., 2010)

3.2. Progression of Alzheimer's disease

Alzheimer's disease is a progressive disease in which cognitive and functional impairment increase through time. Braak and Braak have defined 6 stages describing the changes that occur in the brain of an AD patient, through examination of the distribution pattern of NFT an NT as is visible in figure 1. (Braak & Braak, 1991).

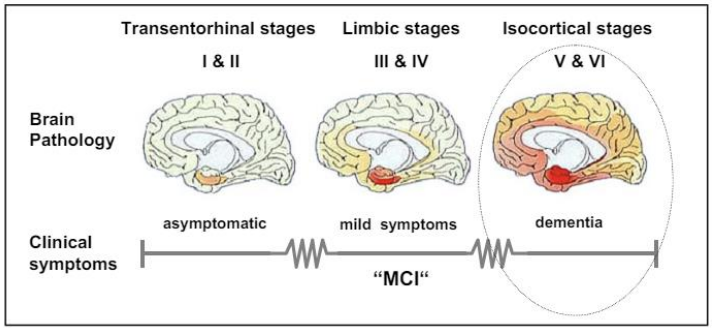

Figure 1. A model of the progression of Alzheimer's disease as described by Braak & Braak (1991). The model includes the presumed clinical symptoms (Wolf., 2006)

3.3. AD risk factors

3.3.1. Non-modifiable risk factors

Late-onset Alzheimer's disease is suggested to occur sporadically however, the APOE gene is found to be linked to LOAD. (Lane et al., 2017). Furthermore, mutations in the PLD3 and TREM2 gene also have been found to increase the risk of developing LOAD (Guerreiro et al., 2013; Cruchaga et al., 2014). Non-modifiable risk factors for the development of AD are age and sex (Herbert et al., 2010; Fisher et al., 2018).

3.3.2. Modifiable risk factors

There are also many modifiable risk factors that can increase the probability of developing AD for individuals. Since these risk factors are modifiable it is important to achieve a good understanding of these, as they could provide insights into strategies to prevent or slow down the development of AD. Firstly, cerebrovascular diseases increase the chance of developing AD through reducing cerebral blood flow and dysfunctionality of the blood-brain barrier (BBB) (Love & Scott, 2016). Secondly, hypertension can increase the risk of developing AD (Skoog et al., 1996). Furthermore, dyslipidemia, type 2 diabetes, and possibly obesity are risk factors for AD (Profenno et al., 2010; Popp et al., 2013; Li et al., 2015). Marital status, stress, depression and inadequate sleep are also linked to a higher chance of developing AD (Håkansson et al., 2009; Huang et al., 2009; Byers & Yaffe, 2011; Proserpio et al., 2018).

3.4. Treatment of Alzheimer's disease

Up till now no actual curative treatments have been found, therapies are mostly aimed at treating the occurring symptoms. There are a few drugs on the market to treat AD (Grossberg, 2003; Bukke et al., 2020). Besides these drug treatments, research has also been done into non-pharmacological therapies, more specifically into multidomain or multimodal interventions. Multidomain interventions might be beneficial, because they can target more than one risk factor for dementia at the same time, and therefore have additive or even synergistic effects. Multidomain interventions include interventions in factors such as diet, physical activity, social engagement, cognitive activity and cardiovascular risk management (Coley et al., 2008).

4. Physical exercise as a tool to prevent AD development

Inactivity has been shown to be one of the major risk factors for patients suffering from Alzheimer's disease. On the other hand an increasing amount of evidence suggests that physical activity (PA) might have a positive effect on cognitive functioning and limit age related cognitive decline (Cass, 2017). A meta-analysis examining the relationship between PA and the risk of developing a neurodegenerative disease found that physical activity is inversely associated with the risk of AD (Hammer & Chida, 2008). This review will examine multiple pathological characteristics visible in AD and compare the effects that cardiovascular exercise and resistance exercise have on these pathologies. Table 1 contains an overview of the beneficial effects of both cardiovascular exercise and resistance exercise.

4.1. Blood flow

One of the pathophysiological characteristics of AD is a dysfunctional vascular system, through which the brain blood flow decreases (Lange-Asschenfeldt & Kojda, 2008). This leads to the hypothesis that protection of the cerebrovascular system may positively affect AD onset. Studies have shown positive effects of different forms of physical exercise on blood flow to the brain and on cognition (Cass, 2017).

Acute resistance exercise (i.e. a single bout of exercise) performed by healthy elderly individuals, showed beneficial effects on general cognition and on working memory, through an increase in blood flow to the brain (Chang et al., 2014 ; Hsieh et al., 2016). However, multiple studies have found these beneficial effects only to be present shortly after performance of the exercise (Chang et al., 2012). Chronic resistance exercise (i.e. long-term exercise) in elderly women also showed an increase cerebral blood flow (Xu et al., 2014).

The effects of cardiovascular exercise on blood flow have also been researched in multiple studies, showing multiple effects. Firstly an increase in vascular endothelial growth factor (VEGF) angiopoietin 1 and 2, and an increase in the density of small vessels in the brain was reported as a consequence of treadmill running by elderly mice (Ding et al., 2006). Secondly, high-intensity interval training has been found to increase VEGFA and brain angiogenesis, through lactate receptors (Morland et al., 2017). Furthermore, a study found an increase in blood flow in the cerebellum, hippocampus, motor cortex and an increase in micro vessel density in the striatum of mice. A more stable cerebral blood flow was also measured in elderly humans that performed cardiovascular exercise regularly (Hooghiemstra et al., 2012).
Cardiovascular exercise can also affect blood flow to the brain through an increase in nitric oxide (NO) availability. This increase in NO is very important for cerebral blood flow, and it furthermore decreases the risk of the development of atherosclerosis, which seems to be closely related to the development of AD (Roher et al., 2003; Eggermont et al., 2006)

4.2. Brain volume

4.2.1. Macroscopic level

A decrease in total brain volume, including hippocampal volume, can be observed in aging individuals and is especially visible in AD patients (DeTure & Dickson, 2019b).
The effects of long-term resistance training on brain volume where tested in healthy elderly, finding positive effects on cognitive functioning (Tsai et al., 2019). A study found a greater decrease in atrophy of cortical white matter, compared to individuals performing cardiovascular exercise. Furthermore performance of the Stroop test increased, brain activation under relatively easy task conditions decreased and an increase in brain activation was visible under more difficult task conditions (Liu-Ambrose et al., 2012).

Evidence was also found for the effectiveness of high intensity resistance training on the protection against degeneration of AD-vulnerable hippocampal subfields for a time period of at least 12 months post-intervention (Broadhouse et al. 2020). A possible explanation for the protection against degeneration could be an increase in serum IGF-1 levels. This increase was visible in a study of older women after RE (Parkhouse et al., 2000). IGF-1 has been found to exhibit neuroprotective effects, including promotion of brain myelinization and assisting recovery of myelin after pathological insults (Ye et al., 1995; Mason et al., 2000). The effects of IGF-1 could provide an explanation for the effects of RE on cortical white matter volume, found in an experiment also performed on older women (Best et al., 2015).
However a previously done study did not report any positive effects of resistance training on reduction of hippocampal atrophy (Best et al., 2015).
Furthermore, in a literary review performed by Cheng et al. (2022) an increase in grey matter was also found as a result of long-term resistance training.

The effects of cardiovascular exercise on whole brain volume and hippocampal volume have also been assessed in multiple studies. Erickson et al. (2011) and Ten Brinke et al. (2015) found a reduction hippocampus atrophy after the performance of CE. These studies also measured improvements in memory. An increase in BDNF levels in the serum is suggested to be involved in mediation of neurogenesis in the hippocampus, as changes in serum BDNF levels showed a correlation with changes in hippocampal volume in elderly participants of CE tests (Erickson et al., 2011; Voss et al., 2013). Long term CE interventions have also reported to increase grey matter in the prefrontal, cingulate and temporal cortices and in the hippocampus (Colcombe et al., 2006 ; Ruscheweyh et al., 2011; Erickson et al., 2011b). Short term CE, on the other hand, did not report any significant changes in the volume of the same brain areas (Maaß et al., 2014; Sexton et al., 2020).

4.2.2. Microscopic level

As was mentioned in the previous paragraph, upregulation of neurotrophic and growth factors, including BDNF and IGF-1, through multiple forms of physical activity, is suggested to mediate the positive effects of physical activity on the brain (Parkhouse et al., 2000; Voss et al., 2013). There are various mechanisms through which BDNF and IGF-1 function.
BDNF for instance was shown to shift APP processing towards the non-amyloidogenic α-secretase pathway, through which production of Aβ decreased (Holback et al., 2005). A decrease in tau phosphorylation, mediate by BDNF was also measured in multiple studies (Elliot et al., 2005; Li et al., 2007). Furthermore, BDNF is essential for neural plasticity. Upregulation of BDNF through CE enhances long-term memory storage, reorganization of dendritic spines and synaptic regeneration (Vivar et al., 2013;. Coelho et al., 2014)
IGF-1 has also been found to effect Aβ levels. IGF-1 firstly acts through inhibiting Aβ production by effecting α-secretase and β-secretase (Song et al., 2018). Additionally, upregulation of IGF-1 increases levels of Aβ transporting proteins like apolipoprotein, which are important for the transport of Aβ across the BBB (Carro et al., 2002). Tau hyperphosphorylation, a prominent AD pathology, is also downregulated by IGF-1 (Hong & Lee., 1997). Similar to BDNF, IGF-1 also affects dendritic growth and synapse formation in the hippocampus (O'Kusky et al.,2000).

4.3. Neuroinflammation

Chronic neuroinflammation is visible in many Alzheimer's disease patients (Kinney et al., 2018). Microglia and astrocytes have been established to play an important role in this core pathology of AD (Koenigsknecht & Landreth, 2004; Liddelow et al., 2017). Furthermore an increase in inflammatory factors including IL-6, IL-1β and TNF- α and a decrease in anti-inflammatory factor IL-10 can be measured in AD patients (Rea et al., 2018).

A study by Campos et al. (2023) found an increase in microglial cell levels in the hippocampus of mice after these were subjected to resistance exercise. In a study on APP/PS1 mice RE increased the number of microglial cells in the hippocampus, surrounding β-amyloid plaques and forming a plaque condensing barrier, thereby protecting the surrounding environment (Condello et al., 2015).
Contrary to this study, an experiment by Liu et al (2020) found a decrease in microglial activation in the frontal cortex and hippocampus accompanied by a decrease in astrocyte activation in the dentate gyrus as a result of resistance exercise.
These changes were accompanied by a decrease in mRNA expression of TNF-α and IL-10.
Furthermore, an increase in IL-6 was measured in the same study, after which was suggested that this factor can play a role in resistance against inflammation. Lastly this study found increases in fibroblast growth factor 21 (FGf-21), in the liver, and PGC-1α, in the liver and hippocampus. Earlier research found that FGF-21 can permeate the BBB and exhibits protective effects on the brain, facilitating remyelination and inhibiting inflammatory responses (Fisher & Maratos-Flier, 2016; Kuroda et al., 2017; Liu et al., 2020).
Other studies also suggested that RE can contribute to a shift from a pro-inflammatory to an anti-inflammatory state of microglial cells (Campos et al., 2023).
Kelty et al. (2022) additionally found that RE impaired neuroinflammation induced by LPS in the dentate gyrus and ameliorated cognitive decline through decreasing the neuroinflammation. These results were however found 24 hours after the exercise, so acute and short-lived characteristics of these results cannot be ruled out.
The effects of RE on proinflammatory chemokine levels of Macrophage Inflammatory Protein 2 (MIP-2), which stimulates neurodegeneration, were also studied. MIP-2 was found to decrease in the hippocampus of elderly rats after RE (Fang et al., 2012; Henrique et al., 2018). The same study by Henrique et al. (2018) also measured a decrease in RANTES/chemokine ligand 5 (CCL5), a neuronal function altering ligand, in the cerebral cortex (Meucci et al., 1998; Henrique et al., 2018). The above described findings of Henrique et al. (2018) could not be measured in rats that underwent CE. Lastly, in the rats that were subjected to CE an increase in cortical levels of IL-13, an anti-inflammatory cytokine, was measured. (Mori et al., 2016; Henrique et al., 2018). This change could not be found in RE rats (Henrique et al., 2018)

Cardiovascular exercise has also further been studied in relation to neuroinflammation, as is visible in figure 2. Suppression of neuroinflammation could be found, which alleviated Alzheimer's disease, through multiple mechanisms (Wang et al., 2023). Firstly cardiovascular exercise, for differing periods of time, in elderly APP/PSI mice showed a reduction in the number of astrocytes in the hippocampus in various studies (Tapia-Rojas et al., 2015; Zhang et al., 2018). However, another study that looked into the effects of voluntary running in rats, showed an increase in the number of astrocytes (Rodrigues et al., 2010). The varying results of astrocyte and GFAP-positive astrocyte levels after cardiovascular training suggest that the intensity and duration of the exercise and the degree of voluntariness affect the impact cardiovascular exercise has on astrocytes (Maugeri et al., 2021).
Attenuation of microglia could also be observed after treadmill running in mice, at young age and later in life (Ke et al., 2011). Another study in a LOAD model established that exercise shifted activated microglia from a pro-inflammatory M1 to an anti-inflammatory M2 phenotype (Lu et al., 2017). There are however also studies that have not found any effects on the number of astrocytes and microglia after the performance of CE (Xu et al., 2013).
Studies have also reported a decrease in IL-1β and TNF- α in the hippocampus (Nichol et al., 2008).
Positive effects on cognition were also seen in an experiment in which an increase of CXCL1 and CXCL12, which act as neuroprotective chemokines, was measured in middle aged and elderly Tg2576 mice (Parachikova et al., 2008). All these studies were performed on mice of different ages, varying from middle aged mice models to elderly mice models. It is important to keep age-dependency in mind, when assessing the effectiveness of cardiovascular exercise on neuroinflammation (Kelly, 2018).

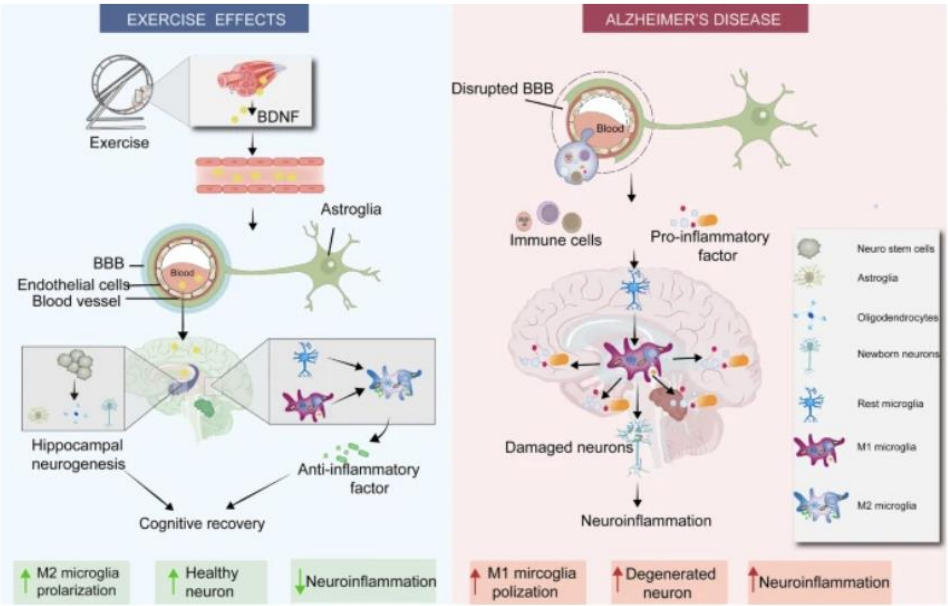

Figure 2. Cardiovascular exercise modulates inflammatory processes in the brain, through which AD is ameliorated (Wang et al., 2023)

4.4. Oxidative stress

An elevation in reactive oxygen species (ROS) and reactive nitrogen species (RNS) production, causing oxidative stress, which is linked to neuroinflammation and neurodegeneration, can be measured in AD patients (Huang et al., 2016). Mitochondrial dysfunction is suggested to be associated with this pathology, through its role as one of the ROS sources in neurons (Leuner et al., 2012). A paradoxical role for physical exercise can be noted regarding the prevention of AD. Exercise has been found to increase ROS levels. These changes however are visible on the short-term, whereas pathological ROS accumulation is chronic in AD (Bernardo et al., 2016).

In AD mice models an upregulation of the activity of antioxidant enzymes, SOD and catalase, was measured after performance of RE. These enzymes are downregulated in this AD mice model under normal circumstances (Um et al., 2008; Um et al., 2011). Secondly, mitochondrial DNA (mtDNA) has been found to be affected by ROS. Subsequently the activity of mitochondrial 8-oxuguanine DNA glycosylase-1 (OGG1), responsible for removing oxidative damage is decreased in certain regions of AD brains. Research has also suggested that adaptive changes occur in the brain after RE due to upregulation of antioxidants and redox regulation in the brain (LiCausi & Hartman., 2018). However, little research has been published up till now on the effects of RE on oxidative stress

Research has suggested that CE activates multiple redox-sensitive signalling pathways, through which the antioxidant system can be improved (Radak et al., 2013). Long term adaptations to exercise have also been found to decrease ROS production (Radak et al., 2010). Additionally, as a consequence of CE, mtDNA repair increased through increasing mtOGG1 in APP/SP1 mice, suggesting that CE can attenuate AD-related mitochondrial impairments (Shao et al., 2008; Bo et al., 2014). Furthermore, CE resulted in a decrease in pro-apoptotic proteins, including cytochrome c, Bax, caspase 3 and 9 and an increase of anti-apoptotic protein Bcl-2 in an AD mice model (Um et al., 2008; Um et al., 2011).
HSP-70, a chaperone protein that protects neurons against oxidative injury was also found upregulated in the brain after CE was performed (Um et al., 2011).
Lastly PGC-1α is upregulated through RE and CE, and has been suggested to improve oxidative stress, mitochondrial dysfunction and insulin resistance, there by preventing neuronal cell damage (Sweeney et al., 2016).

4.5. Peripheral organ fitness as a mechanism to induce brain health

Brain metabolism has clearly been established to be affected by AD. Experiments however have found that not only brain metabolism has been altered, but an increasing amount of evidence has been found that AD affects peripheral organs including the cardiovascular system, gut microbiome, liver, testes and kidneys as is visible in figure 3. (Estrada et al., 2019; Szegeczki et al., 2020; Leszek et al., 2021; Stocker et al., 2023; Seo & Holtzman, 2024).

4.5.1 Gut microbiome

Specific alterations in the gut microbiome are associated with cognitive impairments and synapse formation deficiencies (Bhattacharjee & Lukiw, 2013). AD is also affected by the microbiota-gut-brain axis (Hu et al., 2016). CE in combination with probiotics have been shown to alter the gut microbiota, increasing the amount of microorganisms involved in butyrogenesis, of APP/PS1 mice. When performed on their own, these interventions did not show any effects. These alteration of the gut microbiota improved brain performance, thereby suggesting the interventions were successful in attenuating AD progression. The amount of B12, producing bacteria L.reuteri, also increased after a combination of CE and probiotics. An important role for B12 has been established in preserving brain health. (Abraham et al., 2019). RE has not been found to alter the gut microbiome (Wagner et al., 2024)

4.5.2 Liver

Impaired metabolism is visible in the liver of AD patients, which besides other functions is thought to be involved in peripheral clearance of blood Aβ (Estrada et al., 2019). CE has been found to upregulate liver mitochondrial antioxidant capacity. An increase in antioxidant signalling proteins and a prevention of decrease in superoxide dismutase 2 were measured in cardiovascular trained AD model mice (Téglás et al., 2020).

4.5.3. Kidneys

Renal deficiencies are also associated with AD (Stocker et al., 2023). Performance of CE by APP/PS1 mice reduced kidney fibrosis, thereby increasing Aβ clearance in the kidneys, possibly inhibiting AD progression (Perényi et al., 2020). RE has also been found to attenuate kidney fibrosis, these result however was not obtained from an experiment studying AD patients, but from a experiment studying patients with chronic kidney disease (Souza et al., 2018). CE furthermore led to normalization of TGFβRI expression in AD mice (Szegeczki et al., 2021). Normalization of the levels of cellular proliferation markers, which are influenced by TGF, could also be measured as a consequence of CE (Perényi et al., 2020). Lastly PACAP levels, a signal molecule important for Aβ clearance in the kidneys, were increased in AD mice after CE. These levels differed significantly from those in non CE AD mice, in which PACAP levels were undetectable or majorly decreased (Reglodi et al., 2018; Perényi et al., 2020).

4.5.4. Gonads

In the testis an increase of the downstream PACAP signalling molecule PKA could be found after the performance of CE, potentially positively influencing AD pathology in the brain (Szegeczki et al., 2020). In females PCOS is associated with an increased risk for AD through multiple symptoms of PCOS including, LH-FSH increase, vitamin D decrease, insulin resistance and obesity (Gonzales et al., 2012; Sarahian et al., 2021). Moderate physical exercise is beneficial for PCOS patients, and can decrease the chance of developing AD through this mechanism (Woodward et al., 2020).

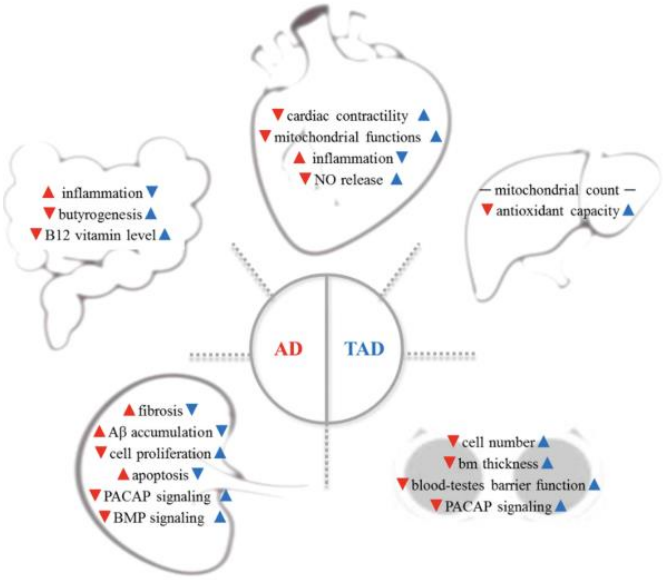

Figure 3. Besides the degenerative characteristics AD has in the brain, these can also be found in peripheral organs (indicated by the red arrows). Physical activity (training in AD (TAD)) can mitigate some of these affects (Indicated by the blue arrows). (Aczel et al., 2022).

4.6. Irisin

The myokine irisin is secreted by skeletal muscle after the performance of both resistance exercise and cardiovascular exercise (Adilakshmi et al., 2023). This myokine has protective functions, through regulating BDNF in both the central and peripheral nervous system. Irisin can cross the blood-brain barrier and can be found in the brain in Purkinje cells, the paraventricular nucleus and the cerebrospinal fluid (Jin et al., 2018; Young et al., 2019). A reduction has been found in a rat AD model in both the hippocampus and CSF, suggesting this myokine plays a role in AD (De Freitas et al., 2020). Irisin has been suggested to stimulate neuronal growth and stabilize synapses through stimulation of BDNF (Moon et al., 2013). Furthermore, irisin suppresses Aβ accumulation in the hippocampus, delaying AD (Jin et al., 2018). Irisin also plays a role in inflammatory processes, reducing neuroinflammation and oxidative stress in the brain directly. In the plasma irisin decreases pro-inflammatory cytokine levels and shifts macrophages from pro-inflammatory to anti-inflammatory activity (Kim & Song, 2018). It can be suggested that irisin, increased through exercise, can play a role in reducing cognitive decline in AD (Chen et al., 2022).

5. Discussion

Alzheimer's disease is a progressive neurodegenerative disorder, that causes dementia in more than 30 million people worldwide, and this number is steadily increasing (Braak & Braak, 1991; WHO 2023). No curative treatments have been found up till now, so therapies have been aimed at treating the occurring symptoms. Multidomain interventions, in which one or more risk factors of AD can be treated at the same time, are also used to delay the progression of AD (Coley et al., 2008). One of the risk factors of AD is inactivity, therefore the effectiveness of physical activity as a treatment for AD has extensively been studied.

The aim of this review was to investigate which form of exercise, either cardiovascular exercise or resistance exercise was most effective to prevent cognitive decline and limit or even restore brain pathology in AD patients.

Studies have shown that exercise can affect the brain in multiple ways. Firstly, blood flow has been found to increase as a response to both CE and RE (Hooghiemstra et al., 2012; Xu et al., 2014). Secondly, a decrease in atrophy of the hippocampus and cortical white matter, and an increase in grey matter were visible as a result of CE and RE (Erickson et al., 2011; Tsai et al., 2019). Additionally, CE and RE both decrease neuroinflammation. Cardiovascular exercise has furthermore been found to decrease oxidative stress in the brain, decreasing neurodegeneration (Campos et al., 2023; Wang et al., 2023). This form of exercise has also been found to positively effect fitness of various peripheral organs, thereby improving brain health and decreasing the effects of AD (Mandolesi et al., 2018). Lastly CE and RE both increase irisin production by skeletal muscle, which decreases neuroinflammation and promotes neurogenesis (Moon et al., 2013; Kim & Song., 2018; Adilakshmi et al., 2023).

The hypothesis of this review was that cardiovascular exercise would have greater beneficial effects for AD patients than resistance exercise. This hypothesis can be supported by the existing literature, in which CE seems to have more effects throughout the different pathways that improve brain functioning in AD patients. However, this result may be biased as more studies have been done into the effects of CE than RE. The smaller amount of evidence for the benefits of RE therefore could be a result of less research into this type of exercise, and not necessarily mean RE is less beneficial. A combination of both CE and RE also seems favourable, as both types of exercise support the brain in different ways, and thereby a combination can have synergistic effects.

Many mechanisms underlying Alzheimer's disease, and especially exercise-induced neuroprotection are still unknown. Further research therefore, especially into the mechanisms through which RE can provide a beneficial instrument in combating AD, is required. It is also beneficial to research how both RE and CE can be integrated into multidomain interventions, often used as treatments for AD. However, until more knowledge is obtained, integration of both types of exercise is instrumental in combating the growing burden of AD worldwide.

Tabel 1. Overview of the beneficial effects of both Cardiovascular Exercise and Resistance Exercise

	Cardiovascular exercise	Resistance exercise
Blood flow	• ↑ VEGF angiopoietin 1 & 2 (Ding et al., 2006) • ↑ Blood flow to cerebellum, hippocampus, motor cortex (Hooghiemstra et al., 2012) • ↑ NO → increase cerebral blood flow (Roher et al., 2003) • ↓ Risk for atherosclerosis (Eggermont et al., 2006)	• Acute resistance exercise: Transient ↑ blood flow (Chang et al., 2012) • Chronic resistance exercise: ↑ Cerebral blood flow (Xu et al., 2014)
Brain volume	• ↓ Hippocampal atrophy (Erickson et al., 2011; Ten Brinke et al., 2015) • ↑ Serum BDNF (Erickson et al., 2011; Voss et al., 2013) • ↑ Grey matter in PFC, cingulate cortex, temporal cortex and hippocampus (Colcombe et al., 2006 ; Ruscheweyh et al., 2011; Erickson et al., 2011b)	• ↓ atrophy of cortical white matter (Liu-Ambrose et al., 2012) • ↓ Hippocampal atrophy (Broadhouse et al. 2020) • ↑ Serum IGF-1 (Parkhouse et al., 2000)
Neuroinflammation	• Altered Hippocampal astrocyte levels (Rodrigues et al., 2010; Tapia-Rojas et al., 2015; Zhang et al., 2018) • ↓ Microglia (Lu et al., 2017) • ↓ IL-1β and TNF- α in the hippocampus (Nichol et al., 2008)	• Altered microglial activation (Condello et al., 2015; Liu et al., 2020) • ↓ TNF-α and IL-10 (Liu et al., 2020) • ↑ FGF-21 (Fisher & Maratos-Flier, 2016) • Pro-inflammatory → anti-inflammatory state of microglial cells (Campos et al., 2023) • ↓ LPS in DG (Kelty et al., 2022) • ↓ MIP-2 in the hippocampus (Fang et al., 2012; Henrique et al., 2018) • ↓ CCL5 (Henrique et al., 2018)
Oxidative stress	• ↑ Activation of redox-sensitive signalling pathways (Radak et al., 2013) • ↓ ROS production (Radak et al., 2010) • ↑ mtDNA repair (Shao et al., 2008) • ↓ Pro-apoptotic proteins (Um et al., 2008) • ↑ Anti-apoptotic proteins (Um et al., 2011) • ↑ HSP-70 (Um et al., 2011) • ↑ PGC-1α (Sweeney et al., 2016)	• ↑ Antioxidant enzymes SOD and catalase (Um et al., 2008; Um et al., 2011) • ↑ PGC-1α (Sweeney et al., 2016)
Peripheral organ fitness	• ↑ Improval of gut microbiome health (Abraham et al., 2019) • ↑ Liver mitochondrial antioxidant capacity (Téglás et al., 2020)	• ↓ Kidney fibrosis → ↑ Aβ clearance (Souza et al., 2018) • Normalization of TGFβRI expression (Szegeczki et al., 2021)

	• ↓ Kidney fibrosis → ↑ Aβ clearance (Perényi et al., 2020) • Normalization of cellular proliferation markers (Perényi et al., 2020) • ↑ PACAP levels (Reglodi et al., 2018; Perényi et al., 2020) • ↑ PACAP signalling molecule PKA in testis (Szegeczki et al., 2020) • ↓ PCOS risk (Woodward et al., 2020)	
Irisin	• ↑ BDNF (Adilakshmi et al., 2023) • ↓ Neuroinflammation (Kim & Song, 2018)	• ↑ BDNF (Adilakshmi et al., 2023) • ↓ Neuroinflammation (Kim & Song, 2018)

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