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## Review

# A systematic review of exercise modalities that reduce pro-inflammatory cytokines in humans and animals' models with mild cognitive impairment or dementia



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## ABSTRACT

**Purpose:** To investigate which type, frequency, duration, intensity, and volume of chronic exercise might more strongly reduce pro-inflammatory cytokines and enhance anti-inflammatory cytokines in human and animal models with Mild Cognitive Impairment (MCI) or dementia.

**Design:** A systematic review.

**Data source:** English-language search of 13 electronic databases: Web of Science, PubMed/Medline, Sport Discus, Scopus, Cochrane, Psych Net, Springer, ScienceDirect, Pascal & Francis, Sage journals, Pedro, Google Scholar, and Sage. Inclusion criteria: (i) human and animal studies that included exercise, physical activity, or fitness training as an experimental intervention, (ii) studies that addressed MCI, dementia, or AD, (iii) studies that focused on measuring cytokines and/or other inflammatory and/or neuroinflammatory immune markers, (iii) studies that examined inflammatory indicators in blood, CSF (Cerebrospinal Fluid), and brain tissue.

**Results:** Of the 1290 human and animal studies found, 38 were included for qualitative analysis, 11 human articles, 27 animal articles, and two articles addressing both human and animal protocols. In the animal model, physical exercise decreased pro-inflammatory markers in 70.8 % of the articles and anti-inflammatory cytokines: IL -4, IL -10, IL-4 $\beta$ , IL -10 $\beta$ , and TGF- $\beta$  in 26 % of articles. Treadmill running, resistance exercise, and swimming exercise reduce pro-inflammatory cytokines and increase anti-inflammatory cytokines. In the human model, 53.9 % of items reduced pro-inflammatory proteins and 23 % increased anti-inflammatory proteins. Cycling exercise, multimodal, and resistance training effectively decreased pro-inflammatory cytokines.

**Conclusion:** In rodent animal models with AD phenotype, treadmill, swimming, and resistance training remain good interventions that can delay various mechanisms of dementia progression. In the human model, aerobic, multimodal, and resistance training are beneficial in both MCI and AD. Multimodal training of moderate to high intensity multimodal exercise is effective for MCI. Voluntary cycling training, moderate- or high-intensity aerobic exercise is effective in mild AD patients.

## 1. Introduction

Mild cognitive impairment (MCI) is often considered the earliest

symptomatic manifestation of Alzheimer's disease (AD) (DeCarli, 2003; Etgen et al., 2011). Reportedly, 10 -15 % of MCI cases convert to AD (DeCarli, 2003; Etgen et al., 2011; Petersen, 2009). AD is by far the most

**Abbreviations:** AB<sub>1-42</sub>, Amyloid -peptide 1-42; AD, Alzheimer disease; A $\beta$ , b-amyloid; APO  $\epsilon$ 4, Apolipoprotein E4; BDNF, Brain Derived Neurotrophic Factor; ELISA, Enzyme Linked Immunosorbent Assay; GSK-3 $\beta$ , Glycogen synthase kinase 3; HHR, Heart rate reserve; HR<sub>max</sub>, Heart rate maximum; IGF-1, Insulin-like Growth Factor One; MAPK, Mitogen-activated protein kinase; MCI, Mild Cognitive Impairment; miRNA, microARN; mRNA, Messenger RNA; MMSE, mini-mental state examination; MoCa, Montreal Cognitive Assessment; MWM, Morris water maze; NF- $\kappa$ B, nuclear factor-kappa B; RCT, randomized controlled trial; TAU, Alzheimer TAU protein; TLR4, Toll Like Receptor 4; VO<sub>2max</sub>, maximal oxygen uptake.

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common cause of dementia and is characterized by the onset of gradual cognitive decline (Kalra and Khan, 2015). It is the most common form of dementia worldwide and accounts for approximately 70 % of dementia cases (Reitz et al., 2011). Reportedly, by 2050, one in 85 people in the world will be living with AD (Brookmeyer et al., 2007). AD is the most common form of age-related dementia characterized by cognitive impairment, neurodegeneration,  $\beta$ -amyloid ( $\beta$ ) deposition, neurofibrillary tangle (NFT) formation, and neuroinflammation (Tanzi and Bertram, 2005). AD progression is characterized by uncontrolled glial cell activation, neuroinflammation, and resulting neuronal/synaptic dysfunction, which triggers a vicious cycle of increased glial activation and neuronal damage (Domingues et al., 2017; Mrak and Griffin, 2005). Higher levels of pro-inflammatory cytokines have been proposed as independent strong predictors of increased risk of progression from MCI to AD (Diniz et al., 2010; McGeer and McGeer, 2010). Moreover,  $\beta$  itself can induce the expression of several proinflammatory cytokines such as interleukin-1 $\beta$  (IL -1 $\beta$ ), IL -6, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and interferon- $\gamma$  (IFN- $\gamma$ ) by glial cells, leading to a vicious cycle (Calsolaro and Edison, 2016; Meraz Rios et al., 2013). Disruption of inflammatory and immune pathways at AD has been strongly associated with altered levels of some acute-phase proteins and pro-inflammatory cytokines in blood, cerebrospinal fluid (CSF), and AD brain (Brosseron et al., 2014; Rubio-Perez and Morillas-Ruiz, 2012). Signs of chronic inflammation occur in pathologically vulnerable regions of the AD brain in response to  $\text{A}\beta$  peptide deposition and the formation of NFTs (Meraz Rios et al., 2013). Major proinflammatory proteins at AD include interleukin 1 (IL -1), TNF- $\alpha$ , and complement C1q, which is secreted by activated microglia and gives rise to a reactive form of neurotoxic astrocytes. The latter are unfavorable for neuronal survival, growth, synaptogenesis, and phagocytosis and therefore lead to neuronal and oligodendrocyte death (Liddelow et al., 2017). IL -1 $\beta$ , IL -6, and IL -8, the most potent inflammatory cytokines, are products of activated microglia and astrocytes and are upregulated in AD brains (Angelopoulos et al., 2008). Indeed, concentrations of inflammatory cytokines have been reported to increase significantly in the brains of AD patients and in experimental animal models (Meraz Rios et al., 2013). Most studies on this topic have observed increased serum levels IL -6 in AD patients (Angelopoulos et al., 2008; Cojocaru et al., 2011; Galimberti et al., 2006). Similar conditions (i.e., higher serum levels of IL -1 $\beta$ , IL -6, and IL -8) were also observed in patients with MCI or AD (Forlenza et al., 2009; Galimberti et al., 2006; Guerreiro et al., 2007; Magaki et al., 2007). Baek et al. (2022) showed that the levels of the proinflammatory cytokines TNF- $\alpha$ , IFN- $\gamma$ , IL -1 $\beta$ , and IL -12 correlated with cognitive dysfunction. It is important to note that some cytokines and chemokines may have opposite effects on TAU and  $\text{A}\beta$  pathologies (Domingues et al., 2017). Mastrangelo et al. (2009) showed that a decrease in IFN $\gamma$  led to a decrease in TAU and  $\text{A}\beta$ . Ghosh et al. (2013) showed that sustained IL -1 $\beta$  overexpression resulted in a large increase in TAU phosphorylation (most likely via p38 MAPK (Mitogen-activated protein kinase) and GSK-3 $\beta$  (Glycogen synthase kinase 3), although amyloid load was significantly reduced (by approximately 70–80 %). Therefore, strategies to reduce neuroinflammation may reduce the risk of sporadic AD (Vlad et al., 2008).

Identifying the inflammatory mediators that are most important in disease pathogenesis may help in the development of novel therapeutic strategies or in the selection of an inflammatory biomarker panel that can help in AD diagnosis (Domingues et al., 2017). Most therapeutic efforts have focused on clearing brain tissue of  $\text{A}\beta$  have failed for various reasons. Therefore, treatments targeting the pathophysiology of AD are strongly recommended to improve brain function and delay disease progression. Much of the literature suggests that exercise promotes neuronal function in various ways, such as improving neurogenesis, synaptic plasticity, and regulating metabolism..... (Sajadi, 2017). Indeed, the increased blood flow triggered by physical activity reduced local concentrations of inflammatory cytokines in the brain (Winkelman, 2004). Exercise training increases antioxidant activity and

decreases TNF- $\alpha$  expression in intestinal lymphocytes and peripheral tissues (Hoffman-Goetz et al., 2009; Petersen, 2009). Exercise-induced IL -6 production, which stimulates other anti-inflammatory cytokines such as IL -1ra (interleukin-1 receptor antagonist) and IL -10 (interleukin-10), inhibits the production of the pro-inflammatory cytokine TNF- $\alpha$  (Pedersen, 2006). Reducing TNF- $\alpha$  expression could promote cell survival by inhibiting the extrinsic pathway of apoptosis. Preventing TNF- $\alpha$  production would potentially ensure cell survival given the potential role of inflammation in the development of dementia, and physical training could provide protection by inducing anti-inflammatory cytokines in neural tissue, thereby attenuating disease progression. Nascimento et al. showed that a multimodal exercise program reduced peripheral levels of IL -6 and TNF- $\alpha$ , increased serum levels of BDNF, and improved several cognitive functions in older people with MCI (Nascimento et al., 2014). However, short-term, high-intensity exercise also elicits a proinflammatory response that activates/exacerbates the immune system, at least systemically (Gleeson, 2007; Hoffman-Goetz et al., 2009). The intensity, duration, and type of physical exercise can influence proinflammatory and anti-inflammatory cytokines and thus affect susceptibility to inflammatory diseases (Pedersen, 2000a, b). Animal models have contributed significantly to our understanding of the underlying biological mechanisms of AD (Shineman et al., 2011). Neurodegenerative animal models are valuable for understanding dementia and developing new therapeutics (Balducci and Forloni, 2011; Laurijsens et al., 2013). To date, few studies have examined the effects of physical exercise on cytokines in MCI and AD. Little is known about the recommended type, frequency, duration (program and session), intensity, and amount of exercise in this population. To address these knowledge gaps, we conducted the present systematic review of preclinical and clinical studies to examine what type of chronic physical exercise might more potentially reduce pro-inflammatory cytokines and enhance anti-inflammatory cytokines in older people with MCI or AD in terms of type, frequency, duration, intensity, and volume of exercise.

## 2. Methods

### 2.1. Preliminary settings

The elements of this systematic review are presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Moher et al., 2009). The systematic review protocol has been registered with the International Prospective Register of Systematic Review (PROSPERO; available at: <https://www.crd.york.ac.uk/PROSPERO/>), the animal registration number is CRD 42020177636, and the human registration number is CRD 42020178214 (Booth et al., 2012).

### 2.2. Eligibility criteria

The present review included studies that examined the effects of short- or long-term physical exercise on inflammatory markers in brain tissue of humans or animals. Outcome measures of interest included the two types of cytokines: pro-inflammatory cytokines and anti-inflammatory cytokines (Nielsen et al., 2016). Cytokine measurements were performed via mRNA (Messenger RNA) gene expression (Parachikova et al., 2008; Souza et al., 2017), from blood (Abd El-Kader, 2016; Nascimento et al., 2014), or from different brain regions: CSF (Cerebrospinal Fluid), brain homogenates, cortex, hippocampus, prefrontal cortex, frontal cortex, hippocampus, global cerebral blood flow) or from salivary glands. Full-text article searches were performed when the terms “inflammation OR inflammatory OR cytokines OR neuro inflammation OR interleukin OR pro inflammatory” AND “Alzheimer OR Alzheimer's disease OR MCI OR mild cognitive impairment OR app tau OR dementia OR amyloid beta” AND “physical exercise OR physical activity OR sport OR fitness OR movement OR physical training.” Occurred in at least

one of the article titles, abstract, or keywords. If the title and abstract indicated that the study was potentially relevant for inclusion in the review, a full-text copy of the article was requested. Articles were included in the review if they met the following criteria:

- 1) they were written in English.
- 2) they included exercise, physical activity, or fitness training as an experimental intervention.
- 3) the population had to have MCI, dementia, or AD.
- 4) they focused on measuring cytokines and/or other inflammatory and/or neuroinflammatory immune markers.
- 5) they examined these indicators in blood, CSF (Cerebrospinal Fluid), brain tissue, etc.

As it is impossible to find a single animal model that can explain all cognitive, behavioral, biochemical, and histopathological abnormalities (Tayebati, 2006), we included all animals studies that respond to our criteria described above. In fact, it has been demonstrated that rodents are able to mimic human diseases and reproduce the complexities of human behavior in an ideal animal model (Agca et al., 2008).

Studies were excluded if they did not use at least one of the groups that did only physical exercise. Articles that combined physical exercise

with other interventions such as cognitive stimulation or nutritional supplementation were excluded (Lieberman et al., 2017). Study designs included pre-post control studies, randomized controlled trials, randomized matched control trials, and true experimental designs. Studies and trials with no indication of randomization method were also included.

### 2.3. Search strategy

We performed our electronic search in 13 databases from their inception to September 2022, these databases are: Web of Science, PubMed, Sport Discus, Scopus, Cochrane, Psych Net, Springer, ScienceDirect, Pascal & Francis, Sage journals, Pedro, Google Scholar, and Sage. We used the following MeSH terms, corresponding alternatives, and Boolean operators: (*inflammation OR inflammatory OR cytokines OR neuro inflammation OR interleukin OR pro inflammatory*) AND (*Alzheimer OR Alzheimer's disease OR MCI OR mild cognitive impairment OR app tau OR dementia OR amyloid beta*) AND (*physical exercise OR physical activity OR sport OR fitness OR movement OR physical training*). The bibliography of retrieved articles was also examined to add studies not found in the

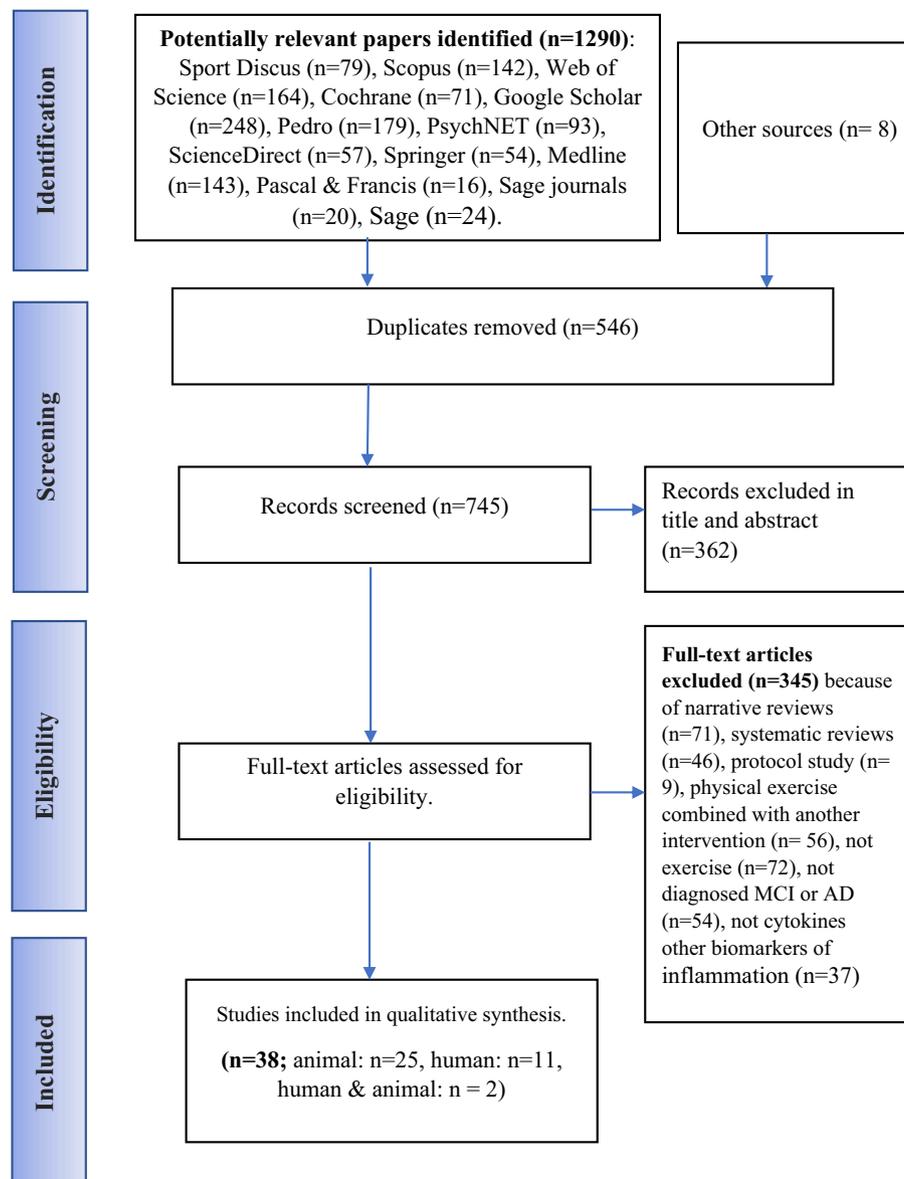


Fig. 1. Selection methodology for study inclusion based on 2009 PRISMA Flow Diagram (Moher et al., 2009).

**Table 1**  
CAMARADES quality assessment of the 27 animal's studies (Macleod et al., 2005).

Score adapted CAMARADES CHECKLIST (on 10)	6	7	7	8	5	7	7	8	6	8	6
Publication in peer-reviewed journal	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Statement of control of cytokines levels	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Randomization of groups	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Allocation concealment	N	N	N	N	N	N	N	N	N	Y	N
Blinded assessment of outcome	N	N	N	Y	N	N	N	Y	N	N	N
Avoidance of combined intervention	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Use of animals with MCI, dementia, or Alzheimer	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Sample size calculation	N	N	N	N	N	N	N	N	N	N	N
Statement of compliance with regulatory requirements	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Statement regarding possible conflict of interest	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y
	Zhang et al., 2022	He and Qiang, 2021	Nakanishi et al., 2021	Belaya et al., 2020	Hashiguchi et al., 2020	Liu et al., 2020	Rosa et al., 2021	Sabouri et al., 2020	Svensson et al., 2020	Li et al., 2020	Jahangiri et al., 2019

initial search. Fig. 1 shows the flowchart of the study selection process.

#### 2.4. Data extraction

Data extraction was performed by two independent researchers (SA and OG) assisted by a third researcher or supervisor (AA) as needed. For each study, we recorded the following characteristics in an Excel spreadsheet: Title, author, publication date, review, impact factor of the review in the year of publication, score on the adapted CAMARADES checklist and MacDermid score, type of population (rats, mice, or humans), age, sex, sample size, pathology stage, duration of the entire intervention, exercise type, exercise intensity, exercise frequency, exercise duration, exercise volume which is the duration of the session multiplied by the number of sessions per week multiplied by the total exercise duration (*duration of the session x number of sessions per week x exercise duration*), experimental or control group (e.g. sedentary vs. treadmill group), forced or voluntary exercise, level of evidence (e.g., RCT), biochemical method of analysis (e.g., Elisa, Luminex), source of samples (e.g., hippocampus, blood), levels of individual cytokines before and after intervention, other outcomes (e.g., BDNF, preclinical memory assessment (Morris Maze)...), and study outcomes.

#### 2.5. Study quality (human/animal studies)

Study quality was assessed by two researchers (SA and OG) using the Tool adapted CAMARADES checklist for articles on animals (Macleod et al., 2005) and using the MacDermid assessment criteria for articles on humans (MacDermid, 2004). The adapted CAMARADES checklist is an assessment tool specific to preclinical quality studies on animals. It contains 10 items and uses 10 total points to assess study quality. The MacDermid evaluation criteria contain 24 items to assess study quality and the total score is 48. No study was excluded from the analysis because of low quality.

### 3. Results

#### 3.1. Included studies (human/animal studies)

Initially, 1290 potentially relevant papers were identified by their title. First, we identified systematic reviews similar to ours and examined them to verify if they addressed the same subject matter to avoid overlap and wasted time. From these systematic reviews, we selected five articles that were considered to be from other sources. After removing duplicates, only 745 records were screened. After reviewing titles and abstracts, 362 articles were removed for irrelevance. We obtained 383 articles that were assessed in full text, of which 345 articles were excluded because they were narrative reviews (n = 71), systematic reviews (n = 46), protocol studies (n = 9), physical exercise combined

with another intervention (n = 54), no physical activity (n = 72), no MCI or AD diagnosis (n = 54), no cytokines or other biomarkers of inflammation (n = 37). Indeed, discrepancies occurred when articles treated a combination of physical exercise and another intervention (e.g., both exercise and diet, both exercise and cognitive stimulation...etc.). Because we are 2 reviewers, we agreed to include only those articles in which there was at least one physical activity-only group; we focused on this group to avoid bias and to assess only the effect of exercise alone on inflammatory cytokines. In addition, we found articles with forced exercise and voluntary exercise, the voluntary exercise is not regular, and duration and frequency vary from day to day, so we almost deleted it but then kept it because our present study aims to understand the effects of different types of exercise on cytokines. Currently, we have 38 articles: 11 articles on humans and 27 articles on animals, as well as two articles addressing both human and animal protocols (He and Qiang, 2021; Li et al., 2020; Fig. 1).

#### 3.2. Quality assessment (human/ animal studies)

The results of CAMARADES and MacDermid are shown in Table 1 and Table 2, respectively. The animal studies received an average score of 6.3 out of a total of 10 points. The human studies received an average score of 28.2 out of a total of 48 points. The animal articles differed in randomization of groups and in the statement of compliance with regulatory requirements. Choi et al. (2018) and Wu et al. (2018) scored 8 out of 10 with the best score 8 on 10 (Choi et al., 2018; Wu et al., 2018). Zhang et al. (2019a) and Souza et al. (2017) scored 7 out of 10 (Souza et al., 2017; Zhang et al., 2019a) and the rest scored 5 or more. Only Choi et al. (2014) scored <5 out of 10. On the other hand, human articles differed greatly in terms of study design and sampling methods. Furtado et al. (2020) scored 38 out of 48, while Tsai et al. (2019) scored 30, in contrast to Abd El-Kader (2016), Chupel et al. (2017), Iyalomhe et al. (2015), Jensen et al. (2019), and Nascimento et al. (2014) who scored <30 based on the statement of compliance with regulatory requirements and potential conflict of interest statement. The bolded articles addressed both human and animal populations (He and Qiang, 2021; Li et al., 2020) and were assessed according to both CAMARADES and MacDermid.

#### 3.3. Study summary (human/animal studies)

The characteristics of each animal and human population are described in Table 3 and Table 4, respectively. A total of approximately 1249 animals and 789 human participants were included in the present qualitative analyses. For animal studies, the number of animals per group varied from 12 (Elahi et al., 2016; Parachikova et al., 2008; Zhang et al., 2022; Zhang et al., 2019b) to 320 (Lu et al., 2017), and for human studies, the number of participants varied from 10 (Iyalomhe et al.,

6	7	8	5	8	7	6	6	5	4	5	6	5	5	5	6
Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
N	Y	Y	N	N	Y	Y	N	Y	N	N	Y	N	N	N	Y
N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
N	N	Y	N	Y	N	N	N	N	N	N	N	N	N	N	N
Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Y	Y	Y	N	Y	Y	Y	Y	N	N	Y	Y	N	N	Y	Y
Y	Y	Y	Y	Y	Y	N	Y	N	N	N	N	Y	Y	N	N
Medhat et al., 2019	Zhang et al., 2019b	Wu et al., 2018	Sun et al., 2018	Choi et al., 2018	Souza et al., 2017	Lu et al., 2017	Elahi et al., 2016	Haskins et al., 2016	Choi et al., 2014	Kang et al., 2013	Souza et al., 2013	Leem et al., 2011	Nichol et al., 2008	Parachikova et al., 2008	Cracchiolo et al., 2007

2015) to 198 (Jensen et al., 2019). The average age of the animal participants was 24 weeks old, while it was 72.2 years old for the human participants.

Of the twenty-seven animal studies, thirteen studies were exclusively focused on male (Belaya et al., 2020; Hashiguchi et al., 2020; Jahangiri et al., 2019; Liu et al., 2020; Lu et al., 2017; Nakanishi et al., 2021; Rosa et al., 2021; Sabouri et al., 2020; Souza et al., 2017; Souza et al., 2013; Sun et al., 2018; Wu et al., 2018; Zhang et al., 2022), while three studies involved female mice (Elahi et al., 2016; Medhat et al., 2019; Svensson et al., 2020). The remaining studies involved both sexes (Choi et al., 2014, 2018; Cracchiolo et al., 2007; Haskins et al., 2016; He and Qiang, 2021; Kang et al., 2013; Leem et al., 2011; Li et al., 2020; Nichol et al., 2008; Parachikova et al., 2008; Zhang et al., 2019b).

In the human studies, three articles focused on female (Chupel et al., 2017; de Farias et al., 2021; Furtado et al., 2020). All other human articles worked on mixed samples (Abd El-Kader, 2016; Anderson-Hanley et al., 2018; He and Qiang, 2021; Iyalomhe et al., 2015; Jensen et al., 2019; Li et al., 2020; Nascimento et al., 2014; Sungkarat et al., 2018; Tsai et al., 2019; Yang et al., 2022).

In animal model, a rodent variety was employed such as Sprague-Dawley rats (Choi et al., 2014; Lu et al., 2017; Wu et al., 2018; Zhang et al., 2022), Wistar rats (Jahangiri et al., 2019; Sabouri et al., 2020), Albino rats (Medhat et al., 2019), APP/PS1 mice (Cracchiolo et al., 2007; Hashiguchi et al., 2020; He and Qiang, 2021; Li et al., 2020; Zhang et al., 2019b), SAMP8 mice (Nakanishi et al., 2021), 5xFAD mice (Belaya et al., 2020; Choi et al., 2018; Svensson et al., 2020), 3xTg AD mice (Haskins et al., 2016; Liu et al., 2020), Swiss Albino mice (Rosa et al., 2021; Souza et al., 2017; Souza et al., 2013), C57BL/6 N mice (Sun et al., 2018), Tg 601 (Elahi et al., 2016), PS2 Tg mice (Kang et al., 2013), Tg 2576 mice (Nichol et al., 2008; Parachikova et al., 2008).

In animal model, to develop AD like phenotype, different substances were induced such as lipopolysaccharide, streptozotocin, A $\beta$  injection (non-transgenic model)... etc. (Choi et al., 2014; Jahangiri et al., 2019; Lu et al., 2017; Medhat et al., 2019; Rosa et al., 2021; Sabouri et al., 2020; Souza et al., 2017; Souza et al., 2013; Sun et al., 2018; Wu et al., 2018; Zhang et al., 2022) or AD phenotype was obtained through genetic modification (transgenic model) (Belaya et al., 2020; Choi et al., 2018; Cracchiolo et al., 2007; Elahi et al., 2016; Hashiguchi et al., 2020; Haskins et al., 2016; He and Qiang, 2021; Kang et al., 2013; Leem et al., 2011; Li et al., 2020; Liu et al., 2020; Nakanishi et al., 2021; Nichol et al., 2008; Parachikova et al., 2008; Zhang et al., 2019b). In human model, MCI (Anderson-Hanley et al., 2018; Chupel et al., 2017; Furtado et al., 2020; Iyalomhe et al., 2015; Yang et al., 2022), aMCI (Nascimento et al., 2014; Sungkarat et al., 2018; Tsai et al., 2019) or AD (Abd El-Kader, 2016; de Farias et al., 2021; He and Qiang, 2021; Jensen et al., 2019; Li et al., 2020; Yang et al., 2022) are spontaneously declared.

Comorbidities were not addressed in animal model. In human model, the criteria of selection were strict, and comorbidities did not occur. Only one study (Chupel et al., 2017) quantified this parameter using a Charlson comorbidity index (Charlson et al., 1994) and declared that the

participants have comorbidity.

### 3.4. Intervention's characteristics (human / animal studies)

#### 3.4.1. Animal studies

The characteristics of the interventions in animals and humans are described in Table 5 and Table 6, respectively.

In animal studies, treadmill exercise (Choi et al., 2014; Elahi et al., 2016; Jahangiri et al., 2019; Kang et al., 2013; Lu et al., 2017; Rosa et al., 2021; Sabouri et al., 2020; Sun et al., 2018; Zhang et al., 2022; Zhang et al., 2019b) and running wheel training (Belaya et al., 2020; Choi et al., 2018; Cracchiolo et al., 2007; Haskins et al., 2016; He and Qiang, 2021; Li et al., 2020; Nichol et al., 2008; Parachikova et al., 2008; Svensson et al., 2020) were most commonly used, or treadmill training was compared with enrichment environment (Parachikova et al., 2008). Other authors used swimming as training protocol (Medhat et al., 2019; Souza et al., 2017; Souza et al., 2013; Wu et al., 2018) and the rest of authors used resistance exercises (Hashiguchi et al., 2020; Liu et al., 2020). Only Nakanishi et al. (2021) used rotarod treadmill. The duration of the intervention ranged from 7 days (Sun et al., 2018) to 24 weeks (Svensson et al., 2020). In the forced exercise, the frequency varied from 1 to 3 times per week (Haskins et al., 2016) to 7 times per week (Li et al., 2020; Medhat et al., 2019; Souza et al., 2013; Sun et al., 2018; Wu et al., 2018). In the voluntary exercise, the frequency cannot be defined (Belaya et al., 2020; Choi et al., 2018; Cracchiolo et al., 2007; He and Qiang, 2021; Li et al., 2020; Nichol et al., 2008; Parachikova et al., 2008; Svensson et al., 2020), except for the study of Parachikova et al. (2008) in which the distance traveled was recorded with the software Mini Meter Bend Gold. In forced exercise, the duration of the session was constantly equal to 30 min.d<sup>-1</sup> from the beginning of the protocol to the end (Choi et al., 2014; Lu et al., 2017; Sun et al., 2018), or varied from 10 min.d<sup>-1</sup> and gradually increased to 1 h.d<sup>-1</sup> (Wu et al., 2018), or started with 20 min.d<sup>-1</sup> and gradually increased to 1 h.d<sup>-1</sup> (Souza et al., 2017).

Indeed, intensity in forced exercise was defined by two methods:

- in the case of a running wheel or treadmill: the distance traveled per minute during a well-defined period of time,
- in the case of swimming, by adding a mass to the tail of the animal according to its weight (Poole et al., 2020).

In wheel running or treadmill exercise, the intensity varies from 2.5 m.min<sup>-1</sup> at the beginning of the training (Nakanishi et al., 2021) and gradually increases to 15 m.min<sup>-1</sup> (Jahangiri et al., 2019). In contrast, during swimming exercises (Souza et al., 2017; Souza et al., 2013) progressively larger weights were attached to the proximal parts of the animals' tails to increase the training intensity. The weights were 0–3 % of body weight. This intensity is considered to be below the anaerobic threshold for swimming training. It has been demonstrated in the literature that workloads up to 6 % body weight for rats (Gobatto et al., 2001) and 4 % body weight for mice (Jolitha et al., 2006) can be considered as a threshold of exercise intensity above which aerobic

**Table 2**  
MacDermid quality assessment of 11 human articles (MacDermid, 2004).

MacDermid score	36	24	24	29	38	18	30	26	37	26	25	26	28
1. Was the relevant background work cited to establish a foundation for the research question?	1	2	2	2	2	1	2	2	1	2	1	1	2
2. Was a comparison group used?	2	1	2	2	2	1	2	1	1	2	2	1	2
3. Was patient status at more than one time point considered?	2	1	2	2	2	2	2	2	2	2	2	2	1
4. Was data collection performed prospectively?	2	2	2	2	2	2	2	2	2	2	2	2	2
5. Were patients randomized to groups?	2	0	0	2	2	1	2	1	2	1	1	1	0
6. Were patients blinded to the extent possible?	2	1	0	0	1	0	1	0	2	0	1	1	0
7. Were treatment providers blinded to the extent possible?	1	0	0	0	2	0	1	0	2	1	0	1	0
8. Was an independent evaluator used to administer outcome measures?	2	0	0	0	0	0	0	0	2	2	0	2	0
9. Did sampling procedures minimize sample/selection biases?	1	1	2	1	1	1	1	1	1	1	1	1	1
10. Were inclusion/exclusion criteria defined?	2	0	0	1	2	2	2	1	2	1	1	1	2
11. Was an appropriate enrollment obtained?	1	0	1	1	1	0	0	0	2	2	0	0	2
12. Was appropriate retention/follow-up obtained?	1	1	1	1	2	0	1	1	1	1	2	0	0
13. Was the intervention applied according to established principles?	2	1	0	0	2	0	1	0	1	2	2	2	1
14. Were biases due to the treatment provider minimized (i.e., attention, training)?	2	1	1	1	2	0	1	1	1	2	2	2	2
15. Was the intervention compared with appropriate comparator?	2	1	1	2	2	1	1	2	1	1	1	1	1
16. Was an appropriate primary outcome defined?	2	1	1	1	0	1	1	2	2	2	1	2	1
17. Were appropriate secondary outcomes considered?	1	0	0	1	0	1	1	0	2	2	0	2	1
18. Was an appropriate follow-up period incorporated?	1	1	1	0	2	0	0	1	0	2	0	0	0
19. Was an appropriate statistical test(s) performed to indicate differences related to the intervention?	2	2	1	2	2	1	2	1	2	2	2	1	1
20. Was it established that the study has significant power to identify treatment effects?	1	2	2	2	1	1	2	2	1	2	2	0	2
21. Was the size and significance of the effects reported?	1	0	2	0	2	1	2	1	2	2	0	0	2
22. Were missing data accounted for the considered in analyses?	1	2	1	2	2	0	0	1	1	0	0	0	1
23. Were clinical and practical significance considered in interpreting results?	1	2	1	2	2	1	1	2	2	1	1	1	2
24. Were the conclusions/clinical recommendations supported by the study	1	2	1	2	2	1	2	2	2	2	2	2	2

(continued on next page)

Table 2 (continued)

MacDermid score	36	24	24	29	38	18	30	26	37	26	25	26	28
objectives, analysis, and results?	Yang et al., 2022	He and Qiang, 2021	de Farias et al., 2021	Li et al., 2020	Furtado et al., 2020	Jensen et al., 2019	Tsai et al., 2019	Anderson-Hanley et al., 2018	Sungkarat et al., 2018	Chupel et al., 2017	Abd El-Kader, 2016	Iyalomhe et al., 2015	Nascimento et al., 2014

capacity is improved. The training volume cannot be calculated if the exercise is voluntary, but in the other studies it varied from 7.5 (Elahi et al., 2016) to 60 (Kang et al., 2013; Leem et al., 2011).

### 3.4.2. Human studies

In human studies, the most commonly used intervention type was aerobic exercise (Abd El-Kader, 2016; Anderson-Hanley et al., 2018; Iyalomhe et al., 2015; Nascimento et al., 2014; Tsai et al., 2019) or multimodal training combining aerobic training with muscular resistance exercise, balance, and motor coordination (Nascimento et al., 2014), or a comparison between aerobic training and resistance training (Tsai et al., 2019), or a comparison between aerobic training and stretching exercises (Iyalomhe et al., 2015), or strength training only (Chupel et al., 2017), or a Tai Chi intervention (Sungkarat et al., 2018). de Farias et al. (2021) used physical-functional training in which we found coordination, flexibility, balance, strength, and endurance activities. Cycling training was found in two studies (He and Qiang, 2021; Li et al., 2020). The duration of the intervention varied from 2 months (Abd El-Kader, 2016) to 7 months (Chupel et al., 2017). The frequency of exercise was constant (3 sessions/week) in 6 of 13 articles (Abd El-Kader, 2016; Iyalomhe et al., 2015; Jensen et al., 2019; Nascimento et al., 2014; Sungkarat et al., 2018; Tsai et al., 2019), while the frequency was gradually increased from 2 sessions/week over 8 weeks to 3 sessions/week over 12 weeks, and then to 2 sessions/week in the last 8 weeks in the study of Chupel et al. (2017). He and Qiang (2021) and Li et al. (2020) didn't define the frequency of exercise.

The duration of sessions varied from a constant 40 min.d<sup>-1</sup> (Tsai et al., 2019) to a constant 60 min.d<sup>-1</sup> (Jensen et al., 2019; Nascimento et al., 2014). Other authors gradually increased the session duration per day from 20 min.d<sup>-1</sup> at the beginning to 40 min.d<sup>-1</sup> at the end (Iyalomhe et al., 2015) or to 45 min.d<sup>-1</sup> (Anderson-Hanley et al., 2018). The duration of the session was not defined in the study of He and Qiang (2021). The intensity of the exercise was precisely defined in seven articles. It varied between 40 and 60 %HRR (de Farias et al., 2021) and 56–85 %HR<sub>max</sub> (Furtado et al., 2020). Tsai et al. (2019) gradually increased the intensity: 50–60 %HRR during the first two weeks and 70–75 %HRR thereafter. For the resistance training, the intensity was 60–70 % of one repetition maximum during the first two weeks, and 75 % of one repetition maximum thereafter (Tsai et al., 2019). Iyalomhe et al. (2015) determined the intensity of the aerobic group only which began the protocol at 50 %VO<sub>2max</sub> per 20 min/session for 4 weeks. Thereafter, the training intensity was increased by 5 %VO<sub>2max</sub> weekly until 70 %VO<sub>2max</sub> was reached. Jensen et al. (2019) used a mean intensity of >70 %HR<sub>max</sub> and participated >80 % of sessions. Abd El-Kader (2016) used an intensity of 60–70 %HR<sub>max</sub>. The entire period of intervention was supervised by a monitor (Iyalomhe et al., 2015; Tsai et al., 2019) or an instructor such as a physiotherapist (Abd El-Kader, 2016) or partially (Anderson-Hanley et al., 2018; Sungkarat et al., 2018). The other authors did not specify whether the sessions were supervised or not (de Farias et al., 2021; Yang et al., 2022).

## 3.5. Cytokines studied (human/animal studies)

### 3.5.1. Animal/human studies

In the studies included in this qualitative review, cytokine levels

were measured before and after the intervention in each experimental group and in the control group or after the intervention, (Fig. 2). TNF- $\alpha$  is the pro-inflammatory cytokine measured in most of the included articles (Belaya et al., 2020; Choi et al., 2014, 2018; Cracchiolo et al., 2007; Haskins et al., 2016; He and Qiang, 2021; Jahangiri et al., 2019; Kang et al., 2013; Leem et al., 2011; Li et al., 2020; Liu et al., 2020; Lu et al., 2017; Medhat et al., 2019; Nakanishi et al., 2021; Nichol et al., 2008; Parachikova et al., 2008; Souza et al., 2017; Souza et al., 2013; Sun et al., 2018; Svensson et al., 2020; Wu et al., 2013; Zhang et al., 2022) in animals and humans (Abd El-Kader, 2016; Chupel et al., 2017; de Farias et al., 2021; Furtado et al., 2020; He and Qiang, 2021; Iyalomhe et al., 2015; Jensen et al., 2019; Nascimento et al., 2014; Sungkarat et al., 2018; Tsai et al., 2019; Yang et al., 2022). The second most dosed pro-inflammatory cytokine is the IL -1 $\beta$  (Cracchiolo et al., 2007; Elahi et al., 2016; He and Qiang, 2021; Jahangiri et al., 2019; Leem et al., 2011; Li et al., 2020; Liu et al., 2020; Lu et al., 2017; Nichol et al., 2008; Rosa et al., 2021; Sabouri et al., 2020; Souza et al., 2017; Souza et al., 2013; Sun et al., 2018; Svensson et al., 2020; Wu et al., 2018; Zhang et al., 2022) in animals and humans (de Farias et al., 2021; Furtado et al., 2020; He and Qiang, 2021; Jensen et al., 2019; Li et al., 2020).

IL -6 is the third cytokine that has been most studied (Belaya et al., 2020; Choi et al., 2018; Cracchiolo et al., 2007; Elahi et al., 2016; Hashiguchi et al., 2020; He and Qiang, 2021; Leem et al., 2011; Li et al., 2020; Liu et al., 2020; Medhat et al., 2019; Nichol et al., 2008; Parachikova et al., 2008; Souza et al., 2017; Svensson et al., 2020; Wu et al., 2018; Zhang et al., 2019b) in animals and humans (Abd El-Kader, 2016; Anderson-Hanley et al., 2018; Furtado et al., 2020; He and Qiang, 2021; Jensen et al., 2019; Li et al., 2020; Nascimento et al., 2014; Tsai et al., 2019; Yang et al., 2022). The anti-inflammatory cytokine IL -10 (Goodwin et al., 1998) (Wei & Jonakait, 1999) has also been studied in several animal articles (Belaya et al., 2020; Choi et al., 2018; Cracchiolo et al., 2007; Hashiguchi et al., 2020; Liu et al., 2020; Parachikova et al., 2008; Souza et al., 2013; Svensson et al., 2020; Wu et al., 2018; Zhang et al., 2022; Zhang et al., 2019b) and in humans (Chupel et al., 2017; Furtado et al., 2020; Jensen et al., 2019; Sungkarat et al., 2018). IL -1 $\alpha$  has been studied only in animal articles (Choi et al., 2014; Cracchiolo et al., 2007; Hashiguchi et al., 2020; Kang et al., 2013; Parachikova et al., 2008; Zhang et al., 2019b). IL -8 (Choi et al., 2018) in animals and humans (de Farias et al., 2021; Yang et al., 2022), IL -11 (Parachikova et al., 2008) in animals, IL -12 (Cracchiolo et al., 2007; Zhang et al., 2019b) in animals, IL -13 (Choi et al., 2018) and humans (Jensen et al., 2019), IL -15 (Tsai et al., 2019), IL -18 (Elahi et al., 2016; Parachikova et al., 2008; Wu et al., 2018) in animals, IFN- $\gamma$  (Belaya et al., 2020; Choi et al., 2018; Cracchiolo et al., 2007; Nichol et al., 2008; Souza et al., 2017; Svensson et al., 2020; Zhang et al., 2019b) in animals, and in humans (Chupel et al., 2017; Jensen et al., 2019) and IL -4 $\beta$  (Lu et al., 2017), IL -10 $\beta$  (Lu et al., 2017), GMC-SF (Cracchiolo et al., 2007), IL -1 (Parachikova et al., 2008), and in humans (Iyalomhe et al., 2015), IL -4 (Cracchiolo et al., 2007; Hashiguchi et al., 2020; Souza et al., 2017; Svensson et al., 2020; Wu et al., 2018; Zhang et al., 2022; Zhang et al., 2019b) in humans (de Farias et al., 2021), IL -12(p70) (Belaya et al., 2020; Cracchiolo et al., 2007; Souza et al., 2017; Svensson et al., 2020; Wu et al., 2018), IL -2 (Choi et al., 2018; Cracchiolo et al., 2007; Souza et al., 2017; Svensson et al., 2020; Zhang et al., 2019b) in animals and in

**Table 3**  
General characteristics of animal studies included for review.

Reference	Animal's characteristics	N sample	Age range & sex	Study design	Exercise type	Cytokines studied	Method of analysis
Zhang et al., 2022	Sprague-Dawley rats-AD model: icv injection of Aβ <sub>1-42</sub> protein	12	8 weeks, male	NM	Treadmill running exercise	IL-1β, TNF-α, IL-4, IL-10	ELISA
He and Qiang, 2021	APP/PS1 double transgenic mice AD model	40	32 weeks,	RCT*	Voluntary wheel running exercise	TNF-α, IL-1β, IL-6	ELISA kit (Boster Bio, Pleasanton, CA)
Nakanishi et al., 2021	SAMP8 mice- AD model	63	28 weeks, male	RCT	Rotarod treadmill	TNF-α	Western Blot Analysis
Belaya et al., 2020	5XFAD- Human APP and human presenilin-1 (PSEN1) including the M146L and L286V mutations, AD model	41	6 weeks, male	RCT	Running wheels	IL-6, IL-10, IL12p70, IFN-γ, TNF-α.	CytoFlex
Hashiguchi et al., 2020	APP/PS1 mice AD model	29	24-28 weeks, male	RCT	Resistance exercise	IL-1 α, IL-4, IL6, and IL-10	Milleplex Map
Liu et al., 2020	3 × Tg (B6; 129-Psen1tm1Mpm Tg (APPSwe, tauP301L) 1 L fa/MmJax) AD model	16	36 weeks, male	RCT	Resistance exercise	IL-6, TNF-α, IL-1β, IL-10	Milliplex Mouse Cytokine Immunoassay Kit (Millipore, 2,620,525)
Rosa et al., 2021	Swiss mice, icv (left lateral ventricle) Aβ <sub>1-40</sub> injection, AD model	24	6–7 weeks, male	RCT	Treadmill exercise	IL-1β	Western blotting analysis
Sabouri et al., 2020	Wistar rats, hippocampal Aβ injection, AD model	144	8 weeks, male	RCT	Treadmill exercise and after aerobic exercise	IL-1β	Nanodrop spectrophotometer
Svensson et al., 2020	5xFAD mice, AD model	30	8–12 weeks, female	RCT	Voluntary wheel running exercise	IL-6, IL-10, IL12p70, IFNγ., IL-1β, IL-4, IL-2, IL-5 and TNF-α	Elisa
Li et al., 2020	APP/PS1 (APPswe/PSEN1dE9) double Tg mice), AD model	48	32 weeks	RCT	Voluntary wheel running exercise	IL-18, IL-6, and TNF-α	Elisa
Jahangiri et al., 2019	Wistar rats, LPS intraperitoneally injection, AD model	32	6–8 weeks - male	RCT	Treadmill exercise	IL-18, TNF-α	Elisa
Medhat et al., 2019	albino rats, LPS intraperitoneally injection, AD model	50	24 to 48 weeks, female	rats were equally divided.	Swimming exercise	IL-6, TNF-α	Elisa
Zhang et al., 2019b	APP/PS1 mice (APPswe/PS1De9 double-transgenic mice with a C57BL/6 background) AD model	12	12 weeks	RCT	Treadmill running exercise	mRNA expression: TNF-α, IL-1β, IL-10, TGF-β	Elisa
Wu et al., 2018	rat Sprague-Dawley, AD model: icv STZ injection	36	10 weeks-male	RCT	Swimming exercise	IL-1β, TNF-α, IL-4, IL-18, IL-6, IL-10	Elisa
Sun et al., 2018	C57BL/6 N mice, AD model: (Aβ) hippocampal injection.	64	8 weeks-male	randomly separated	Treadmill running exercise	TNF-α, IL-1β	Elisa
Choi et al., 2018	mice 5XFAD, (B6/SJL genetic background), AD model	20	8 weeks	True experimental design	Wheel running exercise	IL-2, IFN-γ, TNF-α, IL-8, IL-13, IL-6, IL-10	Elisa
Souza et al., 2017	Swiss Albino mice, AD model: i.c.v. injection of Aβ <sub>1-42</sub>	32	12 weeks-male	RCT	Swimming exercise	IL-4, IL-6	Elisa
Lu et al., 2017	Sprague Dawley rats, AD model: STZ bilateral icv injection	320	10 weeks-male	RCT	Treadmill Exercise	IL-1β, TNF-α, IL-4β, IL-10β	Elisa Duo Set Kits
Elahi et al., 2016	Tg601 and (NTg) mice.	12	4-5 weeks-female	were divided	Treadmill exercise	TNF-α, IL-1β, IL-6, IL-18	Elisa
Haskins et al., 2016	AD mice (3xTg): familial AD mutations: (PS-1 M146 V), (APP-Swe), and (tau-P301L) on a C57BL/6J background	25	8 weeks	RCT	Wheel running exercise	TNF-α	Meso Scale Discovery
Choi et al., 2014	Sprague-Dawley rats, AD = icv STZ injection	21	20 weeks	True experimental design	Treadmill exercise	IL-1 α, TNF-α	Western Blot Analysis
Kang et al., 2013	AD model: PS2 mutant transgenic (Tg) mice & (non-Tg) mice, background of C57BL/6 9 DBA/2 mice,	32	96 weeks	RCT	Treadmill exercise	IL-1α, TNF-α	Western Blot Analysis

(continued on next page)

Table 3 (continued)

Reference	Animal's characteristics	N sample	Age range & sex	Study design	Exercise type	Cytokines studied	Method of analysis
Souza et al., 2013	Swiss Albino mice mice, AD Model: mice received i.c.v. A $\beta$ <sub>1-40</sub> injection	40	8–12 weeks-male	randomly assigned	Swimming exercise	TNF- $\alpha$ , IL-1 $\beta$ , IL-10	Elisa assays,
Leem et al., 2011	AD model:Tg (Tg-NSE/htau23) and NTg mice		64 weeks	were divided	Chronic endurance exercise	IL-1 $\beta$ , IL-6, and TNF- $\alpha$	RT-PCR analysis
Nichol et al., 2008	AD model: Tg2576 (TG) mice & C57Bl6/SJL (WT)	56	68–76 weeks	True experimental design	Wheel running exercise	IL-1 $\beta$ , TNF- $\alpha$ , IFN- $\gamma$	Bio-plex multi-plex analysis for IFN- $\gamma$ Elisa for IL-1 $\beta$ , TNF- $\alpha$
Parachikova et al., 2008	AD model: Tg 2576 (HuApp695.K670-M671L) and NTg: C57Bl6/SJL mice	12	60–76 weeks	Randomized Matched Control Study	Wheel running exercise	mRNA expression: IL-1r1, IL-1f6, IL-1f8, IL-1a, IL1 and its receptor IL1r2, IL-2rg, TNFRsf 1 a, TNFRsf 1b, IL-10 and its receptors IL-10ra et IL-10rb, IL-6st, IL-18, IL-11	Elisa
Cracchiolo et al., 2007	AD model:APP + PS1 and NT mice (background C57B6, B6D2F1, SJL, and SW).	38	24 weeks	RCT	Wheel running exercise	IL-2, IFN- $\gamma$ , TNF- $\alpha$ , IL-1 $\alpha$ , IL-12, IL-6, IL-10, IL-12(p70), GMCSF, IL-1 $\beta$ , IL-4	Mouse Cytokine Antibody Array

Legend: ELISA = Enzyme Linked Immunosorbent Assay, RCT = Randomized Controlled Trial, \* After training half of mice of each group were selected randomly, NM = Not Mentioned, RNA<sub>m</sub> = Messenger RNA, icv = *Intracerebroventricular*, LPS = *lipopolysaccharide*, NTG = non-transgenic, PS-1 M146 V = presenilin-1, APP = amyloid precursor protein, tau-P301L = tau, non Tg = non-Transgenic.

humans. A variety of laboratory techniques have been used to measure these cytokines. These were: Enzyme Linked Immunosorbent Assay (ELISA), radioimmunoassay (RIA), Western blotting, immunohistochemistry, and microplate analysis of plasma. ELISA was used to detect a range of outcomes in most studies (Anderson-Hanley et al., 2018; Choi et al., 2018; Chupel et al., 2017; de Farias et al., 2021; Elahi et al., 2016; Furtado et al., 2020; He and Qiang, 2021; Jahangiri et al., 2019; Jensen et al., 2019; Li et al., 2020; Lu et al., 2017; Medhat et al., 2019; Nascimento et al., 2014; Nichol et al., 2008; Souza et al., 2017; Sun et al., 2018; Sungkarat et al., 2018; Svensson et al., 2020; Wu et al., 2018; Yang et al., 2022; Zhang et al., 2022; Zhang et al., 2019b). In three included studies, it was not possible to measure the desired cytokines due to lack of resources: the method used or the origin of the samples did not allow the markers to be determined (Anderson-Hanley et al., 2018; Haskins et al., 2016; Sungkarat et al., 2018). After training, three types of cytokines were detected in the experimental groups: cytokine levels increased, decreased, or remained stable. Many articles compared two or more groups (Jensen et al., 2019; Leem et al., 2011; Tsai et al., 2019). To avoid bias and to determine the effect of training alone rather than in combination with other measures, we focused on the groups compared in Tables 5 and 6. The other groups that did not receive training, did not have MCI or dementia, or did a combined intervention are not addressed in our tables. Our results show that cytokine levels after exercise depend on several factors:

- 1-) type of exercise.
- 2-) intensity of the exercise.
- 3-) duration of the experimental protocol.
- 4-) frequency.
- 5-) and training volume.

Regardless of these five factors, our results show that exercise generally decreases pro-inflammatory cytokines in animal models and increases anti-inflammatory cytokines in human models

#### 4. Discussion

The aim of the present study was to summarize, through a systematic review of articles from animal and human sources, the evidence that different protocols of physical exercise reduce proinflammatory cytokines and enhance anti-inflammatory cytokines in a population with MCI or dementia. The parameters that determine physical activity are type, frequency, duration (program and session), intensity (Ambrose and Golightly, 2015; Lee and Skerrett, 2001), and volume. Previous

studies on physical activity and the effects on immunological parameters indicated that the profiles of proinflammatory and anti-inflammatory cytokine levels are stimulated depending on the intensity and duration of physical exercise (Nielsen et al., 2016; Pedersen, 2000a, b). The present systematic review combined 25 articles exclusively related to animals, 11 articles exclusively related to humans, and 2 articles that combined human and animal protocols. This review involved 1249 animals and 789 human participants of both sexes. Inflammatory and anti-inflammatory cytokines were dosed before and after exercise and/or in both the intervention and control groups. To our knowledge, this is the first systematic investigation focusing specifically on the parameters of physical exercise.

#### 4.1. Animal model

##### 4.1.1. Main results

With regard to the three major pro-inflammatory cytokines TNF- $\alpha$ , IL-1 $\beta$ , and IL-6, which have been associated with neuronal death, brain dysfunction (Rosenberg, 2005; Wang et al., 2015), and oxygen free radical generation (Zhao et al., 2011), we found that physical exercise reduced these pro-inflammatory markers in 70.8 % of animal model articles. As for the anti-inflammatory cytokines: IL-4, IL-10, IL-4 $\beta$ , IL-10 $\beta$ , and TGF- $\beta$ , it is important to note that we observed an increase in these cytokines after exercise in 26 % of the animal model articles.

##### 4.1.2. Exercise type

Examining the exercise type, treadmill exercise is shown to have a positive effect on cytokines in animal models in 40.8 % of all studies. Proinflammatory factors are decreased in 82 % of articles and anti-inflammatory factors are increased in 27.3 %. Indeed, our results showed that treadmill running, resistance training, and swimming reduced pro-inflammatory cytokines. These results are consistent with the findings of Vasconcelos-Filho et al. (2021) who hypothesized that chronic physical activity could attenuate  $\beta$ -amyloid deposition, including treadmill exercise, swimming, and resistance training, regardless of the experimental model AD and the intensity used. A decrease in proinflammatory cytokines was found in 100 % of swimming exercises authors and an anti-inflammatory enhancement in 50 % of articles (Medhat et al., 2019; Souza et al., 2017; Souza et al., 2013; Wu et al., 2018).

100 % of resistance training (Hashiguchi et al., 2020; Liu et al., 2020) decreased pro-inflammatory cytokines and 50 % showed anti-

**Table 4**  
General characteristics of human studies included for review.

Reference	Participants characteristics	N sample	Average age & sex (in %)	Study design	Exercise type	Cytokines studied	Method of analysis
Yang et al., 2022	Elderly with AD or MCI	48	73–54 ♀	Single blind RCT	Stacking sport	TNF- $\alpha$ , IL-6	Human ELISA kit
He and Qiang, 2021	elderly with AD	90	63.6–53.3 ♀	N.M	Cycling training	IL-1 $\beta$ - IL-6, TNF- $\alpha$	ELISA kit (Booster Bio, Pleasanton, CA).
de Farias et al., 2021	Elderly with AD	15	68.3–100 ♀	Nonrandomized	Physical/functional training: coordination, agility, balance, strength, and endurance activities	serum blood: IL-1 $\beta$ , TNF- $\alpha$ , IL-4	ELISA
Li et al., 2020	Elderly with AD	40	72.4–23♀	Were recruited	Cycling training	IL-1 $\beta$ - IL-6, TNF- $\alpha$	ELISA
Furtado et al., 2020	Elderly with MCI	60	80.7–100 ♀	RCT	Chair elastic band muscle-strength VS chair multimodal	IL-1 $\beta$ - IL-10, IL-6, TNF- $\alpha$ , IFN- $\gamma$	ELISA
Jensen et al., 2019	Elderly with AD	198	70.5–42.9♀	RCT	Moderate to high intensity aerobic exercise	IL-2, IFN- $\gamma$ , TNF- $\alpha$ , IL-8, IL-13, IL-6, IL-10-	IFN $\gamma$ , IL10, IL12p70, IL13, IL1 $\beta$ , IL-2, IL4, IL6, IL8, TNF $\alpha$ by (MSD v-plex proinflammation panel 1 human, Meso Scale Discovery, MA, USA), and plasma ELISA kit, Cayman Chemicals, MI, USA)
Tsai et al., 2019	Elderly with aMCI	55	72.5–69 ♀	RCT	Aerobic exercise VS resistance exercise	TNF- $\alpha$ , IL-1 $\beta$ , IL-15, IL-6, IL-8.	Luminex 200 analyzer (Luminex, Austin, TX, USA)
Anderson-Hanley et al., 2018	Elderly with MCI or risk of MCI or sMCI	60	78.1–66 ♀	RCT	Aerobic exergame tour VS exergame score	IL-6-	ELISA-based array was used (Quantibody custom array, RayBiotech Inc., Norcross, GA, USA).
Sungkarat et al., 2018	Elderly with aMCI	66	67.9–86.3♀	RCT	Tai Chi	TNF- $\alpha$ , IL-10-	Plasma TNF- $\alpha$ and IL-10 levels were determined using the TNF- $\alpha$ human ELISA kit (KHC3011, Thermo Fisher Scientific, MA) and IL-10 human ELISA kit (KHC0101, Thermo Fisher Scientific, MA)
Chupel et al., 2017	Elderly with MCI or moderate cognitive impairment	40	82.7–100 ♀	RCT	Strength training	IL-10, TNF- $\alpha$ , IFN- $\gamma$	ELISA (Invitrogen, CA)
Abd El-Kader, 2016	Elderly with AD	40	70–27.5♀	RCT	Aerobic exercise	IL-6, TNF- $\alpha$ -	Interleukin-6 (IL-6) level was analysed by “Immulite 2000” immunoassay analyzer (Siemens Healthcare Diagnostics, Deerfield, USA). TNF- $\alpha$ level was measured by ELISA kits (ELX 50)
Iyalomhe et al., 2015	Elderly with MCI	10	71.5–30♀	RCT	Aerobic exercise VS stretch exercise	IL-1, IL-2, TNF- $\alpha$ -	Agilent 2100 (Agilent, Santa Clara, CA, États-Unis)
Nascimento et al., 2014	Normal elderly and elderly with aMCI	67	67.6–65.7♀	RCT	Multimodal exercise: aerobic exercise, resistance and balance	IL-6, TNF- $\alpha$ -	Quantikine Human IL-6 Immunoassay ELISA kit and Quantikine Human TNF-alpha Immunoassay ELISA kit (R&D Systems, Minneapolis, USA).

Legend: MCI = mild cognitive impairment, aMCI = amnesic MCI, sMCI = screened as MCI, AD = Alzheimer's disease, ♀ = female, ♂ = male, RCT = Randomized Controlled Trial, NM = not mentioned.

inflammatory decrease. Running wheels and voluntary running wheels showed a slight effect on pro- and anti-inflammatory cytokines (Belaya et al., 2020; Choi et al., 2018; Cracchiolo et al., 2007; Haskins et al., 2016; He and Qiang, 2021; Nichol et al., 2008; Parachikova et al., 2008) compared to treadmill running, swimming, and resistance training (Belaya et al., 2020; Choi et al., 2018; Cracchiolo et al., 2007; Haskins et al., 2016; He and Qiang, 2021; Nichol et al., 2008; Parachikova et al., 2008). Cracchiolo et al. (2007) demonstrated that voluntary wheel running exercise lead not to significant differences between the sedentary and trained groups, either in the central (hippocampus; Cracchiolo et al., 2007) or the peripheral (blood plasma; Svensson et al., 2020). Nevertheless, Parachikova et al. (2008) showed that running led to increased mRNA expression of only a few molecules such as IL-11 and, most importantly, chemokines. These results are consistent with those of Svensson et al. (2020) Moreover, these pathological events in 5xFAD mice are not ameliorated by the running intervention. Running might even exacerbate the pathology, as these mice showed increased exploratory behavior and developed sensorimotor hindleg claspings earlier (Svensson et al., 2020). However, Choi's study, very similar to Svensson's, reported that running was beneficial in this model. Differences in gender and study design could explain these contradictory results. Regardless of the type of exercise, treadmill running, resistance

training, or swimming promote reduction in microglial activation, A $\beta$  amyloid plaques, and pro-inflammatory cytokines after exercise.

#### 4.1.3. Exercise frequency

Lu et al. (2017) and Zhang et al. (2022) demonstrated that high-frequency treadmill training (5 times/week) had an opposite effect on the progression of aging and dementia. It decreased TNF- $\alpha$  and increased anti-inflammatory cytokines IL-4 and IL-10 in the hippocampus after 4 weeks of training. The same effect was observed after 8 weeks of maximal frequency swimming training (7 times/week; Souza et al., 2013). It is important to note that Zhang et al. (2019b) observed a similar effect on mRNA after 12 weeks of treadmill training (5 times/week). Similar results were also found in blood serum after 4 weeks resistance training (7 times/week; Liu et al., 2020) and in brain homogenates after 4 weeks swimming training (7 times/week; Wu et al., 2018). IL-10 is a myokine produced by muscle contractions that can cross the blood-brain barrier and exert anti-inflammatory effects on the brain (Severinsen and Pedersen, 2020). Repeated exercise may therefore have immunomodulatory effects and create an anti-inflammatory microenvironment in the brain that can protect against the inflammatory stimulus mediated by A $\beta$ <sub>1–42</sub> peptide. IL-4 has an immunomodulatory effect in the central nervous system against A $\beta$ <sub>1–42</sub> activation of

**Table 5**  
 Characteristics of physical exercise and its effect on cytokines in animal model and significant changes in cytokines.

Reference	Exercise type	Frequency	duration per session & duration of protocol	Training volume	Intensity	Samples & cytokines studied	Groups compared	Significant* changes in Cytokines after exercise in exercised groups
Zhang et al., 2022	Treadmill running exercise	5*/week	60 min- 4 weeks	20	15 m/min	Hippocampal brain tissues, IL-1, TNF- $\alpha$ , IL-4, IL-10	AD group VS exe + AD group	IL-1 $\beta$ ↓, TNF $\alpha$ ↓, IL-4 ↑, IL-10 ↑
He and Qiang, 2021	Running wheels	Voluntary	4 weeks	Cannot be calculated	Voluntary	RNA, IL-1 $\beta$ - IL-6, and TNF- $\alpha$	VE p-SNHG14 VS control	IL-1 $\beta$ ↓, TNF $\alpha$ ↓, IL-6 ↓
Nakanishi et al., 2021	Rotarod treadmill	5*/week	15 min/day –10 weeks	12,5	2,5 m/min	Right and left hippocampus- TNF- $\alpha$	SAMP8 exercise group VS SAMP8 no exercise group	TNF- $\alpha$ ↓
Belaya et al., 2020	Running wheels	Voluntary	NM –24 weeks	Cannot be calculated	Cannot be calculated	Hippocampus IL-6, IL-10, IL12p70, IFN $\gamma$ , and TNF- $\alpha$ .	5xFAD sedentary VS 5xFAD running	↑IL-10
Hashiguchi et al., 2020	Resistance exercise	5*/week	10 min/day- 4 weeks	3.33	Metal fixed on the tail for 1 min	Hippocampus- IL-1 $\alpha$ , IL-4, IL6, and IL-10	APP/PS1 VS APP/PS1 resistance exercise	IL-6↓ IL-4 ↓
Liu et al., 2020	RESISTANCE exercise	7*/week	120 min –4 weeks	56	Tail weights were equivalent to 15 %, 30 %, 50 %, and 75 % of their body weight in weeks 1, 2, 3, and 4 respectively.	IL-1 $\beta$ , IL-6, IL-10, and TNF- $\alpha$ in the serum Milliplex Mouse Cytokine Immunoassay Kit (Millipore, 2,620,525)	sedentary group VS resistance exercise group	TNF $\alpha$ ↓, IL-1 $\beta$ ↓ IL-10↑
Rosa et al., 2021	Treadmill running exercise	5*/week	40 min- 4 weeks	13.33	Starting at 6 m/min- 12 m/min at the end of the protocol	Hippocampus- IL-1 $\beta$	Sedentary A $\beta$ 1–40 VS treadmill exercise/A $\beta$ 1–40	no significant difference between groups
Sabouri et al., 2020	Treadmill exercise	5*/week	10 min- 4 weeks	3.33	10 m/min for 2 weeks, 15 m/min for 2 weeks	Hippocampus, IL-1 $\beta$	AD treadmill exercise VS AD sedentary	IL-1 $\beta$ ↓
Svensson et al., 2020	Voluntary wheel running exercise	Voluntary	Voluntary-24 weeks	Cannot be calculated	Cannot be calculated	Hippocampus and serum, IL-6, IL-10, IL12p70, IFN $\gamma$ -, IL-1 $\beta$ , IL-4, IL-2, IL-5and TNF- $\alpha$	Sedentary VS running	No significant difference between groups
Li et al., 2020	Voluntary wheel running exercise	Voluntary	Voluntary-4 weeks	Cannot be calculated	Cannot be calculated	Hippocampus, IL-1 $\beta$ , IL-6, and TNF- $\alpha$	Control group VS voluntary exercise group	L-1 $\beta$ ↓, IL-6↓, and TNF- $\alpha$ ↓
Jahangiri et al., 2019	Motorised treadmill exercise	6*/week	30 min/day, 9 weeks	27	15 m/min,	Hippocampal tissues, IL-1 $\beta$ , TNF- $\alpha$	LPS VS LPS + MT	TNF- $\alpha$ ↓, L-1 $\beta$ ↓,
Medhat et al., 2019	Forced swimming	7*/week	30 min/day, 4 weeks	14	NM	Hippocampus, IL-6, and IL-10	AD control VS AD swimming	IL-6↓, IL-10 ↓
Zhang et al., 2019b	Treadmill running exercise	5*/week	45 min- 12 weeks	45	5 m / min for 5 min, 8 m / min for 5 min, 12 m / min for 30 min and 5 m / min for 5 min.	mRNA expression of TGF $\beta$ , TNF- $\alpha$ , IL-10, IL-1 $\beta$	Transgenic group (TG) VS Transgenic exercised (TE)	ARN m gene expression of IL-1 $\beta$ ↓ TNF- $\alpha$ ↓ IL-10 ↑; TGF- $\beta$ ↑
Wu et al., 2018	Swimming exercise	7*/week	10 min/day and gradually increase till 60 min/day- 4 weeks.	48	Measured in m/min	Brain homogenates,IL-1 $\beta$ , TNF- $\alpha$ , IL-4, IL-18, IL-6, IL-10	G stz + swim VS G stz CON	IL-1 $\beta$ ↓; IL-10 ↑ IL-4 ↑; TNF $\alpha$ ↓; IL-6↓; IL-18↓
Sun et al., 2018	Treadmill running exercise	7*/week	30 min- 7 days	24.5	15 m/mn	Hippocampal tissue, TNF- $\alpha$ , IL-1 $\beta$	Running + A $\beta$ VS group A $\beta$	IL-1 $\beta$ ↓; TNF- $\alpha$ ↓
Choi et al., 2018	Wheel running exercise	Voluntary	Voluntary- 12 weeks	Cannot be calculated	Voluntary	Hippocampal homogenates, IL-2, IFN- $\gamma$ , TNF- $\alpha$ , IL-8, IL-13, IL-6, IL-10	Exercised 5XFAD VS 5XFAD sedentary.	IL-6 ↑
Souza et al., 2017	SWIMMING exercise	5*/week	20 min and gradually increase till 60 min- 8 weeks	13.33 and gradually increase till 40	Weights from 0 to 3 % of BW were attached to the tail	Prefrontal cortex and hippocampus, IL-1 $\beta$ , IL-2, IFN- $\gamma$ , TNF- $\alpha$ , IL-4, IL-5, IL-6, IL-10, IL-12p70	A $\beta$ exercise VS group A $\beta$	IL-4↓; IL-6 ↓;
Lu et al., 2017	Treadmill Exercise	5*/week	20 min- 4 weeks	6.66	8 m / min for 5 min, then at 14 m / min for 5 min, and finally at 18 m / min for 20 min	Hippocampal tissues, IL-1 $\beta$ , TNF- $\alpha$ , IL-4 $\beta$ , IL-10 $\beta$	STZ ex-VS STZ group.	IL-1 $\beta$ ↓; IL-4 $\beta$ ↑; IL-10 $\beta$ ↑

(continued on next page)

Table 5 (continued)

Reference	Exercise type	Frequency	duration per session & duration of protocol	Training volume	Intensity	Samples & cytokines studied	Groups compared	Significant* changes in Cytokines after exercise in exercised groups
Elahi et al., 2016	Treadmill Exercise	5*/week	30 min-3 weeks	7.5	Gradient 0 %- 10 m/min	Hippocampus, TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-18	Tg601 exercised VS Tg601 sedentary	IL-1 $\beta$ ↑, IL-18↑, TNF- $\alpha$ ↔, IL-6 ↔
Haskins et al., 2016	Wheel running exercise	1 or 3*/week	60 min- 12 weeks	12 or 36	Increase exercise: intensity (3.0–5.0 m / min) at the end 8 m / min for 60 min	Blood serum and cortex, TNF- $\alpha$	3xTg-AD Sedentary VS 3xTg-AD Exercise	Levels are not detectable
Choi et al., 2014	Treadmill exercise	5*/week	30 min- 6 weeks	15	8 m / min the first 5 min, 11 m / min the following 5 min and 14 m / min for the last 20 min	Cerebral cortex, IL-1 $\alpha$ , TNF- $\alpha$	STZ-exe VS STZ control	TNF-a ↓, IL-1 $\alpha$ ↓
Kang et al., 2013	Treadmill exercise	5*/week	60 min- 12 weeks	60	12 m/min	Hippocampus, IL-1 $\alpha$ , TNF- $\alpha$	TE/PS2m VS SED/PS2m	IL-1 $\alpha$ ↓, TNF $\alpha$ ↓
Souza et al., 2013	Swimming exercise swims 5 cm deep then 20 cm deep	7*/week	20 min/day gradually increased till 60 min/day- 8 weeks	18.66 gradually increased till 56	Added 0 to 3 % rat tail	Hippocampus and prefrontal cortex, TNF- $\alpha$ , IL-1 $\beta$ , IL-10	Sedentary A $\beta$ <sub>1-40</sub> VS exercised A $\beta$ <sub>1-40</sub>	IL-1 $\beta$ ↓, TNF $\alpha$ ↓, IL-10 ↑
Leem et al., 2011	Treadmill chronic endurance exercise	5*/week	60 min/day- 12 weeks	60	12 m/min or 19 m/min	Hippocampus, IL-1 $\beta$ , IL-6, and TNF- $\alpha$	Tg VS Tg LE, Tg VS Tg HE	TNF- $\alpha$ ↓, IL-6↓, IL-1 $\beta$ ↓
Nichol et al., 2008	Wheel running exercise	Voluntary	3 weeks	Cannot be calculated	Voluntary	Hippocampus, IL-1 $\beta$ , TNF- $\alpha$ , IFN- $\gamma$	Tg2576 (Tg <sub>RUN</sub> ) VS Tg2576 (Tg <sub>SED</sub> )	IL-1 $\beta$ ↓, TNF- $\alpha$ ↓
Parachikova et al., 2008	Wheel running exercise	Voluntary	3 weeks	Cannot be calculated	The distance traveled recorded by Mini Meter Bend Gold software	mRNA expression: IL-1r1, IL-1f6, IL-1f8, IL-1a, IL1 and its receptor IL1r2, IL-2rg, TNFRsf 1 a, TNFRsf 1b, IL-10 and its receptors IL-10ra et IL-10rb, IL-6st, IL-18, IL-11	Tg2576 RUN VS Tg 2576 SED	mRNA level of IL-11↑
Cracchiolo et al., 2007	Wheel running exercise	Voluntary	5 weeks	Cannot be calculated	Voluntary	Plasma blood IL-2, IFN- $\gamma$ , TNF- $\alpha$ , IL-1 $\alpha$ , IL-12, IL-6, IL-10, IL-12(p70), GMCSF, IL-1 $\beta$ , IL-4	APP+PS1 (PA) VS APP+PS (IMP)	No significant difference between groups

Legend: \*p < 0,05, ↓ decrease, ↑ increase, ↔ constant, PA: Physical Activity, IMP: Impoverished, MT: moderate exercise, LE = Low exercise intensity HE = High BW = Body Weight, LPS = Lipopolysaccharide, mRNA = messenger RNA.

microglia and the subsequent production of inflammatory cytokines. Thus, the elevated levels of IL -4 detected in our study could be explained as a compensatory mechanism of the brain to counterbalance the A $\beta$ -induced upregulation of IL-6 (Szczepanik, 2001). A high-frequency training (7 times/week or 5 times/week) independently of the type of exercise (treadmill, resistance, and swimming exercise) increases anti-inflammatory proteins and counteracts the progression of AD.

#### 4.1.4. Exercise volume

In treadmill exercise, low (Lu et al., 2017), moderate (Zhang et al., 2022), or high exercise volume (Liu et al., 2020; Zhang et al., 2019b) resulted in a decrease in pro-inflammatory cytokines IL -1 $\beta$ , and an increase in anti-inflammatory cytokines IL -10. A high volume of resistance training lowered the levels of pro-inflammatory cytokines TNF- $\alpha$  and IL -1 $\beta$  and increases anti-inflammatory cytokines IL -10 in blood serum (Liu et al., 2020). However, low volume resistance training decreased proinflammatory cytokine IL -6, but also decreased anti-inflammatory IL -4 in the hippocampus (Rosa et al., 2021). It is possible that increased IL -1 $\beta$  and IL -18 secretion affects the late-phase activation of macrophage proinflammatory responses. Specifically, the increased secretion of IL -1 $\beta$  and IL -18 in the early phase after LPS (Lipopolysaccharide) stimulation may activate macrophages through paracrine and/or autocrine actions, leading to potentiation of the production of other cytokines in the late phase (Shirato et al., 2017). On the

other hand, the stable levels of IL -6 can be explained by the fact that IL -6 is an inflammation-responsive cytokine described as a proinflammatory cytokine, but it can also stimulate anti-inflammatory cytokines. Elahi et al. (2016) indicated that low-volume treadmill training increased the levels of IL -1 $\beta$  and IL -18 and kept the levels of pro-inflammatory cytokines TNF- $\alpha$  and IL -6 stable in the hippocampus. Our results suggest that the volume of treadmill exercise and resistance training elicits an adaptive immune response that modulates pro- and anti-inflammatory cytokines, depending on combination of exercise duration, total exercise duration, and frequency.

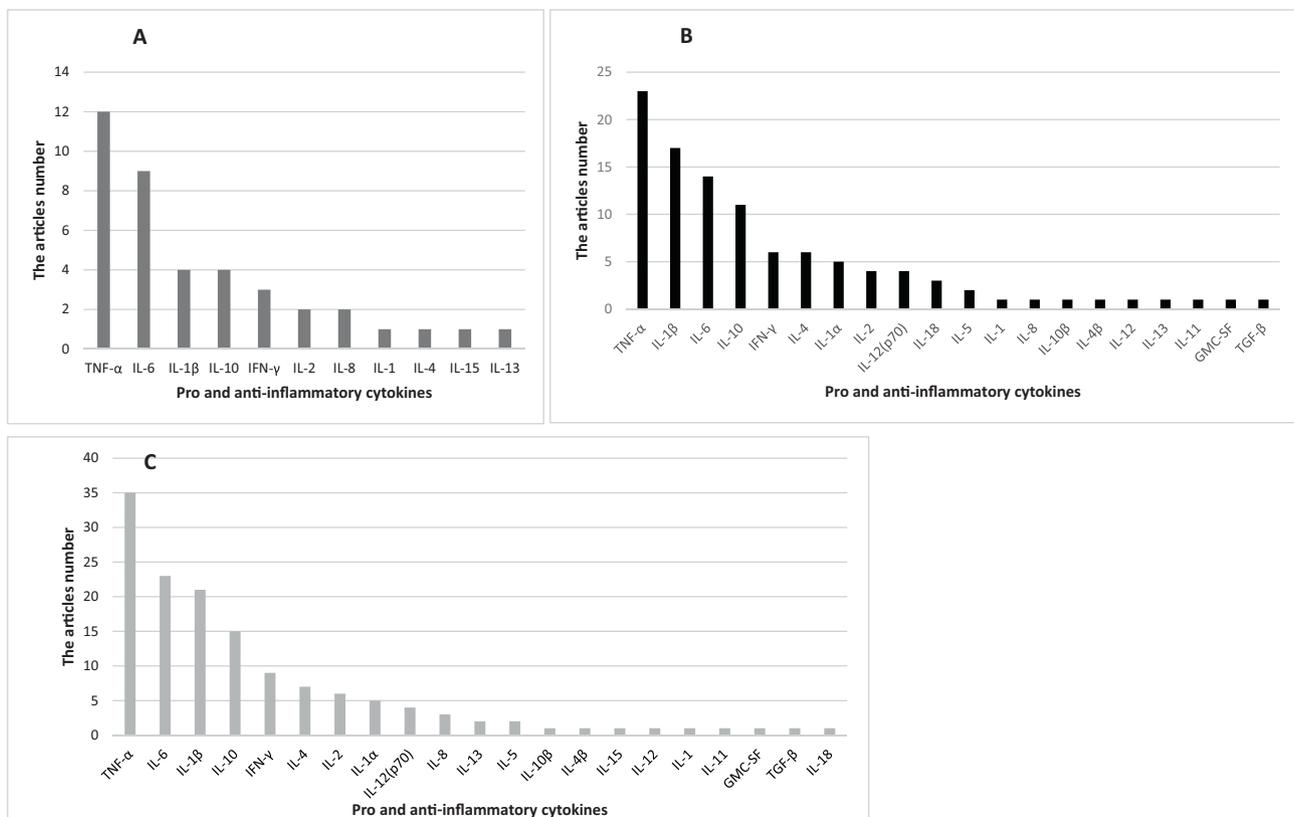
#### 4.1.5. Exercise intensity

Short-term high-intensity swimming training (4 weeks) with fixed tail weights (15 %, 30 %, 50 %, and 75 % of mice body weight) reduced proinflammatory proteins such as TNF- $\alpha$ , IL -1 $\beta$  (Liu et al., 2020) and increased anti-inflammatory such as IL -10 in serum blood. These results are in contrast to the findings of Gleeson (2007) and Hoffman-Goetz et al. (2009) who showed that short-term high-intensity exercise also elicited a pro-inflammatory, immune activating/exacerbating response. In contrast, low intensity exercise (endurance treadmill exercise, 60 min, 15 m per minute) showed a significant decrease in TNF- $\alpha$  and IL -1 $\beta$  (Jang et al., 2017; Zhang et al., 2022) and an increase in the anti-inflammatory factors IL -4 and IL -10 in the hippocampus (Zhang et al., 2022). These results support that low intensity endurance training reverses neuroinflammation.

**Table 6**  
Characteristics of physical exercise and its significant effects in cytokines in human model.

Reference	Exercise type & supervision	Frequency	Duration of session & duration of protocol	Training volume	Intensity of effective exercise	Sample & cytokines studied	Groups compared	Significant* changes in cytokines after exercise in groups
Yang et al., 2022	Stacking exercise-totally supervised	5 t/week	30 min- 12 weeks	30	NM	Blood sample: TNF- $\alpha$ , IL-6	Intervention MCI group VS control MCI group	IL-6 $\uparrow$
He and Qiang, 2021	Cycling training-totally supervised	NM	NM	Cannot be calculated	70 %HRR	Serum blood: IL-1 $\beta$ - IL-6, TNF- $\alpha$	Pre training VS Post training	IL-1 $\beta$ $\downarrow$ IL-6 $\downarrow$ , TNF- $\alpha$ $\downarrow$
de Farias et al., 2021	Physical/functional training: coordination, agility, balance, strength and endurance activities-totally supervised	2 t/week	60 min-11 weeks	22	40–60 %HRR	serum blood: IL-1 $\beta$ , TNF- $\alpha$ , IL-4, IL-10	Pre training VS Post training	IL-4 $\uparrow$
Li et al., 2020	Cycling training-totally supervised	NM	12 weeks	Cannot be calculated	70 %HRR	Serum blood: IL-1 $\beta$ - IL-6, TNF- $\alpha$	Pre training VS Post training	IL-1 $\beta$ $\downarrow$ IL-6 $\downarrow$ , TNF- $\alpha$ $\downarrow$
Furtado et al., 2020	Chair elastic band muscle-strength VS chair multimodal-totally supervised	2–3 t/ week	45 min- 28 weeks	42–63	Multimodal exercise (CME) = 56–85 %HR <sub>max</sub> chair elastic band-muscle strength exercise (CSE) = 56–75 % HR <sub>max</sub>	Plasma blood: IL-1 $\beta$ - IL-6, TNF- $\alpha$ , IFN- $\gamma$	CME VS CSE VS control	CME: IL-10 $\uparrow$ CSE: IL-10 $\uparrow$
Jensen et al., 2019	Moderate to high intensity aerobic exercise- totally supervised	3 t/week	60 min- 16 weeks	48	Intensity >70 %HR <sub>max</sub> and tracking >80 % high exercise group	CSF: IL-2, IL-6, IL-8, IL-10, IL-13, IFN- $\gamma$ , TNF- $\alpha$ Plasma: IL-6, IL-8, IL-10, IL-13, IFN- $\gamma$ , TNF- $\alpha$	CG VS EG, CG VS high exercise subgroup	Plasma: IL-6 $\uparrow$ $\clubsuit$ , IFN- $\gamma$ $\downarrow$ $\blacklozenge$
Tsai et al., 2019	Aerobic exercise, resistance exercise-totally supervised	3 t/week	40 min- 16 weeks	32	AE: 50–60 %HRR in the 2st weeks and 70–75 %HRR for the rest of the program, RE: 60–70 % of individual target 1-RM in the 1st 2 weeks and 75 % of their target 1-RM for the rest of the program.	Serum blood: IL-1 $\beta$ , IL-6, IL-8, IL-15, TNF- $\alpha$	AE pre VS AE post RE pre VS RE post CG (placebo) VS AE	AE: TNF $\alpha$ $\downarrow$ IL-15 $\downarrow$ ; RE: IL-15 $\downarrow$
Anderson-Hanley et al., 2018	Aerobic exergame tour, exergame score-partially supervised	2 t/week for 12 weeks, gradually increase to 3 t or 5 t/week for 12 weeks	20 min for 12 weeks gradually increase to 45 min for 12 weeks –24 weeks	68	NM (average HR was documented on log using the karvonen equation measured by steering handgrips built into the cybecycle)	Saliva: IL-6	Group exer tour VS Group exer score	Levels are not detectable
Sungkarat et al., 2018	Tai Chi- partially supervised	3 t/week	50 min- 24 weeks	60	Target HR level maintained, which was calculated using the Karvonen equation	Plasma blood: IL-10- TNF- $\alpha$	CG VS Tai Chi group	Levels are not detectable
Chupel et al., 2017	Strength training-totally supervised	2 t/ week for 8 weeks, increasing to 3 t/week for 12 weeks, then 2 t/ week over the last 8 weeks	45 min- 28 weeks	51	Between 6 and 8 levels of PSE scale measured by OMNI #	Plasma blood: IL-10, TNF- $\alpha$ IFN- $\gamma$	Intervention group: pre intervention VS post intervention	IL-10 $\uparrow$
Abd El-Kader, 2016	Aerobic exercise-totally supervised	3 t/week	45 min- 8 weeks	12	10–30 min (60–70 %HR <sub>max</sub> )	Blood: IL-6, TNF- $\alpha$	AE VS CG	IL-6 $\downarrow$ , TNF $\alpha$ $\downarrow$
Iyalomhe et al., 2015	Aerobic Exercise (AE) and, Stretch Training Exercise (STE)- totally supervised	3 t/ week and 1 t/ week walking	40 min-24 weeks and 45–60 min of walking after 4–6 weeks of exercise	67	AE = 50 % for 4 weeks, increasing of 5 % / week till 70 % of VO <sub>2max</sub> STE = no intensity	Microarray analysis on blood samples: IL-1, IL-2, TNF- $\alpha$	AE pre intervention VS AE post intervention	IL-1 $\downarrow$ , IL-2 $\downarrow$ , TNF $\alpha$ $\downarrow$
Nascimento et al., 2014	Multimodal exercise: aerobic exercise, resistance and balance-totally supervised	3 t/week	60 min- 16 weeks	48	60–80 %HR <sub>max</sub>	Blood serum: IL-6, TNF- $\alpha$	MCI pre exercise VS MCI post exercise	IL-6 $\downarrow$ , TNF $\alpha$ $\downarrow$

Legend: times, \*p < 0,05,  $\clubsuit$  same effect in the two compared groups vs CG,  $\blacklozenge$  biomarker concentration stratified according to ApoE genotype. Group differences in mean change from baseline high exercise versus control depending on ApoE e4,  $\downarrow$  decrease,  $\uparrow$  increase, NM = Not Mentioned; st = first, VS = Versus, CSF = Cerebrospinal fluid, training volume = frequency\*duration of session\*duration of protocol, 1-RM = one repetition maximum, HRR: Heart Rate Reserve, MHR = Maximum Heart Reserve, OMNI perceived exertion scale (PES) for strength exercises. OMNI consists of an arbitrary scale ranging from 0 at 10 points, with identical intervals and concerning quality effort: (0) extremely (1–2) easy, (3–5) fairly easy, (6–7) a little hard; (8) hard (9–10) extremely hard, CG: Control Group, AE: Aerobic Exercise, EG: Exercise Group, RE: Resistance Exercise, CME = Chair Multimodal Exercise, CSE = Chair Strength Exercise, NM = Not Mentioned.



**Fig. 2.** Number of included studies that have investigated different types of cytokines: A = cytokines studied in human model, B = cytokines studied in animal model, C = cytokines studied in both human and animal models. Twenty cytokines were extracted and analysed from cortex, brain tissue and hippocampus in the animal model, while eleven cytokines were extracted and analysed from blood or cerebral spinal fluid in the human model.

In the light of these results, low-intensity treadmill training or high-intensity swimming training inhibits pro-inflammatory cytokines and stimulates secretion of anti-inflammatory cytokines centrally (hippocampus) or peripherally (serum blood).

#### 4.1.6. Effect of experimental model, gender, age and pathology acquisition mode on cytokines

The most experimental mice model that showed a significant good exercise effect on cytokines is the APP/PS1 (He and Qiang, 2021; Li et al., 2020; Zhang et al., 2019b). Sprague-Dawley rats showed also a significant good exercise effect on cytokines (Choi et al., 2014; Wu et al., 2018; Yang et al., 2022). These two rodent models showed significant pro inflammatory cytokines decrease and significant anti-inflammatory cytokines increase after exercise. Wistar rats showed also a good exercise efficacy on cytokines (Jahangiri et al., 2019; Sabouri et al., 2020). These results are consistent with the findings of Morgese et al. (2022).

Concerning, the sex influence on cytokines, 70 % of articles that focused on male showed a positive effect of exercise on reducing pro inflammatory cytokines and increasing anti-inflammatory cytokines in running wheels, treadmill exercise, resistance exercise, rotarod treadmill and swimming exercise (Belaya et al., 2020; Jahangiri et al., 2019; Liu et al., 2020; Nakanishi et al., 2021; Sabouri et al., 2020; Souza et al., 2013; Sun et al., 2018; Wu et al., 2018; Zhang et al., 2022). Nevertheless, in forced swimming, voluntary wheel running and treadmill exercise, the only three studies conducted in female did not show positive effect of exercise on cytokines and pro inflammatory and anti-inflammatory cytokines (Elahi et al., 2016; Medhat et al., 2019; Svensson et al., 2020).

Regarding the age, we observed a positive effect of exercise on cytokines in young (6 weeks; Belaya et al., 2020), medium age (20 weeks; Choi et al., 2014) or old rodent (64 weeks; Leem et al., 2011; 68–76 weeks; Nichol et al., 2008). 60 % of articles showed that secreted anti-

inflammatory cytokines and inhibited pro inflammatory cytokines secretion after exercise seems to be unrelated to age.

With regard to AD disease acquisition, 60 % of authors used transgenic rodent and 40 % of authors induced cognitive dysfunction by injecting different substances (Streptozotocin, A $\beta$ <sub>1–42</sub>, lipopolysaccharide...etc) in the hippocampus or intracerebroventricular zones. Only 56 % of authors addressing transgenic rodent found a positive effect of exercise on cytokines whereas 73 % of authors addressing induced AD (non-transgenic) found a positive exercise effect on neuro inflammation. In fact, our results state that hippocampal A $\beta$  injection is very effective in 100 % of articles (Sabouri et al., 2020; Sun et al., 2018). Intracerebroventricular STZ injection showed in 66 % of the studies a good effect of exercise on cytokines (Choi et al., 2014; Wu et al., 2018). Intracerebroventricular A $\beta$ <sub>1–42</sub> injection and A $\beta$  lipopolysaccharide intraperitoneally injection were effective on reducing neuro inflammation only in 50 % articles. Our findings support the statement that neuro inflammation is more interesting to be studied in non-transgenic model especially in intracerebroventricular STZ injection rodent model than in transgenic model. Our results are consistent with the findings of Chen et al. (2013).

#### 4.1.7. Conclusion (animal model)

In the animal model, our results support the idea that regardless of the type of exercise (treadmill running, resistance, or swimming), there is a reduction in microglial activation, a reduction in A $\beta$ -plaque deposition, and a reduction in proinflammatory cytokines. A high-frequency training (7 times/week or 5 times/week) of treadmill, resistance, or swimming exercise increases anti-inflammatory proteins and counteracts the progression of AD. Our results suggest that the volume of treadmill exercise and resistance training elicits an adaptive immune response that modulates pro- and anti-inflammatory cytokines when

training duration per session, total training duration, and frequency are considered. Low intensity treadmill training or high intensity swimming training inhibit pro-inflammatory cytokines and stimulate secretion of anti-inflammatory cytokines centrally (hippocampus) or peripherally (serum blood). In transgenic model, APP/PS1 double transgenic mice, voluntary running wheels in 32 weeks aged mice for four weeks is effective to reduce TNF- $\alpha$ , IL-6 and IL-1 $\beta$  (He and Qiang, 2021; Li et al., 2020). In non-transgenic model, Wistar rats and C57BL/6 N mice who received hippocampal A $\beta$  injection and were trained with treadmill running exercise in high frequency (5 times/week; Sabouri et al., 2020), (7 times/week; Sun et al., 2018) and a low intensity of 15 m.min<sup>-1</sup> is effective to reduce TNF- $\alpha$  and IL-1 $\beta$ .

## 4.2. Human model

### 4.2.1. Main results

In the human model, our most important finding was that 53.9 % of chronic exercise articles reduced pro-inflammatory proteins and 23 % of articles increased anti-inflammatory proteins. Given the benefits of chronic exercise in humans, we have focused on exercise modalities in this review.

### 4.2.2. Exercise type

Regarding the type of exercise, we observed a significant reduction in pro-inflammatory cytokines IL -6, TNF- $\alpha$ , IL -15, and IL -1 $\beta$  with four different types of exercise: cycling exercise, aerobic exercise, multimodal exercise, and resistance exercise. Voluntary 12-week cycling training showed that the relative levels of the pro-inflammatory cytokines IL -6, TNF- $\alpha$ , and IL -1 $\beta$ , as well as the expression of small nucleolar RNA host gene 14 (SNHG14), decreased significantly in AD patients. This suggests that exercise can reverse the change in small nucleolar RNA host gene 14 SNHG14 expression. The latter may be involved in the progression of AD (He and Qiang, 2021). Li et al. (2020) also demonstrated that in AD patients, serum expression of miR-129-5p was also increased after 3 months of cycling and correlated with indicators of cognitive function and inflammatory cytokines. Aberrant expression of miRNA has been found in the development of AD, and these functional miRNAs are considered potential targets for the treatment of this disease (An et al., 2017; Gupta et al., 2017). Some of them are involved in the progression of AD by regulating neuroinflammation (Huang et al., 2017). On the other hand, aerobic exercise was found to reduce IL -6 and TNF $\alpha$  over 8 weeks (Abd El-Kader, 2016), TNF- $\alpha$  and IL -15 over 16 weeks (Tsai et al., 2019), and IL -1, IL -2, TNF $\alpha$  over 24 weeks (Iyalomhe et al., 2015) Previously, in a meta-analysis, Firth et al. (2018) confirmed the significant effects of aerobic exercise on hippocampal volume, and found that aerobic exercise interventions may be useful in preventing age-related hippocampal deterioration and maintaining neuronal health. In principle, increased cerebral metabolism or cerebral neuronal activity (Ide et al., 2000; Ogoh and Ainslie, 2009) is accompanied by a transient increase in cerebral blood flow (Ogoh et al., 2005; Sato et al., 2011) and cognitive performance (Brisswalter et al., 2002; McMorris et al., 2011) during and/or after mild to moderate intensity aerobic exercise. Chupel et al. (2017) and Furtado et al. (2020) addressed their studies on focusing on female sex, and found a significant exercise effect on anti-inflammatory cytokine IL-10. This protein increased after exercise.

Multimodal training (3 times/week for 16 weeks), including aerobic exercise, resistance training, and balance training, reduces blood serum levels of IL -6 and TNF- $\alpha$  in older people with MCI (Nascimento et al., 2014). In addition, resistance training (3 times/week for 16 weeks) decreases the pro-inflammatory cytokine IL -15 (Tsai et al., 2019). First, resistance exercise could improve cognitive function by raising IGF-1 (Insulin-like Growth Factor One) levels in the hippocampus and peripheral blood, whereas aerobic and mind body exercise preferentially increase BDNF. Second, resistance training could exert positive influences on both brain and cognition by modulating inflammatory

cytokines such as IL -6, IL -1 $\beta$ , and IL -15, which are normally expressed and released in response to muscle contractions (Huang et al., 2022). In conclusion, voluntary cycling inhibits the progression of AD by reducing SNHG14 expression and increasing serum expression of miR-129-5p, which improves cognitive function and decreases proinflammatory cytokines. Aerobic, multimodal, and resistance exercise are beneficial for MCI and AD patients.

### 4.2.3. Exercise frequency

A frequency of 3 times/week is the most commonly used by the authors. It reduced the pro-inflammatory factors IL -6, TNF- $\alpha$  (Abd El-Kader, 2016; Nascimento et al., 2014), IL -15 (Tsai et al., 2019) in elderly with amnesic MCI or AD. Nevertheless, it has been pointed out that IL -6 could increase in elderly with AD with this frequency (Jensen et al., 2019). Aerobic exercise (3 times/week) with additional of walking 1 time/week is also effective in reducing pro-inflammatory cytokines IL -1, IL -2, and TNF- $\alpha$  in elderly with AD (Iyalomhe et al., 2015). A modulated frequency (2 times/week for 8 weeks, increasing to 3 times/week for 12 weeks, then 2 times/week in the last 8 weeks) did not alter TNF- $\alpha$  and IFN $\gamma$ , but significantly increased secretion of the anti-inflammatory cytokine IL -10 in older people with MCI (Chupel et al., 2017). However, when the training frequency is reduced in older people with AD (2 times/week; de Farias et al., 2021) or with MCI (2–3 times/week; Furtado et al., 2020), pro-inflammatory cytokines IL -1 $\beta$ , IL -6, TNF- $\alpha$ , and IFN- $\gamma$  were not altered, but the anti-inflammatory cytokines IL -4 or IL -10 significantly increased. Interestingly, a high frequency of 5 times/week in older people with MCI or AD did not affect the pro-inflammatory cytokine TNF- $\alpha$  (Yang et al., 2022). Nevertheless, voluntary frequency is effective for AD patients; it reduced IL -1 $\beta$ , IL -6, and circulating TNF- $\alpha$ . Therefore, we suggest that 3 times/week seems to be the most effective frequency for elderly with amnesic MCI, whereas voluntary frequency is effective for AD elderly.

### 4.2.4. Exercise volume

Considering the volume of exercise, voluntary cycling (without a specific volume) reduces the best-known proinflammatory cytokines IL -1 $\beta$ , IL -6, and TNF- $\alpha$  in elderly people with AD. Regardless of volume, low (Abd El-Kader, 2016), moderate (Tsai et al., 2019), or high (Iyalomhe et al., 2015) aerobic exercise reduced pro-inflammatory cytokines in plasma or serum blood. In addition, the anti-inflammatory cytokine IL -4 in AD blood serum and IL -1 $\beta$  increased with moderate volume of training (de Farias et al., 2021). In contrast, Anderson-Hanley et al. (2018) found that high-volume aerobic exercise did not demonstrate pro-inflammatory reductions in saliva of older people with MCI. However, it is important to underline that cytokine levels in saliva are not an accurate representation of cytokine levels in blood (Beigpoor et al., 2021). On contrary, IL-6 levels increased with high volume of aerobic exercise according to Jensen et al. (2019). As discussed above, IL -6 is known as an inflammation-responsive cytokine that is described as a proinflammatory cytokine but can also stimulate anti-inflammatory cytokines. High volume (Chupel et al., 2017) and lower volume (Furtado et al., 2020) of strength training increased the anti-inflammatory cytokine IL -10 in blood plasma of MCI. High volume of multimodal exercise decreases neurological inflammation by decreasing IL -6 and TNF- $\alpha$  in MCI blood serum (Nascimento et al., 2014). We can suggest that independently of the training volume, aerobic exercise inhibits the circulation of pro-inflammatory cytokines in the periphery, but only high-volume multimodal exercise exerts the same effect.

### 4.2.5. Exercise intensity

To date, there is conflicting evidence on the effects of low-to-moderate intensity aerobic exercise (< 70 %HRR) or high-intensity aerobic exercise (> 70 %HRR) on circulating IL -6. Jensen et al. (2019) showed that from moderate to high-intensity aerobic exercise increases plasma levels IL-6 in older people with AD. These results are consistent with the MCI study by Yang et al. (2022). Be. There are three

plausible explanations for the previous findings. It is increasingly recognized that IL-6 has both proinflammatory and anti-inflammatory properties (Pedersen, 2000a). In healthy individuals, it is produced in large amounts in response to physical exertion and decreases rapidly after the end of exertion (Pedersen, 2000b; Petersen and Pedersen, 2005). In addition, IL-6 is also produced locally in muscles and exhibits growth factor properties (Pedersen, 2000a, b). In contrast, moderate intensity aerobic exercise (60–70 %HRR) decreased peripheral proinflammatory cytokines IL-6, TNF- $\alpha$  in elderly with AD (Abd El-Kader, 2016; He and Qiang, 2021; Li et al., 2020), and IL-1 $\beta$  (He and Qiang, 2021; Li et al., 2020). In the same way, moderate intensity reduced proinflammatory factors TNF- $\alpha$  (Iyalomhe et al., 2015; Tsai et al., 2019), IL-15 (Tsai et al., 2019), IL-1, and IL-2 (Iyalomhe et al., 2015). An increase of anti-inflammatory cytokine IL-10 was observed with low intensity of training by de Farias et al. (2021). Nevertheless, aerobic exercise with intensity >70 %HRR increased the secretion of IL-6 (Jensen et al., 2019). We hypothesize that IL-6 shows an adaptive response as a function of exercise intensity. Multimodal exercise at moderate to high intensity (60–80 %HRR) inhibited secretion of the proinflammatory cytokines IL-6 and TNF- $\alpha$  (Nascimento et al., 2014) and stimulated secretion of the anti-inflammatory cytokines IL-10 (Furtado et al., 2020) in older people with MCI.

To date, low and moderate-to high intensity training has shown beneficial effect on anti and pro inflammatory cytokines respectively for AD and MCI patients. Further studies are needed to compare different training intensities with the same exercise modality.

#### 4.2.6. Effect of comorbidity, gender, age and pathology stage on cytokines

In spite of consideration of comorbidities, Chupel et al. (2017) found that strength training was effective to enhance IL-10 levels in older females with MCI. Both Furtado et al. (2020) and Chupel et al. (2017) focused their studies on MCI females aged between 80 and 100 years old. These authors showed that strength training (45 min/session; 2–3 times/weeks; 28 weeks) had an anti-inflammatory effect on females. There are no studies conducted specifically in men and/or comparing by gender. Considering age, four out of six studies in the 60–70 age group, three out of six in the 70–80 age group and two out of two in the over-80 age group showed a positive effect of exercise on cytokines. Furthermore, we observed that exercise had a positive effect on cytokines in 80 % of AD, 75 % of MCI and only 50 % of amnesic MCI studies. Therefore, physical exercise is effective against neuro inflammation regardless of the stage of the pathology and the age of the patient.

#### 4.2.7. Conclusion (human model)

In summary, aerobic, multimodal, and resistance training are beneficial for MCI or AD, regardless of aerobic exercise volume, the latter is effective for both MCI and AD. Our results also show that aerobic exercise inhibits the circulation of peripheral proinflammatory cytokines regardless of exercise volume, but only high-volume multimodal exercise has the same effect. Moderate-intensity or moderate-to-high-intensity training aerobic exercise is the most appropriate training for AD patients. In older people with MCI, moderate- to high-intensity multimodal training (3 times/week) is the most effective in reducing proinflammatory cytokines and improving cognition. We therefore suggest that an exercise frequency of 3 times/week is effective for older people with amnesic MCI, whereas a voluntary exercise frequency is effective for older people with AD. In very older females' patients with MCI, strength training is beneficial by anti-inflammatory effect. In older people with AD, both voluntary cycling training and moderate- to high intensity aerobic exercise are effective. It seems that exercise inhibits proinflammatory cytokines secretion and stimulate anti-inflammatory cytokines secretion regardless of gender and age.

### 4.3. Exercise neuro physiological mechanisms explanation

Given the heterogeneity of methods and results, we critically

reviewed the protocols of animal and human studies to better understand the factors that might explain their findings, as previously suggested by Packer et al. (2010). This systematic review showed that in animal models, treadmill, swimming, and resistance exercise in various forms (frequency, intensity, duration, and volume) are effective in reducing nervous system inflammation (Choi et al., 2014; He and Qiang, 2021; Jahangiri et al., 2019; Kang et al., 2013; Leem et al., 2011; Li et al., 2020; Liu et al., 2020; Lu et al., 2017; Nakanishi et al., 2021; Nichol et al., 2008; Sabouri et al., 2020; Souza et al., 2013; Sun et al., 2018; Wu et al., 2018; Zhang et al., 2022; Zhang et al., 2019b), thus reducing dementia progression by inhibiting microglial activation (Leem et al., 2011; Nichol et al., 2008) and causing a polarization of microglia toward the M2 rather than M1 phenotype. This polarization would be responsible for the reduction of pro-inflammatory cytokines and the increase of anti-inflammatory cytokines (Kang et al., 2013; Lu et al., 2017; Medhat et al., 2019; Nakanishi et al., 2021; Zhang et al., 2019b). Exercise modulated not only the suppression of M1 phenotype microglia but also the suppression of A1 phenotype astrocytes in the hippocampus. These beneficial effects may be related to the inhibition of A $\beta$  accumulation and counteract the decline in age-related behavioral and cognitive performance in the early stages of AD (Nakanishi et al., 2021). Blockade of TREM2 (triggering receptor expressed on myeloid cells 2) in the hippocampus may improve M1 microglia polarization and normalization of inflammatory factors in an AD model after treadmill exercise (Zhang et al., 2022), stabilize anxiety level and attenuate hyperactivity behavior in mice (Belaya et al., 2020; Hashiguchi et al., 2020), and prevent the increase of Iba-1 (calcium-binding adapter molecule 1), TXNIP (Thioredoxin Interacting Protein) and activation of NLRP3 (NOD-like receptor family, pyrin domain containing 3) inflammasome pathway in hippocampus induced by A $\beta$  administration (Rosa et al., 2021). Wheel running exerted neurogenesis through BDNF (Choi et al., 2018). Swimming exercise is an effective approach to inhibit NF- $\kappa$ B activation and neuroinflammatory response in the brain of A $\beta$ <sub>1–42</sub>-treated mice, breaking this vicious cycle of A $\beta$ <sub>1–42</sub> neurotoxicity (Souza et al., 2017), enhance muscle oxidative capacity and promotes adaptation to physical training in rodents and reduce neurotoxicity (Souza et al., 2013), attenuated cognitive impairments (Choi et al., 2014) induced by LPS (Lipopolysaccharide) in Morris water maze (MWM) and passive avoidance tests (Jahangiri et al., 2019). These results are consistent with the findings of Vasconcelos-Filho et al. (2021), who showed that chronic exercise in different forms, intensities and durations promoted the reduction of  $\beta$ -amyloid levels. In contrast, Svensson et al. (2020) showed that 6 months of voluntary wheel running might exacerbate the pathology in mice, increasing exploratory behavior and developing earlier sensorimotor clasp of the hind leg.

In the human model, aerobic, multimodal, and resistance training are beneficial in reducing neuroinflammation for older people with MCI or AD. In fact, reducing the levels of IL-1 $\beta$ , TNF- $\alpha$ , and IL-6 could be partly responsible for the beneficial effects of physical activity on cognitive performance in people with MCI and AD (Stigger et al., 2019). Some studies have established the underlying mechanisms for the positive effects of exercise in the treatment of disease. It has been pointed that aerobic exercise reduced IFN $\gamma$  levels in APO  $\epsilon$ 4 subjects and significantly increased the myeloid cell 2 trigger receptor marker (which measures microglial activation) in the cerebrospinal fluid (Jensen et al., 2019). This has led to an increase in BDNF secretion and thus in neurogenesis (Cassilhas et al., 2012; Sungkarat et al., 2018; Tsai et al., 2019). In addition, voluntary cycling inhibited the progression of AD by reducing SNHG14 expression and increasing serum expression of miR-129-5p, which improved cognitive function and decreased pro-inflammatory cytokines (He and Qiang, 2021; Li et al., 2020). Among all these type of exercise, multimodal exercise tends to be most effective in protecting global cognition and executive functions in patients with MCI. Multimodal training consists of different types of exercises, such as aerobic training, resistance training, or others (Huang et al., 2022). Therefore, they are likely to complement each other in improving

cognitive performance by triggering beneficial biochemical changes via multiple neurobiological mechanisms (e.g., BDNF, IGF-1, homocysteine, inflammatory cytokines; Sanders et al., 2019). Vasconcelos-Filho et al. (2021) demonstrated that chronic exercise training of varying form, intensity, and duration promoted the reduction of  $\beta$ -amyloid levels through several mechanisms, including  $\beta$ -amyloid degradation and processing changes APP. In addition, several physiological systems affected by Alzheimer's disease were improved by the process. Moreover, Hashimoto et al. (2021) suggested that intensity, duration, and type of exercise also affected brain function, possibly through "metabolic myokines" (i.e., lactate). In particular, high-intensity interval exercise could have practical implications for brain health. It is important to note that the potential mechanisms underlying the beneficial effects of habitual exercise on brain function are likely multidimensional (Hashimoto et al., 2021).

#### 4.4. Strengths and limitations review

To our knowledge, our systematic review is the first systematic review focusing on the effects of exercise modalities on inflammatory cytokines. This review not only combines animal and human models, but also attempts to define exercise modalities and address parameter by parameter: type, volume, frequency, and intensity. Our inclusion criteria were strict. We only included articles that dealt with exercise and excluded articles that combined several interventions (exercise plus diet, exercise plus lavender essence...). Contrary to the systematic review of Ma et al. (2022) who included studies with combined interventions (*Glycyrrhiza glabra*, lavender essence, or combined interventions). This could lead to a bias. It made difficult to know whether the positive effect obtained after training was due to the training or to the other interventions or supplementations. This meta-analysis also remained general and inconclusive regarding the type of exercise, duration, and frequency. To date, studies tend to specify exercise modalities to counteract neuroinflammation and cognitive decline in AD patients.

Our systematic review is among the few systematic reviews that searched 13 electronic databases, whereas most systematic reviews and meta-analyses examine 5 or 6 databases. Interestingly, our systematic review is in line with the expectations of some authors. The latter have worked on animals and recommended reproducing the same work in humans to investigate the effects of exercise in human patients with AD, comparing different exercise modalities according to the limitations of the subjects (Vasconcelos-Filho et al., 2021). However, only eleven studies were found and examined the human model. This small number did not allow us to compare different parameters. This is related to the fact that different training regimes, durations, and frequencies were used in these studies, making comparisons difficult. Our results highlight the importance of physical exercise in delaying the progression of pathobiological mechanisms of dementia. These results are consistent with those of Vasconcelos-Filho et al. (2021). Our results may provide guidelines for health professionals. The mechanisms behind the beneficial effects of exercise on brain function need to be understood, especially because these mechanisms are thought to be multifactorial. Research on relevant, carefully designed, well-characterized and controlled animal models will remain for a long time an essential step for fundamental discoveries, for testing hypotheses at the organism level and for the validation of human data. Animal models must be constantly improved to be more reliable and informative (Barré-Sinoussi and Montagutelli, 2015).

Our present review has addressed only the biological aspect.

#### 4.5. Recommendations & perspectives

In future studies in patients with MCI or AD, we recommend evaluating the type of physical exercise, duration, volume, and intensity. It is also necessary to increase the number of participating patients. Moreover, stratifying the effects of the exercise protocol on different stages of

AD, from preclinical to severe AD, remains important. Determining the correlation between cytokine levels and cognitive assessment (MMSE, MoCa...) may help us better understand the relationship between neuroinflammation and cognitive decline. Also, comparing two different types of physical activity, such as strength training and aerobic exercise or multimodal exercise may be more interesting than comparing a sedentary group versus a trained group. In animal models, there are conflicting results regarding voluntary and forced wheel running. Comparing these two groups could help understand whether forced physical activity exacerbates dementia progression. It remains important to systematically examine the other aspects as well. However, gender differences (male versus female), population groups (young versus old), and pathology stages need to be considered in future studies.

## 5. Conclusion

This systematic review shows that chronic physical activity can reduce neuroinflammation in brain tissue of animals with Alzheimer's disease and in the periphery (blood) of people with MCI or AD. The reduction was due to changes in  $\beta$ -amyloid processing and formation, inhibition of NF- $\kappa$ B activation, and neuroinflammatory response in the brains of A $\beta$ <sub>1-42</sub>. These results were obtained thanks to the different modalities of physical exercise. In the animal model, it is possible to counteract the progression of AD by treadmill, swimming and resistance exercises. These exercises polarized microglia for the M2 phenotype instead of M1, stabilized anxiety, attenuated hyperactivity behavior in mice, and promoted neurogenesis through BDNF. In the human model, aerobic, multimodal, and resistance training are beneficial in both MCI and AD. These exercises decreased levels of APO  $\epsilon$ 4 carriers, SNHG14 expression, and increased serum expression of miR-129-5p, which improved cognitive function. Multimodal training with moderate to high intensity is effective in MCI. Voluntary cycling training, moderate or high intensity aerobic exercise are effective in AD patients. In the animal model, exercise had favourable effects on neuroinflammation regardless of age and gender. In the human model, this was also observed independently of age and stage of the disease. These results provide guidelines for healthcare professionals. Nevertheless, this efficacy is only biological and not clinically clear *a priori*. There is still a need to study exercise in humans in more detail by comparing different modalities of exercise, at different stages of dementia and considering gender.

#### CRedit authorship contribution statement

**Sawsen Ayari** Conceptualization, investigation, original draft preparation, writing **Olivier Gavarry** work structuring, organisation, supervision, validation **Alexandre Abellard** visualization, **Marion Carayol** supervision, reviewing manuscript **Éric Guedj** re-reviewing manuscript **Sawsen Ayari**, **Marion Carayol** and **Olivier Gavarry** Methodology, data processing, results, discussion, editing.

#### Declaration of competing interest

The authors declare no competing interests. No grant is required.

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