



REVIEW

Exercise as Potential Therapeutic Target to Modulate Alzheimer's Disease Pathology in APOE ϵ 4 Carriers: A Systematic Review

Sevilay Tokgöz · Jurgen A. H. R. Claassen

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disease for which no effective treatment exists at present. Previous research has found that exercise reduces the risk of AD. Since the apolipoprotein E (APOE) ϵ 4 allele increases the risk of AD and is associated with faster disease progression than the other isoforms, we aimed to highlight the impact of exercise on AD pathology in APOE ϵ 4 carriers. This review focuses on the effect of exercise on cognitive function, dementia risk, amyloid- β (A β) metabolism, lipid metabolism, neuroinflammation, neurotrophic factors and vascularization in APOE ϵ 4 carriers. We searched the literature in the PubMed electronic database using the following search terms: physical activity, exercise, aerobic fitness, training, sport, APOE4, Alzheimer's disease, AD and dementia. By cross-referencing, additional publications were identified. Selected studies required older

adults to take part in an exercise intervention or to make use of self-reported physical activity questionnaires. All included studies were written and published in English between 2000 and 2020. From these studies, we conclude that exercise is a non-pharmacological treatment option for high-risk APOE ϵ 4 carriers to ameliorate the AD pathological processes including reducing A β load, protecting against hippocampal atrophy, improving cognitive function, stabilizing cholesterol levels and lowering pro-inflammatory signals. Variation in study design related to age, cognitive outcomes and the type of intervention explained the differences in study outcomes. However, exercise seems to be effective in delaying the onset of AD and may improve the quality of life of AD patients.

Keywords: Alzheimer's disease; APOE4 genotype; Exercise intervention; Mild cognitive impairment; Physical activity

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Key Summary Points

Why carry out this study?

Alzheimer's disease is a major cause of death and disability and constitutes a large economic burden.

ApoE- ϵ 4 is a strong genetic risk factor for Alzheimer's disease.

This review investigated whether this genetic risk could be modified by environmental factors, specifically physical activity or exercise.

What was learned from the study?

Several studies have examined interactions and associations between exercise and ApoE- ϵ 4 on mechanisms that contribute to the risk of Alzheimer's disease.

Exercise may mitigate the negative effects of ApoE- ϵ 4 on amyloid-beta 42 metabolism, neuroinflammation, neurotrophic factors, cerebral blood vessels and cognitive function, and thereby reduce the risk of Alzheimer's disease.

problems, agnosia, apraxia and executive function impairment [1]. AD is the most common form of dementia. Quality of life is impaired in patients with dementia due to the reduced ability of daily-life functioning. The best known molecular mechanisms behind AD are amyloid plaque deposition and hyperphosphorylated tau proteins forming neurofibrillary tangles in the brain. Neuronal connections within the brain are disrupted by these protein aggregates, leading to regional atrophy. The blood circulation system may have a protective role in preventing aggregation by clearance of these proteins. However, the clearance of protein aggregates is deficient in AD due to cellular, molecular and genetic imbalances.

AD can be divided into an early-onset (age < 60) and the more common late-onset form. Genetic, clinical and lifestyle-related risk factors play a role in the development of AD. Early-onset AD is mainly caused by genetic variations in the APP gene encoding amyloid- β precursor protein, or PSEN1 and PSEN2 genes encoding presenilins I and II, respectively. These three genes have been found to play an important role in amyloid- β (A β) production. Cleavages of APP via β -secretase and γ -secretase secrete A β of several lengths, of which the most common forms are the 40- and 42-amino acid A β (A β 40 and A β 42, respectively). The latter isoform has a more hydrophobic structure, making it more susceptible to deposition in the brain. Both PSEN1 and PSEN2 proteins constitute the catalytic part of the γ -secretase complex [2]. Mutations in PSEN affect the A β 42/40 ratio, resulting in elevated A β 42 [3].

The late-onset form of AD is also genetically determined, albeit to a lesser extent. Genome-wide association studies have revealed the important role of the apolipoprotein E (APOE) gene encoding the ApoE protein on chromosome 19 in late-onset AD [4]. The ApoE protein is involved in the transport and metabolism of lipids, and it exists in three common isoforms: ApoE2, ApoE3 and ApoE4, encoded by APOE ϵ 2, ϵ 3 and ϵ 4, respectively. They vary at amino acid residues 112 or 158, which results in significant differences in their functioning [5]. The APOE ϵ 2 allele is protective against AD, whereas the ϵ 3 allele has a neutral effect [6]. The risk of late-

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INTRODUCTION

Alzheimer's Disease (AD) is a progressive neurodegenerative disease affecting cognitive function. This cognitive decline manifests as deficits including memory loss, communication

onset AD increases with the presence of one or two APOE ϵ 4 alleles [7]. Furthermore, the age of onset will decrease in a dose-dependent relation with the APOE ϵ 4 allele [8]. Besides the risk of AD, APOE ϵ 4 homozygotes also demonstrate neuropathological characteristics of the disease such as increased A β deposition [4]. Previous studies have reported A β accumulation in an isoform-dependent fashion as ApoE4 > ApoE3 > ApoE2 [9, 10]. Since APOE ϵ 4 carriers have lower cerebrospinal fluid (CSF) and plasma ApoE protein levels [10–12], the ApoE protein is suggested to be involved in preventing the accumulation of A β plaques [13, 14]. The ApoE4 protein is implicated in many other processes that may influence AD, including lipid metabolism, tau phosphorylation, cholesterol homeostasis, mitochondrial function, neuroinflammation, vascular function and synaptic plasticity [14].

To date, pharmacological agents only provide symptomatic treatment by targeting, for example, the synaptic dysfunction, A β accumulation and phosphorylation signalling pathways [15], and the efficiency can be increased by combining therapeutics [16]. However, reversing a multimodal disease such as AD still remains a challenge. The risk of AD is also influenced by lifestyle factors such as blood pressure, smoking, physical activity and cholesterol [17]. Much research is focused on non-pharmacological approaches including exercise. Previous studies have found positive effects of exercise on cognition in AD [18, 19]. Burns et al. found cardiorespiratory fitness to be protective against brain atrophy in early AD patients [20]. Furthermore, aerobic exercise in early AD was associated with reduced hippocampal atrophy and improved memory performance [21]. It was suggested that lifestyle intervention in APOE ϵ 4 carriers may modify dementia risk, since the risk of dementia in these individuals was found to increase with adverse lifestyle factors such as physical inactivity [22]. Previous systematic reviews have focused on exercise and AD, but the association with the APOE4 genotype has received limited attention. The objective of this review is to highlight the modulatory role of exercise on AD pathology in APOE ϵ 4 carriers. We will review

the effect on several mechanisms contributing to AD including cognitive function, A β metabolism, lipid metabolism, neuroinflammation, neurotrophic factors and vascularization. We will discuss both human and animal studies. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by either of the authors.

PHYSICAL ACTIVITY IN APOE ϵ 4 CARRIERS

Cognitive Function

Cognitive decline in AD dementia affects most daily life activities. Thus, a growing need arises to ameliorate progressive cognitive symptoms. There is some evidence supporting the effectiveness of exercise as therapy (Table 1). Jensen et al. found that AD patients carrying the APOE ϵ 4 gene and who were engaged in an exercise intervention showed an improvement of neuropsychiatric symptoms and stabilized cognition as assessed by the symbol digit modalities test (SDMT) in comparison to non-carriers and controls [23]. The exercise intervention consisted of supervised aerobic exercise three times a week for 16 weeks. Results showed that these carriers improved the physical, cognitive and neuropsychiatric outcomes compared to non-carriers. Similarly, APOE ϵ 4 mice engaged in aerobic exercise demonstrated improved cognition and hippocampal function [24]. Cognition in these transgenic mice was tested by object and place recognition tests. A study by Etnier et al. supported the protective effect of aerobic exercise on cognition in cognitively normal older women carrying the APOE4 ϵ 4 allele [25], based on different cognitive tests including an auditory verbal learning test, the complex figure test and the Wisconsin Card Sorting Test. Lautenschlager et al. studied the effect of a 24-week home-based physical activity intervention on cognitive function in adults with subjective memory impairment [26]. Physical activity was assessed with a survey in combination with data obtained from a pedometer to avoid bias. This study demonstrated that

Table 1 Studies about physical activity in APOE $\epsilon 4$ carriers

Reference	Species	Study population	Number of APOE $\epsilon 4$ carriers	Age, range or mean (SD)	Assessment of exercise	Follow-up period	Outcome measures	Major study outcome
Schuit et al. (2001) [37]	Human	347 male elderly	79:	74.6 (4.3) years	Self-reported questionnaire	3 years	Cognitive testing: MMSE	Maximal 1 h PA per day group showed a greater risk of cognitive decline, which was stronger in APOE $\epsilon 4$ carriers
			8 homozygotes		3 categories: ≤ 30 min/day, 31–60 min/day and > 60 min/day			
			71 heterozygotes		First two categories were taken together as maximal 1 h PA per day			
Bernstein et al. (2002) [66]	Human	1708 adults	320	35–72 years	Self-reported physical activity frequency questionnaire about total and activity-specific energy expenditures	NA	Lipid profile: HDL cholesterol, LDL cholesterol, triglycerides	Enhanced HDL cholesterol in APOE $\epsilon 4$ carriers due to high-intensity exercise. An increase in high-intensity exercise was associated with a decrease in triglycerides only in male APOE $\epsilon 4$ carriers
					Categorized according to intensity			
Podewils et al. (2005) [39]	Human	3375 cognitively healthy older adults	813	65 years or older	Interview with a modified Minnesota Leisure Time Activity Questionnaire about the frequency and duration of activities over the previous 2 weeks	5.4 years	Dementia risk	Participants with more than 4 activities in the previous 2 weeks had a lower risk of dementia. This association was absent in carriers of the APOE $\epsilon 4$ allele
					Categorized in the number of activities during 2 weeks			
Rovio et al. (2005) [35]	Human	1251 participants for dementia analyses	Dementia analyses: 438	At midlife: 39–64 years, mean age 50.6 (6)	Self-reported questionnaire based on frequency	21 years	Dementia and AD risk late in life	Midlife PA reduced the late-life risk of dementia and AD in especially APOE $\epsilon 4$ carriers
			AD analyses: 433	At re-examination: 65–79 years, mean age 71.6 (4.1)	Active group: leisure-time PA at least twice a week Sedentary group: leisure-time PA less than twice a week			

Table 1 continued

Reference	Species	Study population	Number of APOE ε4 carriers	Age, range or mean (SD)	Assessment of exercise	Follow-up period	Outcome measures	Major study outcome
Etnier et al. (2007) [25]	Human	94 cognitively intact older women	35: 27 heterozygotes, 8 homozygotes	51–81 years Mean age: 62 (7.39)	Maximal aerobic fitness test (graded exercise test)	NA	Cognitive function: auditory verbal learning test (AVLT), the complex figure test (CFT) and the Wisconsin Card Sorting Test (WCST)	Aerobic fitness was associated with better memory performance in APOE ε4 homozygotes
Deeny et al. (2008) [32]	Human	Sternberg test: 54 middle-aged adults MEG testing: 23 middle-aged adults	Sternberg test: 16 MEG testing: 9	50–70 years	Interview with Yale Physical Activity Survey for Older Adults (records minutes and intensity of weekly PA); behavioural Sternberg testing; MEG Sternberg testing	NA	Behavioural Sternberg testing, MEG Sternberg testing	High PA was related to faster reaction time in executive functions of the working memory in APOE ε4 carriers. Sedentary carriers showed lower right temporal lobe activation
Nichol et al. (2009) [24]	Mouse	16 ε3 and 15 ε4 targeted replacement mice	15	10–12 months	Aerobic exercise intervention: 1 min, twice a week for 6 weeks Two groups: exercise (in-cage running wheels) and sedentary group	6 weeks	Cognitive function: object recognition, radial-arm water maze and place recognition testing; BDNF levels	APOE ε4 mice engaged in aerobic exercise improved cognition and hippocampal function Increased hippocampal BDNF levels due to exercise in both groups
Chang et al. (2010) [36]	Human	4761 non-demented and 184 demented participants	583	Midlife examination: mean age 51 Late-life examination: mean age 76	Interview 3 groups: no midlife PA, ≤ 5 h PA and ≥ 5 h PA	26 years	Cognitive tests: digit symbol substitution test, figure comparison, modified Stroop test, California Verbal Learning Test, immediate and delayed recall, digits backwards, short CANTAB Spatial Working Memory Test, Stroop test part III	Faster speed of processing and better memory and executive functions in both midlife PA groups. Midlife PA was associated with reduced risk for dementia in APOE ε4 non-carriers
Sanders et al. (2010) [27]	Human	69 patients with dementia	30: 3 homozygotes, 27 heterozygotes	82.3 (7) years	Exercise intervention: walking and lower limb strength training program with low- and high-intensity training, each 6 weeks: three times/week for 12 weeks	36 weeks	Physical function; cognitive function: neuropsychological tests and MMSE	No effect of exercise on physical or cognitive function in APOE ε4 carriers
Scip et al. (2011) [67]	Human	166 participants	54	18–70 years	Exercise intervention: aerobic training of moderate to vigorous intensity for 6 months, 40 min per training and 4 days/week	6 months	Lipid profile: total glycerides, HDL cholesterol, LDL cholesterol, total cholesterol	Exercise did not modify HDL or LDL cholesterol in APOE ε4 carriers

Table 1 continued

Reference	Species	Study population	Number of APOE $\epsilon 4$ carriers	Age, range or mean (SD)	Assessment of exercise	Follow-up period	Outcome measures	Major study outcome
Smith et al. (2011) [28]	Human	68 cognitively intact older adults	34: 2 homozygotes, 32 heterozygotes	65–85 years	Self-reported questionnaire Stanford Brief Activity Survey based on frequency and intensity Low-PA group: two or fewer low-intensity physical activities per week High-PA group: moderate to heavy physical activities at least 3 times a week	NA	Neuropsychological testing: MMSE, Mattis Dementia Rating Scale 2 (DRS-2), RAVLT, Geriatric Depression Scale (GDS), Lawton Activities of Daily Living (ADLs); name discrimination task; semantic memory activation	More memory-related brain activation in highly active old adults carrying the APOE $\epsilon 4$ allele
Woodard et al. (2012) [30]	Human	78 healthy, cognitively intact older adults	26: 1 homozygote, 25 heterozygotes	65–88 years Mean age: 73.1 (4.9)	Stanford Brief Activity Survey Low-PA group: two or fewer low-intensity physical activities per week High-PA group: moderate to heavy physical activities at least 3 times a week	18 months	Neuropsychological testing: MMSE, DRS-2, RAVLT Trials 1–5, RAVLT Delayed Recall; hippocampal volume	High PA was associated with reduced probability of cognitive decline in APOE $\epsilon 4$ carriers
Deeny et al. (2012) [33]	Human	18 healthy female old adults	9	56.53 (7.36) years	Maximal fitness test; the fitness level was based on the $\dot{V}O_{2max}$ High-PA group: moderate to heavy physical activities at least 3 times a week	NA	Cognitive tests: MMSE, Beck Depression Inventory, California Verbal Learning Test, Trail Making Test, category and verbal fluency; FDG-PET scan, Sternberg testing	Highly active $\epsilon 4$ carriers showed greater glucose uptake in the temporal lobe and low fit carriers in the frontal and parietal lobes
Head et al. (2012) [47]	Human	201 cognitively intact adults: 163 for PIB-PET analysis 165 for cerebrospinal fluid (CSF) sample analysis	PIB-PET sample: 52 CSF sample: 56	45–88 years	Questionnaire administered by telephone Low-exercise and high-exercise engagement groups (high group: at or above 30 min of moderate exercise 5 days/week)	NA	CSF A β 42 samples and in vivo amyloid imaging via PET with [^{11}C]PIB	Sedentary APOE $\epsilon 4$ carriers showed more amyloid deposition The association of exercise with CSF A β 42 did not differ between carriers and non-carriers

Table 1 continued

Reference	Species	Study population	Number of APOE ε4 carriers	Age, range or mean (SD)	Assessment of exercise	Follow-up period	Outcome measures	Major study outcome
Brown et al. (2013) [49]	Human	546 cognitively intact older adults	148	60–95 years Mean age 69.6 (6.8)	International Physical Activity Questionnaire (IPAQ) measured habitual physical activity Categorized into tertiles from low to high activity		Serum insulin, glucose, cholesterol and plasma Aβ measurements; cerebral amyloid imaging by [¹¹ C]PIB-PET	High PA was associated with increased HDL, lower insulin, triglycerides and Aβ _{1–42} /1–40 ratio High PA reduced plasma Aβ _{1–42} /1–40 ratio in non-carriers Low PA was associated with higher brain amyloid burden in APOE ε4 carriers
Braskie et al. (2014) [72]	Human	43 cognitively intact older adults and 39 AD patients	23: 2 homozygotes, 21 heterozygotes	Cognitively intact older adults: 79.3 (4.8) AD patients: 81.9 (5.1)	Modified Minnesota Leisure Time Physical Activity Questionnaire about frequency and duration of activities over the previous 2 weeks	9 years	Regional brain volumes, inflammatory marker TNFα serum levels	High physical activity and low serum levels of TNFα showed independently greater total brain volume
Luck et al. (2014) [38]	Human	2492 general practice patients without dementia	514	75 and older Mean age 81.1 (3.5)	Interview Active group: participating in an activity every day or several times a week	4.5 years (follow-up every 1.5 years)	Cognitive testing: MMSE	Low fit APOE ε4 carriers had a higher risk for dementia and AD and a shorter survival time without clinical symptoms
Smith et al. (2014) [31]	Human	97 healthy, cognitively intact older adults	22: 2 homozygotes, 20 heterozygotes	65–89 years	Self-reported questionnaire based on frequency and intensity Stanford Brief Activity Survey Low-PA group: two or fewer low-intensity physical activities per week High PA group: moderate to heavy physical activities at least 3 times a week	18 months	Neurobehavioural testing: MMSE, Mattis Dementia Rating Scale 2 (DRS-2), Geriatric Depression Scale (GDS), Lawton Activities of Daily Living (ADL); hippocampal volume	A decrease of 3% in hippocampal volume in the high-risk/low-PA group
Tan et al. (2016) [40]	Human	3714 cognitively intact older adults	796	60 years or older Mean age 70 (7)	Interview about the number of activities in a day. PA index was calculated and categorized into 5 quartiles	10 years	Risk of incident all-cause dementia and AD, total cerebral brain volume and hippocampal volume	Low-PA group showed a higher risk of incident dementia; this effect was limited to non-carriers Higher PA index was related to greater hippocampal volume

Table 1 continued

Reference	Species	Study population	Number of APOE $\epsilon 4$ carriers	Age, range or mean (SD)	Assessment of exercise	Follow-up period	Outcome measures	Major study outcome
Allard et al. (2017) [81]	Human	22 elderly African Americans with mild cognitive impairment	9: 2 homozygotes, 7 heterozygotes	55–89 years Mean age 72.0 (7.2)	Exercise intervention: stretch and aerobic exercise groups. Supervised training 3 days a week After 4–6 weeks the aerobic group walked 45–60 min during the weekend	6 months	Serum BDNF levels	No differences in BDNF levels between stretch and aerobic exercise groups, but a smaller change in APOE $\epsilon 4$ carriers
Fenesi et al. (2017) [41]	Human	1646 older adults	376	65 years or older Mean age 76.4 (6.8)	Interview about the type and frequency of PA PA was categorized as exercisers and non-exercisers	5 years	Dementia risk (odds ratio of developing dementia)	BDNF levels were upregulated due to aerobic exercise only in APOE $\epsilon 4$ non-carriers PA was effective in reducing the risk of dementia in non-carriers
Cortier et al. (2018) [74]	Human	335 cognitively intact older adults	57: 4 homozygotes, 53 heterozygotes	65 years and older Mean age 77.3 (3.4)	Self-reported questionnaire about PA in the previous 2 weeks	9 years	Structural MRI analysis: cortical thickness of cortical regions and hippocampal volume; peripheral inflammation by serum CRP levels	High CRP levels were associated with thinner cortex PA was positively correlated with hippocampal volume, but did not have effect on CRP levels
Lee et al. (2018) [64]	Human	28 ischemic stroke patients divided into APOE $\epsilon 3$ and $\epsilon 4$ groups	15	APOE $\epsilon 3$: 56.8 (10.65)	Exercise intervention: 5 days a week for 6 months. 3 days aerobic exercise of 45 min and 2 days resistance training	6 months	Cognition: MMSE; lipid profile: HDL cholesterol, LDL cholesterol, total cholesterol, triglycerides	Exercise increased HDL cholesterol in both groups A larger decrease in LDL cholesterol, total cholesterol and triglycerides due to exercise in APOE $\epsilon 4$ carriers
Jensen et al. (2019) [23]	Human	199 patients with mild AD	144: 54 homozygotes 90 heterozygotes	50–90 years	Supervised aerobic exercise intervention: 1 h, three times a week for 16 weeks	16 weeks	Cognition: symbol digit modalities test (SDMT), neuropsychiatric symptoms: NPI and physical performance	APOE $\epsilon 4$ carriers engaged in exercise improved cognitive, neuropsychiatric and physical performance
Piccarducci et al. (2019) [52]	Human	42 healthy participants	16	20–70 years Mean age 39.5	Habits questionnaire Non-active group: < 150 min per week of physical activity	NA	Oxidative status and membrane composition of erythrocytes, A β levels	A β accumulation in erythrocytes decreases with physical activity in both APOE $\epsilon 4$ carriers and non-carriers, but carriers had higher levels of A β

Table 1 continued

Reference	Species	Study population	Number of APOE ε4 carriers	Age, range or mean (SD)	Assessment of exercise	Follow-up period	Outcome measures	Major study outcome
Jeon et al. (2020) [48]	Human	287 non-demented older adults	66	55–90 years Mean age 71.91 (6.64)	Lifetime Total Physical Activity questionnaire via an interview about frequency and intensity of leisure activities	NA	Cerebral Aβ accumulation by [¹¹ C]PIB-PET, AD-signature cerebral glucose metabolism by [¹⁸ F]FDG-PET hippocampal volume	Midlife PA moderated the effect of Aβ accumulation in APOE4 on cerebral glucose metabolism. At low PA, high Aβ accumulation was associated with low cerebral glucose metabolism
Stringa et al. (2020) [34]	Human	7176 older adults over three cohorts	1863	55 years and older	Self-reported questionnaires(LAPAQ, interview, Zutphen Physical Activity questionnaire) 3 categories: low, moderate and high PA	9 years	Cognitive functioning: MMSE	PA was not associated with cognitive decline in APOE ε4 carriers

AD Alzheimer’s disease, *MEG* magnetoencephalography, *PiB* Pittsburgh compound B, *PA* physical activity, *LAPAQ* LASA (Longitudinal Aging Study Amsterdam) Physical Activity Questionnaire, *MMSE* Mini-Mental State Examination, *Aβ* amyloid beta, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *BDNF* brain-derived neurotrophic factor, *RAVLT* Rey Auditory Verbal Learning Test, *NPI* Neuropsychiatric Inventory, *TNFα* tumor necrosis factor alpha, *IL-1β* interleukin-1β, *CRP* C-reactive protein

exercise improved cognitive function in adults aged 50 years or older, of whom 30% were carriers of the APOE ϵ 4 allele. Additional analysis revealed that APOE ϵ 4 non-carriers in the intervention group scored better on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) test compared to carriers and controls, as expected. On the contrary, a recent study by Sanders et al. showed that a 24-week aerobic exercise program did not modify cognitive function in APOE ϵ 4 carriers with dementia [27]. Methods used to quantify the physical activity in this study were highly variable among patients with dementia. Therefore, the association between physical activity and cognitive function in APOE ϵ 4 carriers could be absent.

The majority of studies assessed the physical activity by self-reported questionnaires (Table 1). Smith et al. found that high physical activity promoted cortical semantic processing activity on the name discrimination task among APOE ϵ 4 carriers who were older cognitively intact adults [28]. Greater cortical semantic activation may protect older adults against future cognitive decline [29]. A follow-up study revealed that reduced predicted probability of cognitive decline in APOE ϵ 4 carriers was associated with high physical activity [30]. Furthermore, APOE ϵ 4 carriers with low physical activity in daily life had decreased hippocampal volume after 18 months, whereas the high physical activity group remained stable over time [31]. Physical activity could have a protective effect against hippocampal atrophy in APOE ϵ 4 carriers, which in turn may reduce cognitive decline. A magnetoencephalography (MEG) study of participants aged between 50 and 70 found that highly active APOE ϵ 4 carriers had a faster processing speed in working memory executive function [32]. In addition, carriers with low levels of physically activity showed decreased right temporal lobe activation. Another study on working memory revealed higher glucose uptake in core regions involved in working memory such as frontal, parietal, temporal and cerebellar regions in highly active ϵ 4 carriers with a mean age of 63.67 ± 6.37 years [33]. However, a recent multi-cohort study by Stringa et al., consisting

of older adults with a mean age of 67.8 years at baseline, indicated that physical activity did not moderate cognitive decline in APOE ϵ 4 carriers [34]. For each cohort, a different self-reported questionnaire was used to assess the physical activity, which was classified into three categories including inactive, light and moderate–high activity based on walking, cycling, diverse sports and hobbies. Cognitive function was assessed with the Mini-Mental State Examination (MMSE).

AD Dementia Risk

Midlife or late-life exercise influences dementia risk. Some studies examined the effect of midlife exercise on dementia risk in adults aged younger than 65. APOE ϵ 4 carriers showed a significant inverse association between midlife physical activity and dementia risk compared to non-carriers [35], while in the AGES-Reykjavik study, the association between midlife physical activity and late-life cognition was strongest in non-carriers [36]. The combination of physical activity and the presence of an APOE ϵ 4 allele may modify the risk of developing AD dementia later in life, but more replication is required. On the contrary, late-life physical activity seems to be effective in reducing dementia risk. The beneficial effect of late-life physical activity on the risk of cognitive decline was more pronounced in APOE ϵ 4 carriers [37]. In addition, physical activity in late life may be beneficial in APOE ϵ 4 carriers by reducing the risk of AD dementia and delaying its onset [38].

One of the studies that did not find any significant interaction between physical activity and the APOE4 genotype is the Cardiovascular Health Cognition Study, wherein a significant association between physical activity and dementia was observed in non-carriers, but not in APOE ϵ 4 carriers, after a follow-up period of approximately 5 years [39]. However, only 28 APOE ϵ 4 carriers showed cognitive decline in this period, making the interaction with physical activity subject to variability. In addition, the Framingham study showed increased risk of dementia in sedentary non-carriers aged 60 years and older, suggesting an inverse

association between physical activity and dementia risk [40]. A study of 1646 older adults followed over a 5-year period reported that physical exercise was effective in preventing dementia in non-carriers [41]. No significant differences were observed between active and non-active APOE ϵ 4 carriers. Several findings have been reported about the association between midlife or late-life exercise and AD dementia risk in APOE ϵ 4 carriers. Exercise seems to modify AD dementia risk, but more replication is required to infer whether this is characteristic of APOE ϵ 4 carriers.

A β Metabolism

Aggregation of A β peptides in the brain is one of the pathological hallmarks of AD. The most abundant forms are A β 40 and A β 42, with the latter known to be deposited more easily because of its hydrophobic and fibrillogenic composition [42]. In the healthy central nervous system, A β is rapidly produced and cleared, with a production rate of 7.6% per hour and a clearance rate of 8.3% per hour [43]. Due to molecular, cellular and genetic imbalances, the clearance of A β via the blood circulation system is deficient in late-onset AD. Mawuenyega et al. found impaired clearance of both A β 40 and A β 42 in the central nervous system of late-onset AD patients compared with cognitively healthy controls, whereas the production rates did not differ [44]. The effectiveness of A β clearance depends on APOE isoforms, decreasing from APOE2 to APOE3 to APOE4 [45]. This defect in clearance could lead to A β plaques that aggregate in the cortex. Transgenic AD mice showed reduced A β plaques and amyloid angiopathy if they performed aerobic exercise in their enriched housing [46]. This raises the question of whether exercise is associated with cerebral A β deposition in APOE ϵ 4 carriers. Head et al. suggested that APOE ϵ 4 carriers with low exercise levels might have increased risk for cerebral A β deposition [47]. A recent study by Jeon et al. investigated whether APOE ϵ 4 status combined with high midlife physical activity could modify A β retention [48]. APOE ϵ 4 carriers with a mean age of 72 years in a low physical activity

state had higher A β accumulation, and this was absent in highly active carriers. Furthermore, a study of 546 cognitively healthy elderly individuals with an average age of 69.6 ± 6.8 years revealed decreased cerebral amyloid load in physically active APOE ϵ 4 carriers, whereas high physical activity was associated with a reduced plasma A β 42/40 ratio only in non-carriers [49].

A difference between A β in the brain and the periphery related to the ApoE4 protein seems plausible. The APOE ϵ 4 allele alters the permeability of the blood–brain barrier, which may result in increased levels of A β in the peripheral system of carriers compared to non-carriers [50]. This could be one explanation why reduced plasma A β levels were observed only in highly physically active non-carriers. A β fibrils in the periphery have an increased affinity for binding erythrocytes that can take up these fibrils, resulting in oxidative stress [51]. Piccarducci et al. confirmed that APOE ϵ 4 carriers have higher levels of A β in erythrocytes than non-carriers [52]. The A β levels in erythrocytes decreased with physical activity in both carriers and non-carriers, but the decrease in APOE ϵ 4 in non-carriers was significantly greater than that in carriers. Although the reduction in A β accumulation in erythrocytes related to physical activity seems to be independent of the APOE4 genotype, physical activity may have a beneficial role in relieving oxidative stress in APOE ϵ 4 carriers.

Nepilysin (NEP) and insulin-degrading enzyme (IDE) are important enzymes in maintaining the A β levels in the brain. NEP, a zinc metalloendopeptidase, is involved in the degradation of A β in monomeric and oligomeric forms in the brain [53]. IDE, also a zinc metalloendopeptidase, has the ability to degrade extracellular A β in the brain and to clear cytoplasmic products of APP [54]. Studies have shown that these enzymes are downregulated due to age-dependent genetic mutations which could lead to AD by disrupting cerebral A β clearance (Fig. 1) [54–56]. Moore et al. used AD transgenic mice with elevated A β levels to show the effect of exercise on A β metabolism [57]. They investigated reduced levels of both soluble A β 40 and A β 42 in the cortex and hippocampus by exercise in a dose-dependent

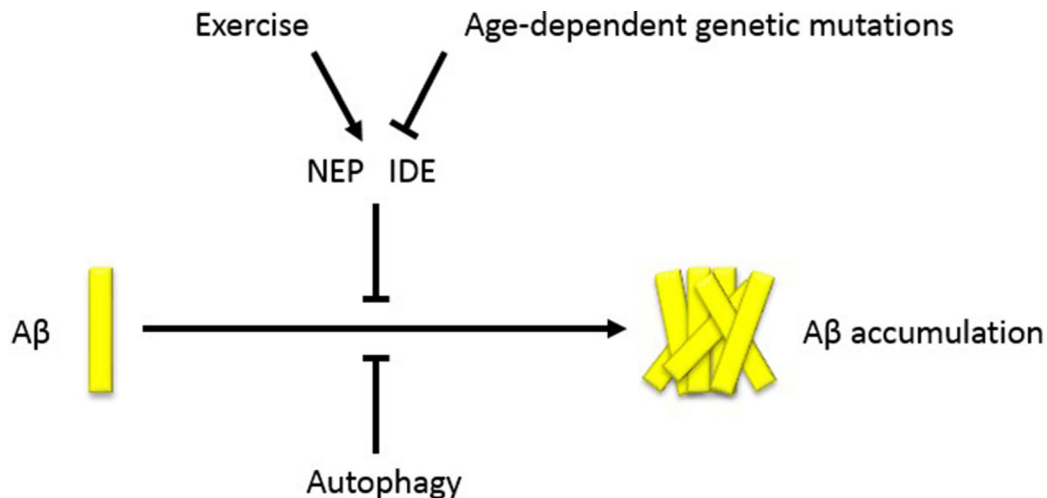


Fig. 1 The influence of exercise on A β accumulation. In the healthy brain, A β levels are maintained by autophagy and A β -degrading enzymes NEP and IDE. Age-dependent genetic mutations may affect NEP and IDE, leading to A β

accumulation. Exercise engagement may promote A β clearance indirectly by upregulating the A β -degrading enzymes. A β amyloid- β , NEP neprilysin, IDE insulin-degrading enzyme

manner. Exercise may be beneficial for APOE ϵ 4 carriers, since the ApoE4 protein can enhance A β 40 and A β 42 aggregation compared to the other two isoforms [58]. NEP and IDE expression were also increased in the exercise groups in a dose-dependent fashion, providing further evidence that exercise may upregulate these A β degradation enzymes, leading to A β clearance (Fig. 1).

Lipid Metabolism

Lipids are crucial molecules in the human body. The central nervous system has the second highest lipid content after the adipose tissue [59]. Signal transduction in the brain depends on lipids as well, since axons are surrounded by a myelin sheath consisting of lipids. In addition, the ApoE protein is involved in lipid transport by regulating lipoprotein concentrations. ApoE proteins are attached to the surface of lipoproteins filled with lipids, enabling the binding to receptors on tissue or cells. In the central nervous system, ApoE released by astrocytes is needed to transport cholesterol inside lipoproteins to neuronal cells [6, 52]. This process starts with the binding of ApoE to high-density lipoprotein (HDL) filled with

cholesterol. ApoE has high affinity for binding to the low-density lipoprotein (LDL) receptor family at cell surfaces mediating endocytosis, where HDL is degraded and cholesterol is released [60]. Cholesterol is crucial for axonal growth and formation and remodelling of synapses, which are important for learning, memory formation and neuronal repair [6]. Previous studies found lower ApoE levels in the serum, brain and cerebrospinal fluid in both APOE ϵ 4-carrying AD patients and cognitively normal persons [61]. A reduction in ApoE can affect cholesterol transport in the brain. In AD, brain cholesterol levels are commonly reduced in hippocampal neurons and cortical areas. Furthermore, cholesterol transport to hippocampal neurons occurs in an isoform-dependent manner, where the ApoE3 protein is more efficient than ApoE4 [62]. Animal studies have shown consistent results of decreased brain cholesterol in homozygous ϵ 4 mice [63].

Cholesterol can be transported by either HDL or LDL in serum; the latter enhances the risk of atherosclerosis, leading to cardiovascular disease, stroke and dementia [64]. It has been widely demonstrated that APOE ϵ 4 carriers show lower HDL and higher LDL cholesterol serum levels [52, 65]. ApoE4-knock-in mice also

showed increased serum LDL cholesterol [63]. Evidence was found that physical activity may modify the altered lipid profile; for instance, physical activity in older adults was positively associated with HDL cholesterol [49]. Bernstein et al. (2002) found that high levels of physical activity may reduce the atherosclerosis risk of the APOE4 genotype on the lipid profile [66]. Furthermore, highly active APOE ϵ 4 carriers consisting of men and women between the ages of 35 and 74 years showed enhanced HDL cholesterol. Due to the large age range, the groups were divided into < 55 and 50+ years, where the association between high physical activity and the APOE4 genotype was more pronounced among the 50+ group. Lee et al. (2018) suggested that exercise training may decrease LDL cholesterol levels and total cholesterol in APOE ϵ 4-carrying ischemic stroke patients [64]. In particular, in relatively young participants, no change in HDL or LDL cholesterol level was observed after physical training in APOE ϵ 4 carriers [67]. These results indicate that age is an important factor in modifying cholesterol levels in APOE ϵ 4 carriers by exercise. High physical activity reduces the high-risk LDL cholesterol in older APOE ϵ 4 carriers compared to their younger counterparts. Taken together, these observations build a strong case supporting the association between exercise and lipid profiles of APOE ϵ 4 carriers.

Neuroinflammation

Neuroinflammation is involved in the neurodegenerative process in AD. Microglia and astrocytes are the central innate immune cells of the central nervous system. Microglia can be activated by the presence of A β to induce phagocytosis of A β plaques. However, activated microglia are not able to clear A β aggregation, leading to inflammation and thereby recruitment of more microglia, which can lead to cytotoxicity [68]. Upon activation, microglia release cytokines to regulate neuroinflammation, but these pro-inflammatory cytokines can induce damage to surrounding neurons and

even cause neurodegeneration as occurs in later stages of AD. ApoE is involved in microglia suppression, which has a protective effect on neuroinflammation by inducing anti-inflammatory cytokines. ApoE-deficient mice showed enhanced levels of pro-inflammatory cytokines including tumor necrosis factor alpha (TNF α), interleukin-1 β (IL-1 β) and interleukin 6 (IL-6) mRNA by stimulation with lipopolysaccharide [69]. These pro-inflammatory cytokines were significantly increased, especially in APOE4 mice [70]. Administration of an ApoE-mimetic peptide derived from the receptor-binding region of the ApoE holoprotein counteracts this effect, showing its protective role in neuroinflammation. The innate immune response seems to be influenced by specific APOE isoforms. Soto et al. demonstrated evidence to support ApoE as a key player in neuroinflammation [71]. Aged mice engaged in exercise showed a reduction in microglia activation and improved neurovascular functioning and behaviour, whereas ApoE-deficient mice did not benefit from the intervention, suggesting the important role of ApoE in neurovascular functioning. Another animal study revealed that exercise in an enriched housing environment was effective in downregulating pro-inflammatory genes and upregulating anti-inflammatory genes in transgenic AD mice, which may reduce A β deposition in the brain [46]. Braskie et al. studied the relation between physical activity, inflammation and risk of AD in cognitively healthy older adults and AD patients [72]. They did not find an association between physical activity and TNF α , but lower TNF α and high physical activity levels were both independently associated with reduced regional brain atrophy. On the contrary, the animal study by Nichol et al. showed that exercise in aged AD mice reduced pro-inflammatory cytokines such as TNF α and IL-1 β , thereby activating an adaptive response around A β plaques leading to decreased A β [73].

During inflammation, C-reactive protein (CRP) is mainly upregulated in serum. At the same time, pro-inflammatory cytokines are released. The study by Corlier et al. (2018)

followed cognitively healthy older adults for 9 years [74]. Over time, CRP levels were enhanced, which was associated with greater cortical thinning. Physical activity was not related to CRP levels, which could be due to bias in the self-reports. The APOE4 genotype showed lower CRP levels and thinner cortex, which is contradictory in terms of inflammation. Therefore, Corlier et al. suggested that other mechanisms could be responsible for the enhanced AD risk in APOE4 carriers. The low CRP in APOE ϵ 4 carriers was also supported by a previous study [75]. It was suggested that the low CRP levels in ϵ 4 carriers are not associated with neuroinflammation, due to contradictory findings of increased inflammation in these carriers and low CRP levels. It remains unclear, but a possible explanation may be the production of cholesterol by the mevalonate pathway of the liver, because this pathway is known to be downregulated in APOE ϵ 4 carriers, leading to low levels of CRP [75].

Neurotrophic Factors

We previously mentioned that exercise can reduce pro-inflammatory cytokines. Exercise is also indirectly involved in growth factor stimulation. Insulin-like growth factor 1 (IGF-1) and brain-derived neurotrophic factor (BDNF) are growth factors involved in hippocampal function, synaptic functioning and learning. Exercise may upregulate both growth factors in the brain and periphery directly by increasing the concentrations or indirectly by reducing pro-inflammatory cytokines, which could alter IGF-1 and BDNF signalling in neurons [76]. IGF-1 has a protective role in AD because of its ability to decrease A β deposition. This growth factor is involved in upregulating the transport of A β carrier proteins to the brain to increase the clearance of A β plaques [77]. In this way, cognitive functioning is improved. A recent study by Galle et al. found low IGF-1 levels in homozygous APOE ϵ 4 carriers showing increased risk of dementia [77]. Besides the role of IGF-1 in AD, BDNF is important in

maintaining the memory function. The APOE ϵ 4 allele reduces BDNF expression, which may induce synaptic loss in the hippocampus, leading to cognitive deficits [78]. Aerobic exercise was found to compensate the hippocampal volume loss in late adulthood that was associated with increased plasma levels of BDNF [79]. In addition, plasma BDNF levels were increased in AD patients due to aerobic exercise [80]. Conversely, BDNF levels were upregulated due to aerobic exercise only in APOE ϵ 4 non-carriers and not in carriers [81]. However, this study was restricted to one ethnic group with a higher risk of AD. An animal model showed increased hippocampal BDNF levels upon exercise in both APOE ϵ 4 and APOE ϵ 3 transgenic mice [24]. Studies assessing the effects of exercise on neurotrophic factors in APOE ϵ 4 carriers are sparse, but the available evidence may support a relation between the two, suggesting more replication is needed.

Vascularization

Vascular risk factors including hypertension, hypercholesterolemia, atrial fibrillation and smoking can affect the incidence and progression of AD [82]. For example, high systolic blood pressure in APOE ϵ 4 carriers may lead to cognitive decline [83, 84]. Caselli et al. noted that any of the cerebrovascular risk factors including hypercholesterolemia, hypertension, smoking and diabetes mellitus may potentiate age-dependent memory deficits in APOE ϵ 4 homozygotes [85]. These vascular risk factors induce vascular oxidative stress by downregulation of vascular nitric oxide (NO) and endothelial NO synthase (eNOS) pathways, which can impair vascular reactivity in the form of hypercontractility. Cerebral blood flow (CBF) will decrease due to impaired vasodilation, which mediates oxidative stress and promotes neuronal degeneration. In addition, A β plays a role in this process by inhibiting eNOS activity. This is supported by the finding that hypertensive mice showed increased permeability of the blood–brain barrier in the cortex and

hippocampus and A β deposition [86]. A human study demonstrated that hypertensive APOE ϵ 4 carriers aged 49–89 years had greater cortical amyloid burden as quantified by PET imaging compared to hypertensive non-carriers, normotensive carriers and non-carriers [87]. Zhang et al. found decreased eNOS activity, increased A β in the hippocampus and cortex, and decreased cognition in hypertensive mice [88]. Engagement in exercise led to improved eNOS levels, cognition and AD pathology. In addition, long-term exercise increased IGF-1 levels in these hypertensive mice, which is important in attenuating A β clearance.

Reduced CBF is another hallmark of AD. Older adults carrying the APOE ϵ 4 allele showed lower CBF than non-carriers, along with reduced memory [89]. Adult APOE4-mice had reduced CBF in regions susceptible to AD pathology compared to wild-type mice and younger mice with the APOE ϵ 4 allele, suggesting an age-dependent interaction [90]. Since APOE ϵ 4 carriers have lower levels of the ApoE protein, a complete knock-out of the ApoE protein resulted in lower CBF compared to wild-type mice already at a young age, demonstrating the importance of the ApoE protein. It has been shown that exercise is effective in increasing CBF. Aged mice showed increased CBF in the hippocampus with walking [91]. Burdette et al. reported increased hippocampal CBF with a 16-week exercise program in older adults at risk for cognitive decline and with subjective cognitive impairment [92]. Furthermore, greater hippocampal connectivity was observed in the exercise group. Conversely, a 16-week aerobic program was not sufficient to increase CBF in AD patients [93].

Vascular endothelial-derived growth factor (VEGF) is another important factor involved in vascularization. VEGF is lower in AD [94], and especially in APOE ϵ 4 carriers, compared to the other isoforms, which may lead to vascular impairment. By increasing the VEGF levels using a viral vector, the AD-related pathology in APOE ϵ 4-carrying mice was reversed [95]. Exercise may increase the VEGF plasma levels to improve vascularization [76]. Increased VEGF

expression was found to induce angiogenesis in aged mice through exercise engagement [96]. Studies about the association between VEGF levels in APOE ϵ 4 carriers and exercise are sparse.

DISCUSSION

This review focused on both human and animal studies that highlighted the role of exercise in APOE ϵ 4 carriers with respect to the risk of AD dementia for the following domains: cognitive function, A β metabolism, lipid metabolism, neuroinflammation and vascularization. Exercise may modify the association between the APOE ϵ 4 allele and AD-related pathology (Table 1).

The APOE ϵ 4 allele increases the risk of AD. Carriers of this allele were shown to have lower levels of the ApoE protein, which is needed in many processes for proper functioning. Due to this lack of the ApoE protein in APOE ϵ 4 carriers, cholesterol transport is affected, which may lead to higher LDL and lower HDL cholesterol transport and increased AD pathology. Through engagement in exercise, the risk of atherosclerosis may be lowered. Together with deficits in cholesterol transport, neuroinflammation may be induced by lack of ApoE. Since ApoE is involved in suppression of microglia to reduce pro-inflammatory cytokines, lower levels of ApoE could reverse this process. Upregulation of pro-inflammatory cytokines, as shown in APOE ϵ 4 carriers, may downregulate IGF-1 and thereby increase A β pathology. In addition, BDNF levels may inhibit the induction of hippocampal volume loss. Lower levels of both IGF-1 and BDNF were observed in APOE ϵ 4 carriers. Exercise is known to be effective in enhancing the levels of these growth factors, but the exact effect in APOE ϵ 4 carriers remains unknown. However, our findings suggest that exercise may play a role in reducing pro-inflammatory cytokines and upregulating IGF-1 and BDNF in APOE ϵ 4 carriers, because of the lower levels of the ApoE protein.

The majority of studies showed that A β metabolism could be improved by exercise. Exercise was found to reduce the cerebral amyloid load in APOE ϵ 4 carriers. We observed that carriers with low physical activity levels had increased risk of A β deposition. In contrast, enzymes involved in the clearance of A β were upregulated by exercise. Improvement of A β metabolism may reduce cognitive deficits in AD. Low IGF-1 levels in APOE ϵ 4 carriers were found to play a role in impaired clearance of A β deposition. Since exercise may ameliorate A β metabolism in APOE ϵ 4 carriers and can increase IGF-1 levels in general, we suggest a relation of exercise with IGF-1 levels on the APOE ϵ 4 allele.

In terms of cognitive function, exercise seems to be effective in reducing cognitive decline in APOE ϵ 4 carriers. Exercise interventions improved cognition and hippocampal function in both human and animal studies [23–25]. Cognitive function was assessed mainly by neuropsychological tests. For example, Jensen et al. used the SDMT neuropsychological test, which is sensitive to very early changes in determining dysfunctional aspects of executive function in AD [23]. Intervention studies with contradictory findings related to cognitive function in APOE ϵ 4 carriers were limited by participant age or variability in cognitive tests. A portion of the studies assessed physical activity by survey, increasing the subjectivity of these outcomes. Most of the studies found positive associations between cognition in the APOE ϵ 4 genotype and physical activity. High physical activity may induce increased semantic processing activity, protection against hippocampal atrophy and faster speed of processing of the working memory. Physical activity might delay the onset of AD by acting on memory processes in the hippocampus of APOE ϵ 4 carriers.

The findings as to whether physical activity can ameliorate cognitive decline in APOE ϵ 4 carriers were heterogeneous. Multiple factors were shown to play a key role, including the type of cognitive test, the type of exercise, the

use of exercise intervention versus self-reported questionnaires, the follow-up time, the age of participants and the course of dementia. We noted that most of the studies with contradictory results used less sensitive outcome variables, such as clinical diagnosis of dementia or MMSE scores, and these kinds of tests are not sensitive to preclinical cognitive ageing [32]. Furthermore, the type of exercise intervention is crucial, because of the differences between aerobic and anaerobic exercise. Aerobic exercise was proven to be more effective in AD pathology by reducing amyloid angiopathy in transgenic mice [46]. Exercise interventions also avoid the risk of bias, which is more prominent in self-reported assessment of physical activity. Participant age and the course of dementia are crucial factors in determining the outcomes, because dementia occurs mostly in the elderly and progresses with age: the older the participant, the greater the neural pathology accumulation and the greater the further decline in dementia. Some studies showed differences between midlife and late-life exercise, suggesting that age plays a crucial role. There are still questions as to whether a threshold related to age exists in the protective effect of exercise on neural pathology accumulation in APOE ϵ 4 carriers [41]. However, since the APOE ϵ 4 allele causes deleterious effects in neural protection and repair mechanisms, these carriers may be more influenced by lifestyle-related modifications [35].

CONCLUSION

Exercise could be a potential non-pharmacological therapeutic or prevention option for reducing the risk of AD in APOE ϵ 4 carriers (Fig. 2). By preventing or slowing neurodegeneration, exercise could increase the quality of life of AD patients. In the future, further research targeting midlife exercise will expand our knowledge about early prevention and therapeutic opportunities to delay the onset of AD in APOE ϵ 4 carriers.

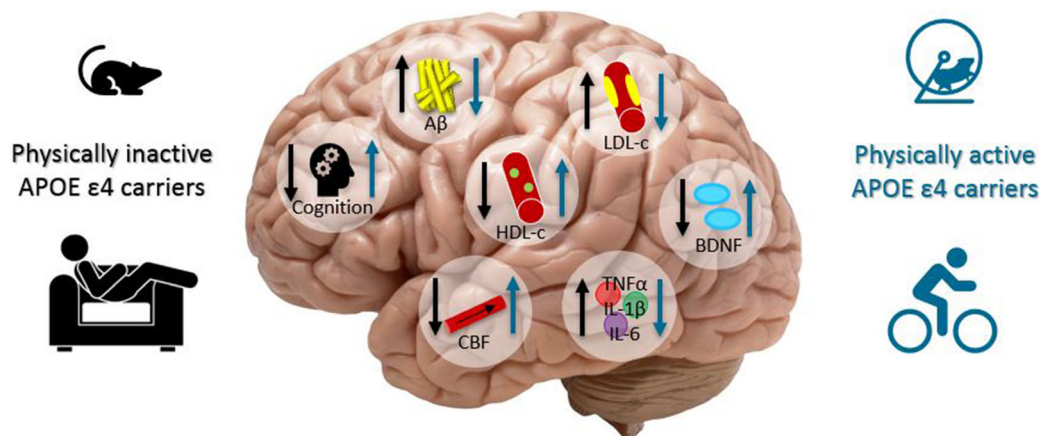


Fig. 2 Graphical summary of the results. Physically inactive APOE $\epsilon 4$ carriers may have lower cognitive functioning, CBF, HDL cholesterol, BDNF and higher A β accumulation, LDL cholesterol and neuroinflammation factors such as TNF- α , IL-1 β and IL-6 compared to physically active APOE $\epsilon 4$ carriers. Physical activity may be involved in the reduction of A β accumulation, LDL cholesterol, neuroinflammation factors such as TNF- α ,

IL-1 β and IL-6 and in the increase of cognitive functioning, HDL cholesterol, CBF and BDNF in APOE $\epsilon 4$ carriers. A β amyloid- β , HDL-c high density lipoprotein cholesterol, LDL-c low density lipoprotein cholesterol, CBF cerebral blood flow, BDNF brain-derived neurotrophic factor, TNF α tumor necrose factor α , IL-1 β interleukin-1 β , IL-6 interleukin-6

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