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Exercise and Alzheimer’s disease in individuals with Down syndrome

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Thesis

EXERCISE AND ALZHEIMER'S DISEASE IN INDIVIDUALS WITH DOWN SYNDROME

by

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DEDICATION

I would like to dedicate this work to my father, Bill Erickson. May he soar on.

ACKNOWLEDGMENTS

Dr. Ira Lott has been instrumental in shaping my future medical journey. His guidance has opened numerous avenues for my development and knowledge expansion. Under his mentorship, I not only honed my research skills but also truly learned how to write. Dr. Lott's profound influence didn't stop there; it inspired the inception and flourishing of my Taekwondo program for individuals with Down syndrome. Now in its sixth year, the program brings joy to my students, their families, and myself.

EXERCISE AND ALZHEIMER'S DISEASE

IN INDIVIDUALS WITH DOWN SYNDROME

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ABSTRACT

Individuals with Down syndrome (DS) face a heightened risk of developing Alzheimer's disease (AD) due to triplication of chromosome 21, which harbors the amyloid precursor protein (APP) gene. The resultant overexpression of APP leads to elevated amyloid plaque production, a hallmark of AD neuropathology. With increasing longevity, age-related dementia of the AD type is prevalent in people with DS. Given the need for targeted interventions, we explore exercise as a potential avenue to mitigate AD onset in this vulnerable population. While exercise is known to modulate AD pathways in the general population, its specific effects on individuals with DS remain understudied. We review three AD pathophysiological pathways—oxidative stress, mitochondrial dysfunction, and neuroinflammation—and highlight evidence demonstrating exercise's potential to modify these pathways. Clinical trials in the general population demonstrate exercise's efficacy in reducing neuroinflammation and oxidative stress, suggesting its promise as a non-pharmacological intervention for AD. Longitudinal exercise studies in DS are lacking, warranting further investigation into exercise-induced biomarkers and neuroprotective mechanisms. To advance this field, blood-based biomarker exploration and longitudinal studies are needed in further exercise trials in individuals with DS. This review serves to establish a framework to deepen the knowledge where comprehensive

data exists, such as oxidative stress studies. The framework also extends to where there is a paucity of data, including mitochondrial dysfunction and neuroinflammation. Future research should focus on elucidating exercise-induced biomarkers, optimizing exercise prescriptions, and exploring novel pathways, ultimately paving the way for effective AD prevention and management strategies in this vulnerable population and beyond.

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LIST OF ABBREVIATIONS

AD.....Alzheimer's disease

ADAS-cog.....Alzheimer’s Disease Assessment Scale-Cognitive subscale

AD-DS .....Alzheimer's disease in individuals with Down syndrome

AD-DS .....Alzheimer's disease in individuals with Down syndrome

AD-GP .....Alzheimer's disease in the general population

APOE .....apolipoprotein E

APP .....amyloid precursor protein

Aβ..... amyloid beta protein

Aβ..... amyloid beta protein

BBB.....blood-brain barrier

BDNF..... brain derived neurotrophic factor

CAMDEX ..... Cambridge Examination for Mental Disorders of Older People with Down Syndrome and Others with Intellectual Disabilities

CRP..... c-reactive protein

CSF ..... cerebrospinal fluid

CTSB.....cathepsin B

DS .....Down syndrome

FTCD ..... formimidoyltransferase cyclodeaminase

HIIT.....high intensity interval training

IL.....interleukin

MCI.....mild cognitive impairment

miRNA ..... micro ribonucleic acid

MMP ..... metalloprotease

mTOR ..... mammalian target of rapamycin

PGC-1α ..... peroxisome proliferator-activated receptor gamma coactivator 1-alpha

PiB ..... Pittsburgh compound-B

ROS ..... radical oxidative species

SOD ..... superoxide dismutase

TFAM ..... mitochondrial transcription factor A

TNF-α ..... tumor necrosis factor alpha

VEGF ..... vascular endothelial growth factor

VO_{2max} ..... maximal oxygen consumption

INTRODUCTION

Alzheimer's is a Feature of Down Syndrome

Individuals with Down syndrome (DS), or trisomy 21, are vulnerable to Alzheimer's disease (AD), in part due to the triplication of chromosome 21 (Head et al., 2016; Wiseman et al., 2015). The amyloid precursor protein (APP) gene resides on the 21st chromosome; therefore, a gene dosage-dependent overexpression results in elevated production of amyloid plaques, a hallmark feature of AD (Korenberg et al., 1990; Margallo-Lana et al., 2004; Sawa et al., 2022). This neuropathology is nearly ubiquitous in adults with DS by age 40 (Lott & Head, 2019). AD, the most prevalent form of dementia worldwide for all individuals older than 65 years (Atri, 2019), afflicts over 6 million in the United States ("2021 Alzheimer's Disease Facts and Figures," 2021). With improved longevity, people with DS show increasing age-related dementia of the AD type (McCarron et al., 2017).

Exercise as a Nonpharmacological Intervention for Alzheimer's Disease

The heightened AD risk for individuals with DS necessitates targeted interventions that may ameliorate or prevent dementia onset. Among a myriad of nonpharmacological interventions being explored for AD management, (Buccellato et al., 2023; Huynh et al., 2022; Ribarič, 2022; Wang et al., 2020; Zucchella et al., 2018) exercise emerges as an avenue with the potential to reshape the trajectory of AD pathways. Physical inactivity is a risk factor for AD (Norton et al., 2014), and people with DS are predisposed to a sedentary lifestyle (Block, 1991; Fernhall et al., 1989). Considering the triad of genetic, lifestyle, and aging factors for people with DS amplifies

the findings that the mechanisms underlying exercise benefits can systemically augment the biology of AD.

Traditional biomarkers like amyloid beta fail to capture the intricate biomolecular progression of AD disturbances, driving recent exploration of additional AD pathways. Thus, at the forefront of the literature are three AD pathophysiological pathways shown to be modifiable by exercise and thereby form the focus of this review: oxidative stress (López-Ortiz et al., 2021), mitochondrial dysfunction (Berchtold et al., 2019; Bernardo et al., 2016; Santos et al., 2012), and neuroinflammatory processes (Cervenka et al., 2017; Improta-Caria et al., 2020; Jensen et al., 2019; Ribarič, 2022). Specifically, clinical trials for AD in the general population (AD-GP) confirm that exercise reduces neuroinflammation (Abd El-Kader & Al-Jiffri, 2016; Nascimento et al., 2014) and oxidative stress (Ionescu-Tucker & Cotman, 2021).

Although comprehensive reviews exist on exercise in AD-GP, such as those by Valenzuela et al. (2020) and Huuha et al. (2022), a review for the population with DS is absent. Exercise succeeds in diminishing oxidative stress in individuals with DS (Janmohammadi & Moghadasi, 2021; Ordonez et al., 2012; Rosety-Rodriguez et al., 2010, 2021). The literature also strongly suggests that mitochondrial function and neuroinflammation should be considered in exercise analyses in people with DS.

Due to limited DS-specific research, insights from the general population will be considered supplementarily to establish a foundation for future biomarker studies. Given that exercise is established in the literature as a mediator of AD biomarker expression with potential for AD interdiction, our approach aims to enrich our understanding of

exercise's neuroprotective roles in DS. This may lead to unlocking strategies for preventing and mitigating AD in this vulnerable population and beyond.

Rationale for Exercise in Individuals with DS

Adults with DS show significant fitness improvements and changes in body composition with ranging effects depending on intensity, adherence to exercise routines, and personal congruence with the physical activity regimen (Barnard et al., 2019; Dodd & Shields, 2005; González-Agüero et al., 2010; Seron et al., 2014). These benefits are particularly significant considering the high prevalence of inactivity (Block, 1991; Fernhall et al., 1989) and a notable shortfall in meeting recommended physical activity guidelines within the population with DS. How exercise activities are introduced can enhance engagement in physical activity programs for individuals with DS (Murray & Ryan-Krause, 2010). For instance, family involvement, facilitator methods, and personal beliefs about the activities play pivotal roles (Alesi & Pepi, 2017). It is necessary to consider participants' affective state and motivation as it can mediate longitudinal physical activity adherence. A review examining 19 studies arranging positive reinforcements as a strategy to increase regular exercise showed positive results although few studies lacked methodological strength (Rotta et al., 2023). Exercise can cause measurable improvements in cognition and robust changes in the physical health of individuals with DS, supporting the inclusion of physical activity (Pastula et al., 2012).

Metabolic and Endocrine Benefits of Exercise

DS is associated with metabolic and endocrine pathway disruptions. Metabolic syndrome, reduced basal metabolism, dyslipidemia, hypothyroidism, and high type I and

II diabetes rates are observed (Alexander et al., 2016; Bergholdt et al., 2006; Grammatikopoulou et al., 2008; Johnson et al., 2019; Konings et al., 2001; Murray & Ryan-Krause, 2010). This denotes increased comorbid risk of AD through metabolic and vascular mechanisms. Increased circulating leptin, a marker of leptin resistance in obese children with DS, is analogous to levels in neurotypical children with simple obesity, highlighting early insulin resistance in people with DS (Yahia et al., 2012). These metabolic symptoms and a sedentary lifestyle can be mitigated with physical activity. For example, decreased leptin, tumor necrosis factor alpha (TNF-α), and interleukin-6 (IL-6), as well as weight and waist circumference in male adults with DS have been observed upon completing a resistance training program (Rosety-Rodriguez et al., 2013).

Thoroughly profiling the metabolic condition of individuals with DS is relevant to AD treatment research as pharmacokinetics, pharmacodynamics, and pharmacogenetics may differ in this population compared to the general population (Alaama et al., 2015). In parallel, the unique DS phenotype shows altered responses to exercise. Further AD-relevant pathway research could target aspects of the typical metabolic condition and other characteristics of DS using physical activity as an alternative intervention.

Fitness and Physiological Benefits for Individuals with DS

Multiple studies have quantifiably shown that adults with DS can improve common markers of fitness. Applying systematic and well-designed protocols of moderate training programs has yielded measurable improvements in parameters such as VO_2 max, walking economy, heart rate recovery, cardiometabolic risk profile, strength, and aerobic work capacity (Balic et al., 2000; Barnard et al., 2019; Mendonca et al.,

2011, 2013; Rimmer et al., 2004; V. K. Tsimaras & Fotiadou, 2004). In more strenuous activities such as swimming, eight weeks of training showed significant differences between the exercise and control groups in other parameters, including body mass index, aerobic capacity, dynamic balance, and muscular strength (Boer & de Beer, 2019). Activities such as rowing have also been shown to increase the duration of physical stamina of participants with DS (Varela et al., 2001). Another study measuring shifts in grip strength after exercise showed strength increases after a singular exercise session (Chen et al., 2014). It was also found that weight, body mass index, and waist circumference were positively correlated with grip strength in young men with DS (Chen et al., 2013). Within exercise protocols, trackable fitness markers offer participants measurable goals that could serve as proxies for AD-relevant biomarkers requiring more invasive testing.

A 12-week resistance training protocol showed improved salivary testosterone levels in sedentary adults with DS (Fornieles et al., 2014). Testosterone levels indicate the anabolic processes that underly recovery from training and, consequently, the retention of performance gains. This demonstrable capacity to change exercise performance abilities is notable. Improved performance may lead to greater satisfaction, and therefore, motivation to continue exercise regimens.

Despite capacity for gains, exercise in individuals with DS meets physiological barriers. Reduced maximal heart rate and peak oxygen consumption may be related to reduced sympathetic drive and circulating catecholamines in this population (Baynard et al., 2004). The synergy of a lessened sympathetic response with cardiopulmonary

limitations may contribute to challenges in self-exertion during physical activity. Blunted acute responses to exercise may lead to heightened perceptions of exercise difficulty, consequently increasing the likelihood of adopting a sedentary lifestyle (Kerstiens & Green, 2015).

Additionally, The prevalent higher body mass index (BMI) and body fat percentage in individuals with DS, compared to their age- and sex-matched counterparts (González-Agüero et al., 2011; Gutierrez-Hervas et al., 2020; Loveday et al., 2012) may contribute to a potential decline in peak oxygen uptake. However, improvements in peak oxygen uptake following aerobic exercise are often substantial (Mendonca et al., 2011; V. Tsimaras et al., 2003). Without intervention, peak oxygen uptake can worsen as people with DS age, resulting in a degradation of the ability to perform activities of daily living and work duties. This is often observed as contributing toward a reduction of physical activity (Barnhart & Connolly, 2007; Fernhall, 1993). Cognitive abilities may suffer in concordance with losses of physical independence and together these findings suggest that exercise should be a part of the overall care plan for adults with DS. Given the estimation that physical inactivity contributes to 21% of AD-GP cases, (Norton et al., 2014), it is evident that there is a need for thorough examination of the role of exercise in modulating AD pathways for individuals with DS.

Neurocognitive Benefits of Exercise

Studies show that exercise ability may parallel neurocognitive changes. This relationship is crucial because it has also been shown that reduced physical activity is correlated to AD susceptibility (Balsamo et al., 2013). Exercise may delay a third of

dementias globally by modulating Aβ, inflammation, and neurotrophins (De la Rosa et al., 2020). Exercise may also delay the onset of AD in individuals with the apolipoprotein E4 allele, (APOE ε4) a genetic AD risk factor (Tokgöz & Claassen, 2021). However, the enhanced AD risk for the general population resulting from APOE4 may be less pronounced for individuals with DS (Rohn et al., 2014).

Studies have shown positive impacts of exercise on cognition in the population with DS. Verbal fluency changes often presage the onset of AD in DS, and moderate-level intensity exercise has been shown to improve semantic fluency (Chen & Ringenbach, 2019). Even short bouts of exercise have been shown to improve executive function in young adults with DS (Chen et al., 2015). A study found a 12-week community-based exercise program for 13-35 year old individuals with DS to improve executive function, but failed to augment processing speed or working memory (Shields et al., 2022). However, a 12-week exercise intervention did show positive implications for memory and cognition in adults with DS (Ptomey et al., 2018).

Exercise intensity may have a dose-dependent effect on cognitive function in individuals with DS (Chen & Ringenbach, 2016). In 2-year study involving 214 adults with DS, Cambridge Examination for Mental Disorders of Older People with Down Syndrome and Others with Intellectual Disabilities (CAMDEX-DS) assessment showed that consistent physical activity at moderate, and even more so, at high intensity levels lowered the risk of decline in personality and skills that precedes AD (Pape et al., 2021). Moderate-intensity exercise was also found to be associated with hippocampal volume in individuals with DS (Peven et al., 2022). Another study found the percentage of

sedentary time showed an inverse link with cognitive function, while moderate-to-vigorous activity was positively associated. Both respectively related to white matter integrity in the superior and inferior longitudinal fasciculus (Fleming et al., 2021).

Various training modalities yield distinct advantages. A single resistance training session with adults with DS has been shown to have a greater increase than cycling in executive function, specifically in measures of cognitive control and cognitive planning. Both cycling and resistance training led to significant increases compared to the no training session (Ringenbach et al., 2021).

EXERCISE AND OXIDATIVE STRESS

Overview of Oxidative Stress and AD in Individuals with DS

A specific AD risk factor exacerbated by physical inactivity is oxidative stress (Laufs et al., 2005) referring to the imbalance in the body's handling of reactive oxygen species (ROS) that are generated within cells as normal metabolic byproducts of cellular respiration. Oxidative damage is of high importance because it is associated with early aging (Zamponi et al., 2018) and neurodegeneration in individuals with DS (Lott et al., 2006; Manna et al., 2016). Heightened oxidative stress due to trisomy 21 may directly contribute to neuropathological changes associated with AD (Zigman & Lott, 2007).

Oxidative damage peaks in the early AD phases and decreases with disease progression (Nunomura et al., 2001). Beyond AD risk, the highly oxidative condition of DS has been associated with morphological abnormalities, immune disorders, intellectual disability, premature aging, and other biochemical abnormalities of DS individuals

(Muchová et al., 2014). Major biomarkers that indicate the process of or play a role in mitigating ROS are listed in **Table 1**.

Table 1. Oxidative Stress Biomarkers in Individuals with DS.

Biomarker:	Type:	Indicative of:	Effect of Exercise:	References:
SOD	Antioxidant Enzyme	cytochrome oxidase activity and DS pathologies	Identified, but not studied.	Muchova et al., 2014
Plasma carbonyl content	Oxidized protein product	Protein oxidation	↓	Ordonez et al., 2012
PINK1/PARKIN	Serine/threonine-protein kinase and ubiquitin ligase	Mitophagy	Identified, but not studied.	Bordi et al., 2019
Malondialdehyde	Lipid peroxidation product	Oxidative stress (directly)	↓	Meguid et al., 2014
glutathione peroxidase-1 (GPX)-1	Antioxidant Enzyme	H202 detoxification	↑	Sinet, 1982 Ordonez et al., 2006
Pyruvic acid	Glycolytic end-product	Shift between glycolytic and fermentative metabolism	Identified, but not studied.	Gross et al., 2019
Methyl adipic acid	Glycolytic end-product	Shift between glycolytic and fermentative metabolism	Identified, but not studied.	Gross et al., 2019
Allantoin	Metabolic Intermediate	Oxidative stress	↓	Rosety-Rodriguez, 2010

Aberrant Proteins and Oxidative Stress

Oxidized proteins are increased in the hippocampus as well as other brain regions in patients with AD (Butterfield et al., 2006). Oxidative stress is linked to amyloid beta plaque formation. However, it is controversial if the mechanisms underlying the benefits

of exercise directly improve amyloid beta clearance or improve redox regulation resulting in cognitive benefits (Cui et al., 2018). Therefore, it is key to look at protein and gene expression to elucidate these mechanisms. In people with DS, oxidative stress may result from PTEN-induced kinase 1 and E3 ubiquitin ligase (PINK1/PARKIN) impairment and abnormal suppression of macroautophagy (Bordi et al., 2019). Animal model studies indicate that PINK1/PARKIN expression can be increased with moderate exercise (Li et al., 2021); this is yet to be researched in individuals with DS.

Still, oxidative stress human studies represent the most comprehensive data from exercise trials in this population. Reduced global protein oxidation measured by plasma carbonyl content was seen after a 12-week moderate-intensity aerobic training program involving adolescents with DS (Ordonez et al., 2012). A similar exercise protocol reduced the biomarker allantoin, the main product of uric acid oxidation via ROS (Rosety-Rodriguez et al., 2010).

Lipid Peroxidation

The intersection of lipid metabolism and oxidative stress mechanisms represents a growing overlap between AD research in the general population and those with DS (Mapstone et al., 2020). Within AD-GP, oxidative stress is associated with increased brain concentration of lipid peroxidation products such as malondialdehyde and 4-hydroxynnonenal (Markesbery & Carney, 1999). Lipid metabolic disturbances are implicated in autosomal dominant AD, specifically, the pathologies involving *PSEN1-2* (Cai et al., 2015). These lipid disturbances are thought to also influence pathology in late onset AD (Zhang et al., 2011). A genetic risk factor, the APOE ε4, is also prevailing

indicator of AD susceptibility (Safieh et al., 2019; Stocker et al., 2020). Patterns of brain oxidative damage precede symptom onset, and increased lipid peroxidation may be associated with an increased risk of AD in general (Chew et al., 2020; Peña-Bautista et al., 2019, 2021). Additional lipid dysfunction leads to abnormal oxysterols, prostanes, phospholipids, and other fatty acids in the CSF or plasma, including numerous molecules that can serve as individual biomarkers or a complex profile (Yoshida et al., 2013; Zarrouk et al., 2018). There are alterations observed in preclinical AD, such as with plasma sphingomyelins, and more insight will emerge with further lipidomics examination (Fote et al., 2021).

In individuals with DS, glutathione peroxidase (GPX) activity is reduced, and high erythrocytic hexose monophosphate shunt activity is observed (Sinet, 1982). Aerobic training over a 12-week period in adolescents with DS has been shown to increase GPX, leading to less oxidative stress from oxidized lipids (Francisco Javier et al., 2006). In the same demographic, a 12-week treadmill program significantly increased GPX and decreased another biomarker of lipid peroxidation, malondialdehyde (Meguid et al., 2014). An 8-week SPARK fitness regimen also reduced malondialdehyde in adolescents with DS (Janmohammadi & Moghadasi, 2021). Resistance training, i.e. weightlifting, for 12 weeks reduced markers of oxidative damage in adults with DS as measured by malondialdehyde and carbonyl levels.

Redox Enzyme Regulation

Resistance training has also shown to increase the antioxidant biomarker glutathione reductase and the plasma total antioxidant status in adults with DS (Rosety-

Rodriguez et al., 2021). Even walking has shown to improve the oxidative state representative of DS (Zambrano et al., 2009), however, this was a salivary measurement rather than plasmatic. Further confirmation of redox augmentation exists with the finding that chronic aerobic exercise increased mRNA expression of antioxidant enzymes such as catalase, GPX-1, and SIRT3 in healthy individuals in the general population (Tsukiyama et al., 2017).

Reduced superoxide dismutase (SOD) is seen in early phase AD (Puertas et al., 2012; Torres et al., 2011) and is proposed as an inducer of ROS in DS (Perluigi & Butterfield, 2012). SOD lies on the 21st chromosome and its triplication results in an imbalance in the ratio of SOD to catalase and GPX causing ROS accumulation (Zana et al., 2007). The APOE4 allele, a known AD risk factor, is also linked to reduced SOD activity (Chico et al., 2013). It has been suggested that exercise can stimulate SOD and decrease NADPH oxidase activity, limiting the progression of oxidative stress and therefore reducing dementia risk through vascular health (Luca & Luca, 2019). Although AD-DS is not thought to be of primary vascular origin, SOD has research potential in this population. In a study of cognitively healthy individuals, 12 weeks of endurance training increased plasma SOD activity and decreased oxidative stress (Edwards et al., 2004).

Notably, there is bioenergetic and redox pathway overlap among other pathological conditions outside of AD or MCI; therefore, broad metabolic oxidative stress biomarkers may be limited in their singular utility (Arslan et al., 2020).

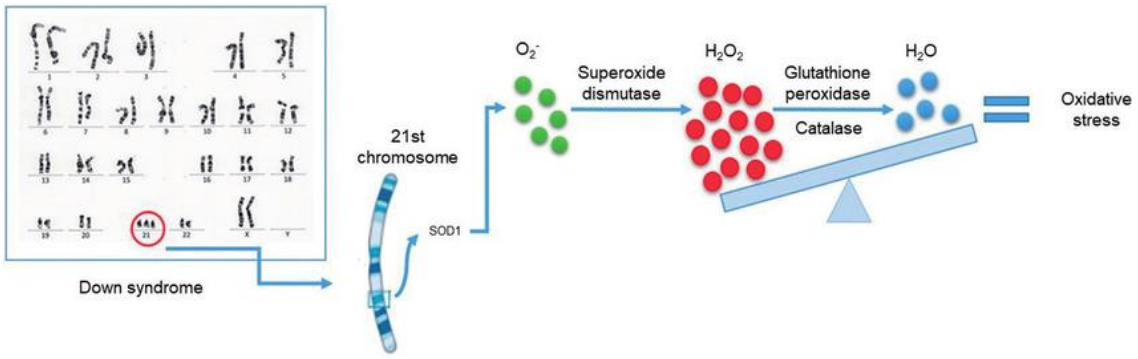

Figure 1. Oxidative stress as a downstream product of trisomy 21. ROS overproduction results from insufficient antioxidation enzymes to mitigate overactive SOD levels (Ravančić et al., 2022).

Oxidative DNA Damage

In addition to oxidized proteins, oxidative modifications of nuclear, cytosolic, and mitochondrial nucleic acids have been reported in the brains of patients with AD (Ding et al., 2005; Kowalska et al., 2020; J. Wang et al., 2006). DNA damage can be estimated with levels of 8-hydroxy-deoxyguanosine (8oHdG); likewise, measurement of RNA can be correlated to 8-hydroxyguanine (8OHG) levels (Butterfield & Halliwell, 2019). Since ROS can accelerate lesions in the highly susceptible mitochondrial DNA due to compartmental proximity (Santos et al., 2012), alleviation of nucleic acid oxidants through exercise requires exploration in AD-DS.

Conjunctive Therapeutic Avenues

Oxidative stress is a possible therapeutic target in people with DS who are in the preclinical AD state (Strydom et al., 2009). A clinical trial of high-potency antioxidants did not alter the course of dementia in individuals with DS (Lott et al., 2011). However,

exercise as a “physical antioxidant” (Ďuračková, 2010) can be explored as an extension of this line of investigation or paired in tandem with antioxidant supplementation.

In general, the effects of exercise on the oxidative state and ROS metabolism are positive. However, it is crucial to consider the uncertainty regarding individual metabolic conditions; a meta-analysis has shown a lack of exercise response patterns in the biomarkers of oxidative stress in individuals with DS (Shields et al., 2018). The severity of metabolic aberrations may differ among individuals with DS; therefore, the oxidative response may be highly variable. The aspects underpinning exercise variation are beginning to be explored in the general population (Kelly & Pomp, 2013); the molecular knowledge from exercise research in people with DS could provide approaches to understanding the modulation of protective or deviant AD-associated pathways.

It is also important to note that the acute effects of exercise include oxidative stress, while the impact of regular exercise diverges in the opposite direction, effectively reducing oxidative damage. This reduction depends on the type of exercise and intensities (Bouzid et al., 2014; Kozakiewicz et al., 2019). The beneficial mechanism may be an adaptive physiological signaling pathway triggered by the initial impulse of exercise-induced ROS (Markesbery & Carney, 1999). It is important to establish and consider the elevated baseline oxidative state of people with DS in future exercise studies.

Modulation of microRNAs and Oxidative Stress

Oxidative stress is recognized as one of the signals linked to the levels of microRNAs that are proposed to be involved in the pathogenesis of AD (Prasad, 2017). Exercise-induced alteration of microRNAs is of growing interest due to their

maintenance of cellular homeostasis through negative gene regulation (dos Santos et al., 2022) and specifically in AD research as a molecular mechanism underlying the benefits of exercise (Improta-Caria et al., 2020). MiRNAs can target and regulate the expression of genes involved in oxidative stress pathways. Some miRNAs may suppress the expression of antioxidant genes, leading to increased oxidative stress in cells. Conversely, certain miRNAs might target pro-oxidant genes, providing a protective role.

miRNA-409 and miRNA-501 have a role in cognition, and through cross-correlation with healthy and disease data profiles have been proposed as biomarkers with the potential to be studied using exercise (Goldberg et al., 2021). In patients with DS, microRNA-155 may be involved in brain pathology, as it has immune and neural roles while microRNA -802 is associated with hippocampal deficiencies (Brás et al., 2018). These two microRNAs may hold significant oxidative stress biomarker value for physical activity trials for people with DS.

Omics Potential for Examining Oxidative Stress

Studies examining broad antioxidant profiles or utilizing omics approaches are increasingly recommended for exercise research (Alu et al., 2022; Menzel et al., 2021; Radom-Aizik & Cooper, 2016). Comprehensive assessment of various antioxidants present within the human body provide a holistic view of the individual's ability to counteract oxidative stress and are standard in the general population. Examples include a study examining antioxidant response to a half marathon in recreational runners (Vassalle et al., 2020) and an omics-based analysis of the response to yoga (Khokhar et al., 2022). These comprehensive and multi-domain studies should be considered for exercise

research in the population with DS because oxidative stress is dynamic, and its effects may evolve over time. Longitudinal studies in people with DS employing omics approaches can enable researchers to track changes in antioxidant profiles arising from increased fitness or other changes resulting from chronic exercise, illustrating the temporal aspects of oxidative stress modulation.

EXERCISE AND MITOCHONDRIAL FUNCTION

Overview of Mitochondrial Dysfunction in Individuals with DS

In general, a prime target of ROS damage is the mitochondria. In DS, deficits in cAMP/PKA-dependent phosphorylation, NADH ubiquinone oxidoreductase, ATP synthase, and adenylate kinase are observed. Additionally, mitochondrial DNA (mtDNA) alterations, ineffective mtDNA repair system, and altered mitochondrial morphology and biogenesis have been demonstrated (Arbuzova et al., 2002; Coskun & Busciglio, 2012; Helguera et al., 2013; Valenti et al., 2010, 2011). Trisomic mitochondrial dysfunction contributes to a general loss of cellular functions that strictly depend on ATP availability (Butterfield et al., 2014; Valenti et al., 2018). These aberrations are pertinent to more than just the metabolic disorder present in DS; they have neuropathological implications. Mitochondrial control region mutations are observed concurrently with AD in general and population with DSs (Coskun et al., 2010). Mitochondrial dysfunction is also considered a trigger for the onset of the AD process in DS (Kim et al., 2000).

Literature shows that exercise can mitigate some pathological mitochondrial changes due to aging (Moreira et al., 2017). Yet, there is a lack of AD studies in all populations using exercise as an intervention on mitochondrial dynamics. However, this

is now feasible with new techniques, such as positron emission tomography (PET) tracers of mitochondrial complex I function that validate rescuing AD dysfunction (Terada et al., 2020). Major biomarkers distinguishing healthy or lesioned mitochondria are found in Table 2.

Table 2. Mitochondrial Function Biomarkers in Individuals with DS.

Biomarker:	Type:	Indicative of:	Effect of Exercise:	References:
fibroblast growth factor-21 (FGF21)	Hepatokine	Metabolic Syndrome	Identified, but not studied.	Chang and Namkung, 2021
growth differentiation factor-15 (GDF15)	Transforming growth factor β cytokine	Metabolic Syndrome	Identified, but not studied.	Chang and Namkung, 2021
angiopoietin-like 6 (ANGPTL6)	Vascular endothelial growth factor	Metabolic Syndrome	Identified, but not studied.	Chang and Namkung, 2021
Thiosulfate	Oxyanion of sulfur	Suppression of electron transport	Identified, but not studied.	Szabo, 2020
Sulfhemoglobin	Irreversible oxidation product of hemoglobin	Suppression of electron transport	Identified, but not studied.	Szabo, 2020
Adenosine	Nucleoside	Neural metabolism	Identified, but not studied.	Patterson, 2009 Gross et al., 2019
Mitovesicle exocytotic secretions	Extracellular vesicle	Mitochondrial function	Identified, but not studied.	D'Acunzo et al., 2021
peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1α,	Protein	increased brain mitochondrial biogenesis	↑	Mollo et al., 2020 Glynn et al., 2008 Kou et al,. 2019

Mitochondrial Biogenesis

The loss of mitochondrial structural and functional integrity is foundational to the neurodegeneration in AD. Mitochondrial dysfunction is also a key facet of DS caused by overexpression of numerous critical oxidative phosphorylation and mitochondrial function genes on the 21st chromosome (Tan et al., 2023). These include NRIP1, RCAN1, CBS, DSCAM, and DYRK1A (Valenti et al., 2010, 2011).

Brain mitochondria biogenesis may be a modifiable pathway that can disrupt AD pathology. This has been demonstrated with an exercise study of the general population showing significant increases in plasma insulin growth factor (IGF-1) in AD patients compared to controls who were older adults without dementia (Stein et al., 2021) IGF-1 is involved in cerebral angiogenesis along with vascular endothelial growth factor (VEGF) which has been linked to mitochondrial biogenesis (Wright et al., 2008). In an exercise study with MCI patients, by Suzuki et al, plasma VEGF was examined, but non-significant effects were observed. However, it is documented that exercise increases plasma VEGF in neurotypical athletes and sedentary individuals (Kraus et al., 2004). Research is needed on the effects of exercise on brain mitochondrial biogenesis in individuals with DS to possibly mitigate the downstream effects of dysfunctional oxidative phosphorylation and mitochondrial control genes.

An angiogenic muscular response to exercise facilitated by VEGF represents a beneficial outcome for overall health; however, within the realm of AD research, investigation into VEGF serves as an essential juncture between nonpharmacological and pharmacological therapeutic approaches. This is due to its capacity to enhance BBB

permeability in mice, potentially improving drug delivery into the brain (Jiang et al., 2014; Sharma et al., 2023). Consequently, there is a compelling rationale to investigate exercise-induced VEGF in individuals with DS since it may contribute to augmenting future AD drug treatments.

Signaling Pathways

Exercise is shown to affect the activity and turnover of mitochondria by increasing peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and mitochondrial transcription factor A (TFAM), serving as evidence of increasing biogenesis (Moreira et al., 2017). TFAM and PGC-1α are both lowered in DS (Lee et al., 2003; Piccoli et al., 2013). PGC-1α is a transcriptional coactivator that plays a key role in regulating the expression of genes involved in mitochondrial biogenesis and function. PGC-1α induced mitochondrial biogenesis may depend on BDNF secretion in response to exercise (Cheng et al., 2012). Research indicates that exercise exerts favorable effects on enhancing mitophagy and boosting proteins involved in mitochondrial function, which together may affect the neurodegenerative process of AD.

Strategies targeting the vulnerable mitochondria in DS show potential for new treatment regimens (Valenti et al., 2018). It has been proposed that stimulating the PGC-1α activity or inhibiting mammalian target of rapamycin (mTOR) signaling could reverse mitochondrial dysfunction in DS, thereby providing evidence for pharmacological targeting of these pathways (Mollo et al., 2020). There are animal studies showing exercise respectively upregulating and attenuating these pathways, and therefore improving mitochondrial dysfunction (Glynn et al., 2008; Kou et al., 2019). Overall,

implementing such strategies may exert protective effects on individuals with DS. Therefore, as physical activity is widely recognized as a protective measure against AD, this can be extended to AD in individuals with DS (Radak et al., 2010).

Tricarboxylic Acid Cycle and Related Metabolic Pathways

Plasma from individuals above the age of 10 with DS has been reported to have abnormal levels of amino acids and Krebs Cycle intermediates, possibly associated with accelerated aging and due to genetic disposition (Caracausi et al., 2018). Increased urinary thiosulfate and circulating sulfhemoglobin levels have been detected in patients with DS (Szabo, 2020). Accumulation of Krebs cycle intermediates in dermal fibroblasts derived from people with DS results from suppression of mitochondrial electron transport in these cells; this is related to the elevated expression cystathionine-beta-synthase and subsequent overproduction of the gaseous transmitter hydrogen sulfide (Panagaki et al., 2019).

Formimidoyltransferase cyclodeaminase (FTCD) is another gene located on the long arm of 21st chromosome, encoding an enzyme that participates in histidine and folate metabolism, both essential for purine, pyrimidines, and amino acids biosynthesis. In addition, aberrant adenosine, homocysteine, and folate metabolism are also observed in adults with DS (Gross et al., 2019; Patterson, 2009).

These numerous energetic pathway intermediates affected in individuals with DS may be ideal targets to elucidate the patterns that underlie the effects of exercise. It has been suggested that physical exercise can improve the metabolic state characteristic in

individuals with DS by inducing increases in the mitochondrial count and structural and functional changes (Pecze et al., 2020).

Bioenergetics in Individuals with DS

With AD in DS, there are increased levels of pyruvic and methyl adipic acids resulting from a shift from aerobic respiration toward less efficient glycolytic and conjunctive fermentative metabolism. This suggests that bioenergetically derived metabolites in the blood could monitor this shift (Gross et al., 2019). Cells of subjects with DS have been shown to exhibit what describe as a pseudo-hypoxic state: cellular metabolic and bio-energetic mechanism alterations resemble the hypoxic cellular response (Pecze et al., 2020). This may be responsible for various functional deficits associated with DS, including reduced exercise disparity, compromised neurocognitive state, and neurodegeneration.

Despite the distinction between pseudo-hypoxia and an actual hypoxic energy-deficient state, exercise may cause mitochondrial and cellular metabolic changes that reduce these functional deficits. There have been exercise studies in which peak oxygen uptake rate and VO_{2max} levels have improved from the naturally low baseline state commonly seen in individuals with DS (Barnhart & Connolly, 2007; Fernhall, 1993). However, a bridge between the pseudo-hypoxic cellular state and implications for the macro-oxygenation system in individuals with DS is yet to be studied.

Mitovesicle Secretions

The novel mitovesicle exocytotic secretions—identified as differing from canonical intracellular mitochondria and extracellular vesicles—are altered in brains of

individuals with DS (D'Acunzo et al., 2021). This pathway of constitutive secretion of mitochondrial vesicles by brain cells is altered in conjunction with mitochondrial dysfunction. Mitochondrial membrane potentials measured in blood cells from individuals with DS are more susceptible to damaging agents than controls (Roat et al., 2007). The DS mouse model this evidence is based upon excludes APP and SOD1 mutations. Therefore, oxidative stress is caused by a pathway alternative to these genetic aberrations, elucidated by decreased mitochondrial membrane potential and other biomarkers (Shukkur et al., 2006). The distinction between oxidative stress and mitochondrial dysfunction pathways allows exercise studies to probe each independently.

Much research has been done on muscle mitochondria, while further studies of changes in neuronal mitochondrial are needed. Emerging data supports adaptations featured by neuronal and glial mitochondria elicited by exercise (Iulita et al., 2016). Studying these changes with exercise protocols in people with DS may elucidate pathway-specific patterns.

EXERCISE AND NEUROINFLAMMATION

Overview of Neuroinflammation in Individuals with DS

Targeting neuroinflammation is a potential therapeutic strategy for combating AD. Amyloid beta is central to AD, and neuroimaging assays can visualize its deposition, though there are complex molecular pathways involved in amyloid beta pathology. In order to complement a number of neuroimaging exercise studies in people with DS, there is a critical need for blood-based biomarker explorations of anti-neuroinflammatory

pathways via exercise-induced neurotrophic factors (Nay et al., 2021; Parrini et al., 2017) and signaling and crosstalk pathways (Green et al., 2021; Sleiman et al., 2016).

Changes in the innate immune system and neuroinflammation are early characteristics shared by both DS and AD that potentially impact the clinical presentation of cognitive deterioration (Ahmed et al., 2021). This neuroinflammatory profile develops throughout the lifespan in individuals with DS (Flores-Aguilar et al., 2020). These insights are crucial for identifying stage-specific anti-inflammatory exercise trials aimed at AD. Major neuroinflammatory biomarkers are listed in Table 3.

Table 3. Inflammatory Biomarkers in Individuals with DS or Metabolic Syndrome.

Biomarker:	Type:	Indicative of:	Effect of Exercise:	References:
C-reactive protein (CRP)	Protein	Systemic inflammation	↓	Alizaei Yousefabadi et al., 2021
TNF-α	Proinflammatory cytokine	Neuroinflammation	↓	Alizaei Yousefabadi et al., 2021
BDNF	Neurotrophin	Anti-neuroinflammation	↑	Salimi Avansar, 2017 Szuhany et al., 2015
Interleukin 8 (IL-8)	Proinflammatory cytokine	AD pathogenesis	↓	Alizaei Yousefabadi et al., 2021
Interleukin 10 (IL-10)	Proinflammatory cytokine	AD pathogenesis	↓	Alizaei Yousefabadi et al., 2021

Neuroinflammatory Biomarkers

Alterations in the metalloproteases (MMP) and neuroinflammatory mediators are seen in DS. Whether in symptomatic or asymptomatic AD stages, the plasma of

individuals with DS displays increased levels of inflammatory molecules including neurotrophin nerve growth factor (proNGF), MMP-1, MMP-3, MMP-9, tumor necrosis factor alpha (TNF-α), and interleukins (IL) 6 and 10 (Iulita et al., 2016).

Young adults with DS have been found to have elevated inflammatory cytokines, C-reactive protein (CRP), and increased expression of a gene known as triggering receptor expressed on myeloid cells-2 (TREM2) (Weber et al., 2020), all of which are associated with increased AD risk (Hegazy et al., 2022; Rani et al., 2022). IL-6, VEGF-A, MCP-1, IL-22, and TNF-a are documented as elevated in adults with DS (Sullivan et al., 2017). TNF-a and IL-6 may represent biomarkers that specifically reflect the neuropathology of DS (Zaki et al., 2017). These numerous molecules can serve individually or as a panel, indicating changes in oxidative state in response to exercise.

The Role of Brain Derived Neurotrophic Factor in Neuroinflammation

Aggravated inflammatory signaling cascades, and a general proinflammatory state is seen in DS. Brain-derived neurotrophic factor (BDNF) signaling represents a potentially new pharmacological target in humans, particularly for treatments aimed at ameliorating cognitive issues in patients with DS (Parrini et al., 2017). BDNF can serve as a potential biomarker for changes in neuroinflammation pathways as it can be efficiently sampled from blood samples. In a study using specific protocols to measure blood leaving the human brain, exercise increased the amount of BDNF released after three months of endurance training in healthy sedentary neurotypical adults compared to controls (Seifert et al., 2010). Another study found 6 months of a strong exercise prescription of 90 minutes per day twice per week to reveal a significant association

between BDNF and the Alzheimer's Disease Assessment Scale-Cognitive subscale in elderly patients with MCI (ADAS-cog) (T. Suzuki et al., 2013). Patients of the same demographic showed significant improvements in plasma BDNF and cognition from a thrice-weekly Tai Chi exercise routine for six months (Sungkarat et al., 2018).

BDNF has a wide array of proposed functions in the brain, and its expression is reduced in DS and AD (Dogliotti et al., 2010; Peng et al., 2005). BDNF is a significant biomarker because its decline precedes the decline in choline acetyltransferase activity in AD and is correlated with cognitive function (Peng et al., 2005). In mice models of DS, cholinergic neurons are pathologically compromised, yet this decline can be attenuated by the expression of neurotrophic factors such as BDNF (Lockrow et al., 2012). Several studies demonstrate a link between exercise and increased BDNF expression in humans and animal models (N. Berchtold et al., 2005; N. C. Berchtold et al., 2010; H. Liu et al., 2011; Y. F. Liu et al., 2008; Nichol et al., 2009). In children and teenagers with DS, BDNF expression is often elevated; however, at later ages, a striking drop in peripheral BDNF is observed (Dogliotti et al., 2010). This age-dependent expression pattern may reflect presymptomatic AD progression, as Aβ levels are known to already be elevated in children and adolescents with DS (Mehta et al., 2007). Future exercise protocols examining BDNF levels will need to account for this unique trend within population with DS.

Examining individuals with metabolic syndrome in studies may act as a proxy to enhance our comprehension of exercise-induced anti-inflammatory effects in those with DS; nevertheless, further research is essential to validate this connection. Individuals with

metabolic syndrome undergoing eight weeks of interval training combined with curcumin consumption had significantly reduced inflammatory factors and increased BDNF expression (Avansar, 2017). A meta-analysis also illustrated the effects of exercise on BDNF (Szuhany et al., 2015). This consistency underscores the therapeutic potential of exercise interventions on neuroinflammation.

Studies have shown that BDNF can be increased in an exercise-dependent manner in both older individuals with MCI and healthy younger adults particularly with high-intensity interval training (HIIT) (Coetsee & Terblanche, 2017; Robinson et al., 2018). Research sufficiently demonstrates a single bout of exercise can increase BDNF secretion from the brain (Rasmussen et al., 2009), in addition to still being continually released after three months of endurance training (Seifert et al., 2010).

In a study examining BDNF levels, physical activity was moderately correlated with plasma BDNF, and acute aerobic exercise significantly increased plasma BDNF in late onset AD patients (Coelho et al., 2014). In lengthened studies, plasma BDNF significantly increased over four months of aerobic training in the MCI group compared to the control group (Nascimento et al., 2014). In a six-month intervention with amnestic MCI participants, aerobic exercise increased plasma BDNF levels in men but not in women compared to the control group. One year of moderately intense aerobic exercise was shown to increase the hippocampal volume and the plasma concentration of BDNF in older healthy subjects (Erickson et al., 2011).

Conversely, in another six-month intervention with vascular cognitive impairment, participants reported BDNF improvements but increased in women while

decreased in men (Barha et al., 2017). One year of moderately intense aerobic exercise was shown to improve the volume of the hippocampus and the plasma concentration of BDNF in elderly general population patients with AD (Coelho et al., 2014). Future research may be assisted by the notion that BDNF expression is dose-dependent; the duration and intensity of exercise affect the BDNF response level (Szuhany et al., 2015).

The evidence for the effects of exercise varies widely across the biomarkers measured, suggesting exercise affects multiple physiological systems and with differing impacts. The changes associated with biomarkers such as BDNF for individuals with AD/MCI supports the notion of physical activity promoting brain health. Further investigations are required to identify appropriate protocols for AD-DS.

It should be acknowledged that BDNF released by human skeletal muscle in response to exercise remains localized to the muscle cells. Therefore, muscle-derived BDNF is not released into circulation (Matthews et al., 2009). This suggests that neuroinflammatory improvements are either due to BDNF directly released in the brain or an indirect muscle-BDNF axis (Nay et al., 2021). With the ease of modifying BDNF via exercise, research is needed to elucidate changes in the neuroinflammatory-BDNF axis in AD-DS.

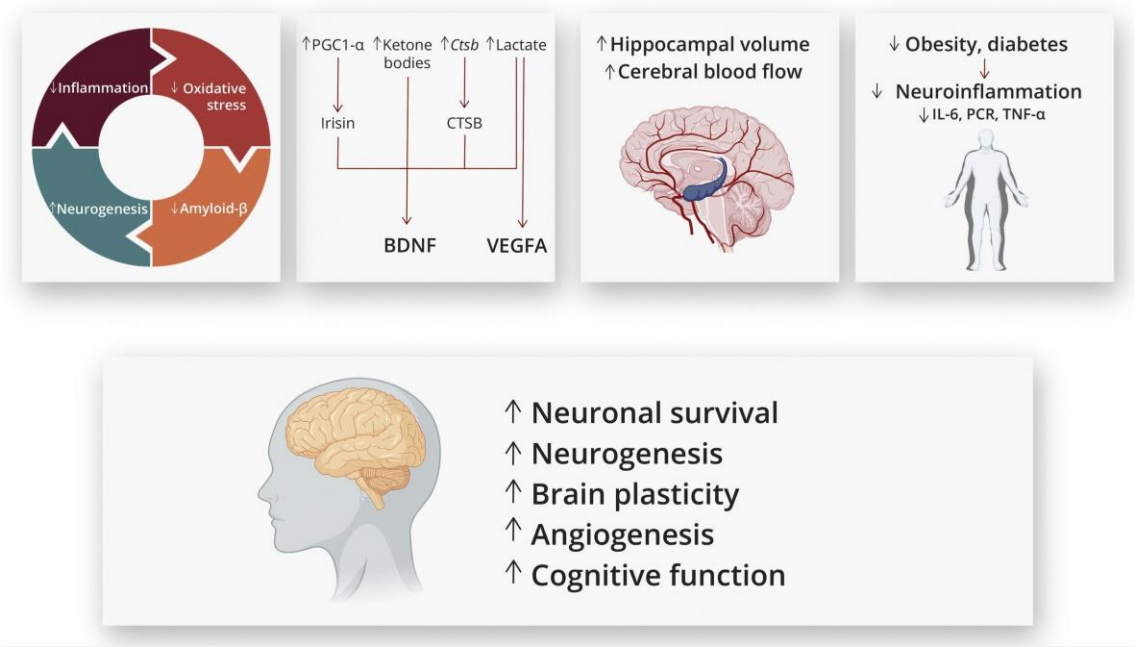

Figure 2. Summary of BDNF and Related Pathways. Homeostatic biomolecules including growth factors and neurotrophins have secondary effects on neuroinflammation. Additionally, diet- and exercise-mediated molecules such as irisin and ketone bodies can augment neuroinflammation (Valenzuela et al., 2020).

Ketone Bodies Anti-neuroinflammatory Effects

Ketone bodies, namely β-hydroxybutyrate and acetoacetate, are produced during prolonged exercise and utilized by muscle during exercise (Féry & Balasse, 1986, 1988). Ketone bodies released into the bloodstream traverse the blood-brain barrier and initiate BDNF production (Sleiman et al., 2016). Even with sufficient glucose supply, which would normally inhibit ketogenic pathways, this holds true (Hu et al., 2018). This discovery is intriguing as it establishes a link between ketone bodies and the anti-neuroinflammatory properties of BDNF.

In a neuroimaging study, the induction of ketosis in both ketogenic diet and ketone supplementation scenarios can foster greater stability within brain networks, promoting brain activity and cognitive acuity (Mujica-Parodi et al., 2020). This provides further evidence to the neuroprotective influence of exercise-induced ketone production. However, these findings may be tempered by the heightened prevalence of diabetes in individuals with DS, manifesting with sustained hyperinsulinemia that has the potential to impede glucagon-mediated ketogenesis (Alberti et al., 1978).

Myokines and Muscle Organ Crosstalk

Lactate is proposed to be examined in a future AD studies study as a potential biomarker because it is well documented as a mediator of the signaling pathways of BDNF expression that are responsible for anti-neuroinflammation (Green et al., 2021; Valenzuela et al., 2020). Myokines cathepsin B (CTSB) and irisin are also potential exercise-induced mediators of BDNF (Moon et al., 2016; Wrann et al., 2013). Irisin may mediate signaling between skeletal muscle and the brain and, therefore, may in part be responsible for exercise benefits in the brain.

PGC-1alpha is also involved with BDNF signaling and is shown to be an exercise-induced regulator of kynurenine's ability to cross the blood-brain barrier (BBB) and induce neuroinflammation (Irrcher et al., 2003; Cervenka et al., 2017; Agudelo et al., 2014). Dysregulation of the kynurenine pathway promotes neuroinflammation which can be converted into a metabolite unable to cross the BBB through exercise; this process can be plausibly examined in the domain of AD research (Agudelo et al., 2014; Cervenka et al., 2017; Mithaiwala et al., 2021; Valente-Silva & Ruas, 2017).

Cytokines and Acute-Phase Proteins

Exercise training has shown to improve inflammatory biomarkers in individuals with metabolic syndrome, including TNF-α, CRP, IL-8, and IL-10; resistance exercise may be optimal for these individuals (Alizaei Yousefabadi et al., 2021). Since metabolic syndrome is frequently seen in individuals with DS, neuroinflammatory improvements may occur with exercise intervention in this population.

IL-6, a proinflammatory cytokine implicated in late onset AD pathogenesis (Cojocaru et al., 2011), correlates with severity of dementia in AD-DS (Kálmán et al., 1997). It has been significantly reduced in response to aerobic exercise in several studies on AD patients within the general population. These studies also demonstrated a reduction of plasma and serum TNF-α (Abd El-Kader & Al-Jiffri, 2016; Nascimento et al., 2014).

Previously described as a proinflammatory cytokine affecting several neuropathologies (Rothaug et al., 2016), IL-6 is produced by contracting muscles and released into the blood (Pedersen & Fischer, 2007). New research shows that IL-6 may play a role in inducing a systemic anti-inflammatory response to exercise, designating it a myokine (Muñoz-Cánoves et al., 2013; Pedersen & Fischer, 2007). Increased IL-6 concentration in plasma is followed by increases in well-known anti-inflammatory cytokines such as IL-1ra and IL-10 (Ostrowski et al., 1999, 2000). IL-6 likely may be able to cross the BBB (Banks et al., 1994). The trans-signaling properties of IL-6 allow it to function as proinflammatory or anti-inflammatory depending on the signaling mode

(Scheller et al., 2011). This multifaceted characterization makes IL-6 both a target and biomarker.

Aβ

Returning to neuroimaging, the literature points toward exercise being a nonpharmacological treatment for AD pathology because it may reduce common AD biomarkers such as Aβ load (Tokgöz & Claassen, 2021). Studies in people with DS have linked moderate-to-vigorous physical activity effects to shifting hallmark AD neuroimaging markers (Fleming et al., 2021; Peven et al., 2022).

Besides being recognized as one of the hallmark biomarkers associated with AD, Aβ is correlated to the trajectory of neuroinflammation (Ismail et al., 2020). A controlled trial with MCI patients found that the mean plasma levels of Aβ42 decreased in the aerobic exercise group while increasing in the control group (Baker et al., 2010). Although not statistically significant, another four-month high intensity exercise intervention showed decreases in the Aβ42/Aβ40 ratio in a mixed group of MCI and cognitively healthy participants (Baker et al., 2012). In older adults with MCI, CSF phosphorylated tau significantly fell after six months of aerobic exercise (Baker et al., 2015).

Although previously only supported with transgenic mice models, newer studies reflect that exercise provides an abundance of research points on neuroinflammatory processes. The effects of exercise vary widely across the biomarkers measured, suggesting exercise both affects multiple physiological systems and with different

impact. This is critical for people with DS because neuroinflammation may result from multiple sources.

Within the hallmark AD biomarkers, exercise has been shown to have substantial effects. Physical activity meeting the guidelines designated by the American Heart Association has been shown to reduce the levels of AD-associated biomarkers neurotypical adults, including amyloid measured in the brain by positron emission tomography PET scans using Pittsburgh compound-B (PiB) and levels of phosphorylated tau in the cerebrospinal fluid (CSF) of cognitively normal older adults (Liang et al., 2010).

Complement Dysregulation

The role of exercise in anti-inflammation has been demonstrated in the general population with increases in the chaperone protein, clusterin, and reductions of the complement immune pathway in response to long-term training (De Miguel et al., 2021). Clusterin is seen to accumulate with Aβ lesions; the chaperone protein is proposed to affect the Aβ aggregation and neuroinflammatory processes (Fareed et al., 2022).

Anomalies of the complement system in DS is potentially indicative of a state of immune dysregulation. This suggests the utility of clusterin as a measure for identifying inflammatory events in individuals with DS. Within this population, the disparities in complement biomarkers between those with and without clinical AD may offer diagnostic and predictive value (Veteleanu et al., 2023).

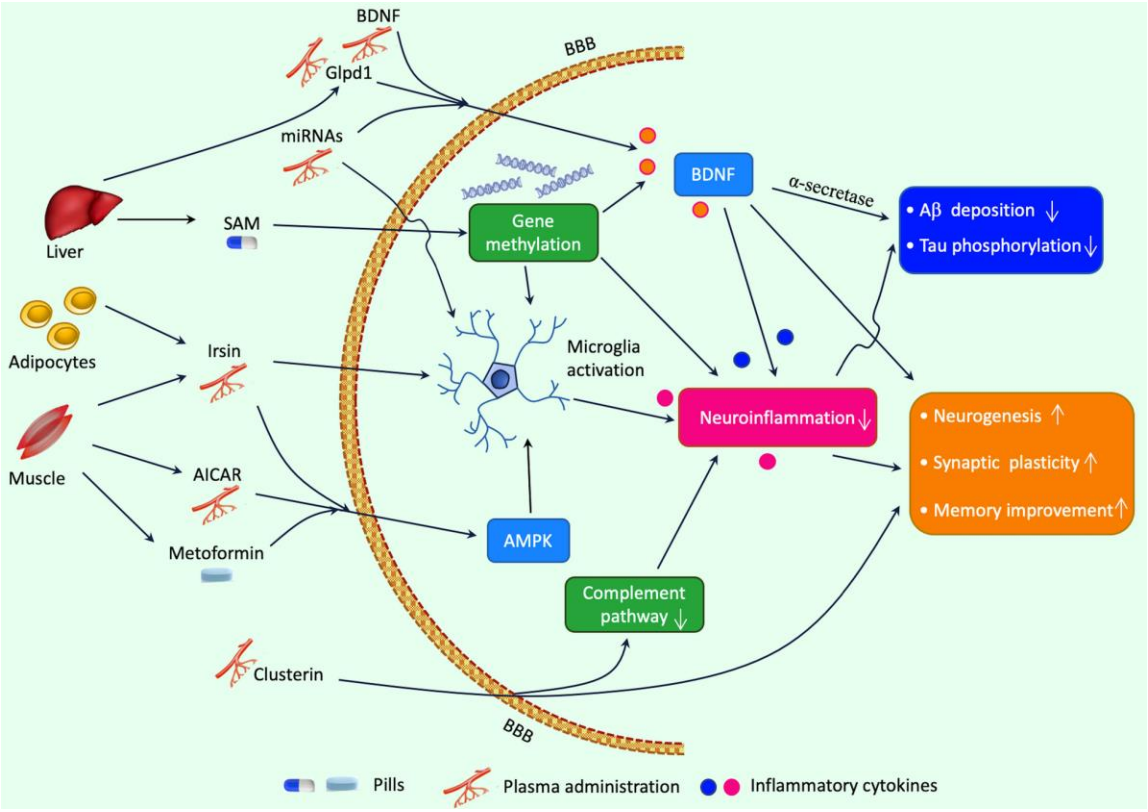

Figure 3. Junction of immune and neural pathways involved in neuroinflammation. Numerous pathways play roles against neuroinflammation. These pathways range from immune-based to nucleic acids. (Zhao, 2024).

Membrane-spanning Pattern Recognition Proteins

Toll-like receptor-8 (TLR)-8 expression is correlated to aggravated neuroinflammation (Brea et al., 2011) and CNS pathologies (Buchanan et al., 2010). Several microRNAs (miRNAs), including miRNA-21 and miRNA-155 have a role in regulating TLR signaling and inflammation and were upregulated in TLR-associated inflammatory conditions (O'Connell et al., 2007; Sheedy et al., 2010). Preclinical development of a miRNA-155 antagonist is underway to treat neuroinflammation (Gao et al., 2017), displaying the opportunity that TLR pathways may pose for future research.

Both acute aerobic and chronic resistance exercise decreased monocyte cell-surface expression of TLRs (Lancaster et al., 2005; Simpson et al., 2009; Stewart et al., 2005). The exercise-induced regulation of TLR expression may mediate these anti-inflammatory effects (Collao et al., 2020), and over the long term, reduce whole-body chronic inflammation (Gleeson et al., 2006). TLRs participate in the inflammatory response of AD pathology (Landreth & Reed-Geaghan, 2009; Minoretti et al., 2006; Walter et al., 2007) and future research is needed to identify if these systemic effects of exercise can be observed in the brain.

Exercise Eliciting a Systemic Pro- or Anti-inflammatory Response

In humans, acute, unaccustomed exercise can increase oxidative stress thus acting as a proinflammatory stimulus (Powers et al., 2011; K. Suzuki, 2018), however, this response is attenuated when exercise is performed regularly and may upregulate an endogenous systemic anti-inflammatory response (McGeer & McGeer, 1995). Extensive cohort studies on elderly neurotypical adults indicate that higher physical activity levels are inversely associated with inflammatory biomarkers, for instance, C-reactive protein (CRP) (Geffken et al., 2001; Wannamethee et al., 2002). Meta-analytical evidence suggests that regular physical exercise can reduce inflammation-related biomarkers (e.g., CRP, TNF-α) in healthy middle-aged and older adults (Monteiro-Junior et al., 2018; Sobol et al., 2016) along with individuals with cognitive impairment (Nascimento et al., 2014).

Exercise is universally regarded as beneficial, but scrutiny must be given to assess the safety, weigh the cognitive benefit, and pair or contrast exercise with standard drug

treatments for late onset AD (Ströhle et al., 2015). Special considerations such as these criteria have begun; in a study comparing the effects of exercise to the effects of cholinesterase inhibitors and memantine, exercise had a more substantial pooled effect than the medications for late onset AD (Hoffmann et al., 2016). A systematic review with meta-analysis found six randomized controlled exercise trials that demonstrated a decreased rate of cognitive decline and positive impact on cognitive function in AD patients (Farina et al., 2014).

DISCUSSION

Interpretive Summary

Exercise holds promise as a non-pharmacological intervention for AD, with potential benefits extending to individuals with DS. The evidence that exercise mitigates oxidative stress in people with DS and its potential in unexamined territories including mitochondrial function and neuroinflammation underscores the need for comprehensive exercise studies. Furthermore, there exists a paucity of longitudinal exercise studies in this population. Biomarkers well-suited for future clinical trials can contribute to a deeper understanding of the role of exercise in preventing or ameliorating AD.

To support neuroimaging exercise studies, there exists an urgent call for blood-based biomarker explorations into exercise-induced neurotrophic factors and signaling pathways aimed at mitigating neuroinflammation.

Mitochondrial dysfunction either resulting from or contributing to AD pathology is an overlooked path in research. There are modifiable protein products of mitochondrial function genes. These are of great significance because numerous mitochondrial and

oxidative phosphorylation genes are disrupted due to trisomy 21. Additionally, mitochondrial biogenesis pathway analysis using exercise interventions could lead to breakthroughs in conjunctive AD drug therapies.

Finally, current research predominantly revolves around oxidative stress biomarkers in individuals with DS. To broaden this area of research, we consider novel avenues for investigating exercise responses, such as lipidomics or analyzing microRNAs and oxidized nucleic acids. Data from future trials could optimize exercise prescriptions by quantifying ideal duration, frequency, and intensity, thus paving the way for comprehension of exercise-induced neuroprotective mechanisms in people with DS.

With the framework presented and ongoing research already being conducted, parallels should begin to be drawn between AD research and the advances of the last half century in cardiac biomarkers that became components of diagnosis, intervention and treatment. As people with DS are susceptible to both cardiac and neurological conditions, there is room for major breakthroughs in the neurological aspects for this population. With these advances, the general population will benefit as well.

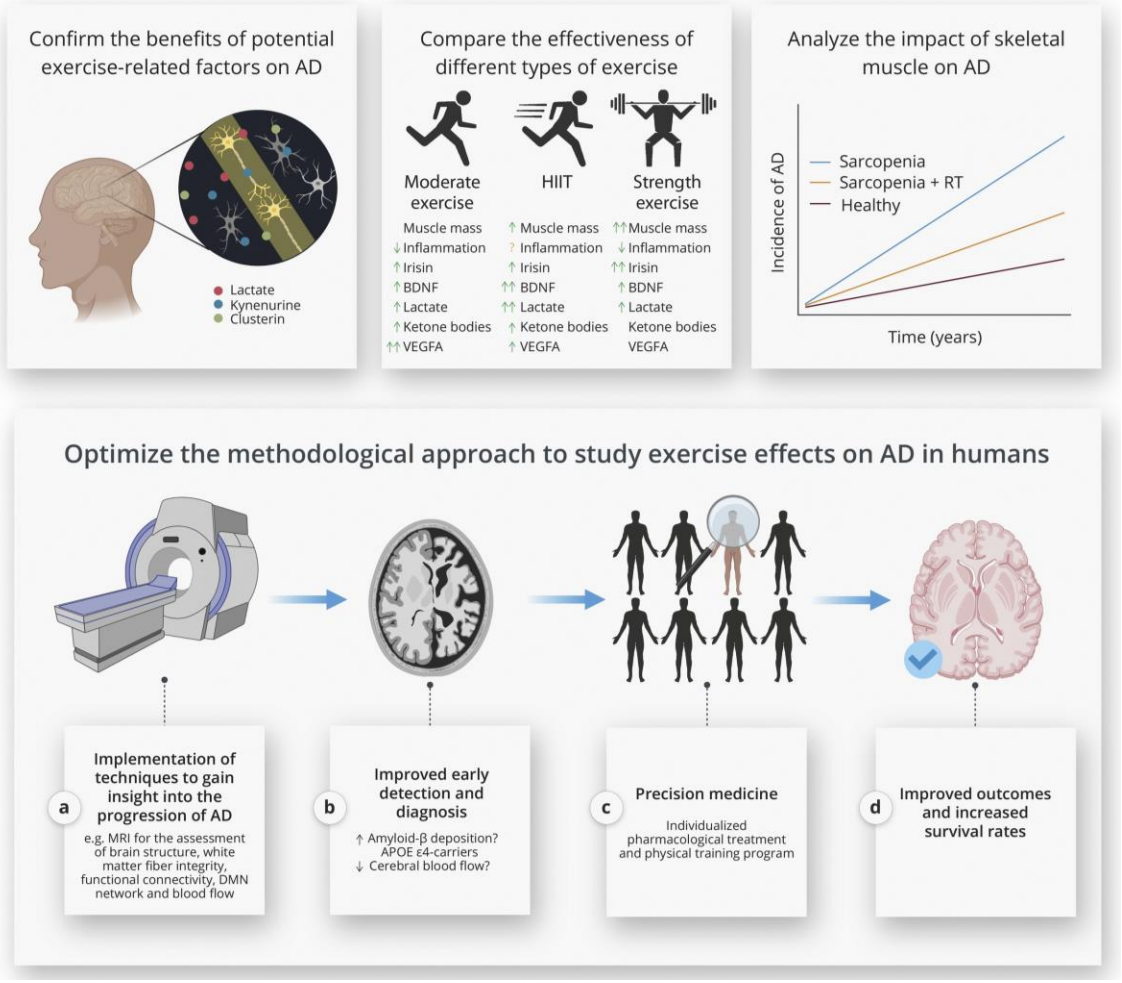

Figure 4. Summary of Framework for Future Research. The susceptibility of people with DS to AD necessitates medical research based in exercise science due to the ease of intervention. Exercise studies can fine tune the physical activity type, dose, and frequency in addition to providing insights about the underlying molecular pathways that may lead to greater understanding of AD pathology (Valenzuela et al., 2020).

Future Approaches for Exercise Trials

Neuroimmune Cell Roles on Exercise-Mediated Processes

Immune modulation is known to play a role in learning and memory (Yirmiya & Goshen, 2011) and this has already been viewed in the field from an exercise perspective (Loprinzi, 2019). The link between glial and astrocyte roles on the responsiveness of neurons to inflammatory cytokines such as IL-1, Il-6, and TNF-α and molecules including prostaglandins and neurotrophins requires investigation in physical activity trials in people with DS.

Changes in the Brain Insulin Pathway Induced by Exercise

With the observed differences in age-dependent glucose hypometabolism or hypermetabolism in DS, exercise poses itself as a useful interventional tool. Within the general population, six months of training has been shown to improve cognitive function and insulin sensitivity in older glucose-intolerant adults in a small randomized controlled trial (Lautenschlager et al., 2008).

With parallels frequently drawn between AD pathology and insulin dysregulation, larger-scale studies and further examination is needed to determine if the aforementioned results are due to shifts in the periphery, the brain, or a combination of the two. The extension of this research to the unique glucose metabolic trajectory in DS neuropathology can give further credence toward the hypothesis of compensatory mechanisms that may underly DS hypermetabolism (Head et al., 2007).

Unique Opportunities at Discrete Age Ranges

Different age groups may have superior responses to specific types of training. This may be due to perceived benefit from the style of exercise. However, it is also likely that exercise protocols will produce differential effects on biomarkers depending on the age group studied. This will exclusively result from the metabolic condition that changes over the lifetime of an individual with DS as part of the typical accelerated aging, metabolic changes, and degree of neuropathological progression (Alaama et al., 2015). For instance, exercise protocols that induce greater anti-neuroinflammatory effects may suit younger individuals as ROS, and concurrent oxidizing processes of DS are already proceeding at youth.

As a second example, physical activity that activates neurotrophin or clusterin expression may be best for young adults with DS to potentially augment amyloid accumulation that starts at this age range. Future trials should identify the most age-appropriate interventions for the population with DS regarding physiological and behavioral divergences.

Age-Specific Longitudinal Exercise Studies

Longitudinal studies that track the progression of a group of individuals from one age range to the next may provide distinct results. An exercise protocol that trains individuals with DS for greater confidence in physical ability, psychological attachment to an activity, and physiological gains that bleed into their next phase of life may equip these participants for enhanced results. Proprioceptive and balance-demanding activities

that enhance motor development and strength in youth, for example, may elevate the potential for changes in exercise-induced biomarkers years later. Conversely, a typical trend among novice exercisers in the general population is that they are subject to substantial fitness gains after commencing a new training routine, while experienced athletes lack this (Coffey & Hawley, 2017).

Whether this athletic priming that negates quick improvements exists in DS has not yet been studied. Future trials can answer this question while focusing on identifying potential amplification of the biomarkers that indicate staving off pathological oxidative, mitochondrial, or inflammatory processes. This may be especially beneficial for older participants, as preceding strength and flexibility training in their middle-ages can provide confidence in physical ability and longevity of motor independence.

Exercise research on individuals with DS over the age of 40 is lacking. Studies of ultra-endurance activities have shown that interesting endurance improvements may occur over the age of 40 in the general population (Lepers et al., 2013; Lepers & Stapley, 2016). A deeper endurance understanding in the population with DS may translate better AD-DS exercise protocols in older individuals. Allowing a more significant number of older individuals with DS to participate in robust exercise studies safely can be beneficial to the field.

Circumventing Abnormal Sympathovagal Imbalance in DS

The population with DS is subject to abnormal catecholamine response and sympathovagal imbalance, leading to lower exercise capacity. This, in part, may explain

the sedentary lifestyle often seen in the population with DS. Additionally, this imbalance may reduce long-term adherence to physical activity; this could be an obstacle for longitudinal studies.

Studies have indicated that exercise training can improve this dysfunction in people with DS by increasing parasympathetic modulation (Giagkoudaki et al., 2010). Therefore, the solution to this physiological issue lies with exercise itself to overcome the naturally diminished capacity. Both strength and endurance training are known to enhance the ability of the brain and body to work for extended periods (Aagaard & Andersen, 2010; Hughes et al., 2018).

Exercise interventions must account for ways to circumvent this obstacle. This may enrich the health of the population with DS as a whole and yield more consistent results by avoiding participant attrition for each workout session and over the course of entire studies.

Endurance Training

It has been suggested that endurance training may directly affect the brain more than other types of training though animal studies (Lan et al., 2018; Nokia et al., 2016). It is known that endurance activity increases vascularization in muscles with the generation of capillary beds (Shono et al., 2002). This coincides with subcellular modifications, including increases in the mitochondrial count and oxygenation efficiency; alterations in cerebral structure have also been identified (Colcombe et al., 2003, 2006). In comparison, cognitive improvements from exercise training are thought to be associated with changes

in cerebral blood flow (Endres et al., 2003; Sawyer et al., 2014; Swain et al., 2003). Although cerebral circulation modification may be a potential explanation for improvements of brain health for cognitively normal individuals who perform endurance training, enhanced vascular health alone cannot overcome amyloid and tau pathologies. Therefore, the neurotrophic stimulation pathway must be further examined with rigid protocols for quantifying results in the population with DS.

High-Intensity Training Modalities

There are numerous anaerobic workouts, with the HIIT method being a popular example with short bursts of high intensity, and occasionally, the extreme nature of regimen. Microdialysis trials on acute exercise in animals have demonstrated neurotransmitter increases in the brainstem and hypothalamus (Meeusen et al., 2001). In contrast, chronic exercise shows different regional pattern (Meeusen et al., 1997). In general, exercise-induced catecholamine turnover in the brain is supported in animal and human studies (Dienstbier, 1989; McMorris et al., 2009).

Greater challenge and exertion are correlated with increased catecholamine levels (Tomporowski, 1997). In one study, the most prominent acute increase of catecholamines was found to coincide with the greatest BDNF release resulting from intense sprint training (Winter et al., 2007). Longitudinal trials focused on anti-neuroinflammation can examine if this short-term BDNF response consistently remains as sharp with high-intensity anaerobic activity.

Lactate may augment BDNF expression and blood lactate concentrations are correlated with perceived exertion levels during physical activity (Borg et al., 1987). These findings together serve as an indicator that physical effort might correspond with the level of BDNF-mediated reduction of inflammation. Also, it is feasible that the variation of catecholamine release may modify this neurotrophin response. Deeper investigations into high-intensity training can inform exercise protocols seeking to achieve the most potent anti-inflammatory response in the population with DS.

The Muscle-Brain Connection on Anti-Inflammatory Pathways

The myokines irisin and kynurenine, and a principal metabolic byproduct, lactate, participate in a muscle-brain axis that reduces inflammation by playing a role in the BDNF secretory pathway. With the fact that several exercise-induced molecules which are produced peripherally can cross the BBB, further investigation is needed to evaluate their influence on AD pathological processes.

Since muscle tissue is the facilitator of these pathways, trials could assess if increased muscle mass in the short-term or enhanced muscular endurance via mitochondrial and vasculature remodeling can boost these anti-inflammatory effects in the longer term. This is a critical issue; endurance training is known to reduce muscle mass (Knechtle & Nikolaidis, 2018; Lebus et al., 2010). If lower levels of inflammation can be yielded with increases of muscle tissue or hypertrophy, then training protocols should reflect this.

Significant Differences Within Modalities

In addition to the contrast between endurance and resistance training, specific routines within these modalities should be scrutinized. Exercise knowledge can inform efficient and safe routines for individuals with DS. Individuals in this population commonly have physical characteristics such as hyperflexibility and reduced muscle tone. Quantified examination and proof-of-concept trials have not yet been done to determine exercise effectiveness for the common DS body type.

Much scientific effort has poured into finding the optimum activity for weight loss, muscle toning, endurance, and elite athletic performance in the general population. Similarly, precise crafting and standardization should be undertaken for neuropathology studies attempting to elicit an accurate change in oxidant state, mitochondria, or inflammation in AD or AD-DS confines.

Within resistance training, there lies a range of schemes such as powerlifting, functional training, or hypertrophy training with documented variations in physiological outcomes. Additionally, crossovers between resistance and endurance such as rowing, or circuit training should be considered in future trials. For endurance training, there are major differences in terms of body composition, immune system, and inflammatory marker responses such as among walking, jogging, sprinting, skating, cycling, swimming, and long-distance running (H. Carter et al., 2000; King et al., 2003; Liberman et al., 2017; Nieman et al., 2014; Snyder et al., 1993).

Even without regarding the personal preference that participants may have for an activity, a priority in designing trials must be the feasibility for scientific inquiry

depending on the exercise modality and the appreciable potential for AD-DS biomarker outcomes. Additionally, it is essential to consider that oxidative stress and inflammatory biomarkers vary considerably in healthy populations.

Group Training

Just as compound weightlifting exercises cause entirely different systemic, hormonal, and fitness changes compared to isolated muscle exercises, fitness routines that are practiced in a group setting will have different results than individual activities. Stress reducing effects have been reported in a group workout setting (Stults-Kolehmainen & Sinha, 2014). There are also psychological and neuroscience data that explain better performance in team settings resulting from interpersonal synchrony, enhanced social connection, and changes in pain perception (Bingel et al., 2011; Eisenberger et al., 2011; Miles et al., 2010).

Group training can be a uniquely effective exercise method for individuals with DS. The synergistic impact of group training, be it through family or a group of friends, may elevate overall physical activity levels. This is evident in research revealing no significant difference in exercise levels among siblings comprised of at least one individual with DS (Whitt-Glover et al., 2006). This is noteworthy given that individuals with DS are predisposed to suboptimal activity levels (Phillips & Holland, 2011). Tailoring physical activity routines to individuals with DS, particularly through group training, can be advantageous in addressing physiological and motivational challenges in order to elicit maximal changes in AD markers.

One example of strength changes in young adults with DS suggests Taekwondo, typically practiced in a group fashion, leads to physical function and independence benefits (K. Carter & Horvat, 2016). Another group activity, soccer, provided motor and psychosocial improvements compared to the control group (Perić et al., 2022). The DSFit pilot study examined the feasibility of a customized exercise program for this population with positive implications (Hojlo et al., 2022).

Maintaining an active lifestyle in individuals with DS may have positive outcomes in their daily lives (Chen et al., 2014). Therefore, the motivational and social aspects of group training may enhance long-term adherence to exercise regimens and the benefits of exercise itself. These findings emphasize the need for examining various group training regimens within methodical biomarker protocols for AD in individuals with DS (AD-DS).

Given the importance of supervision, emotional support, and exercise satisfaction to protocol adherence in the neurotypical population (Firth et al., 2018; Fleig et al., 2011; Jordan et al., 2010), the benefits of group or team-based exercise merits more study in the population with DS. A Judo trial in DS produced interesting preliminary results and warrants further exploration (Aguiar et al., 2008). The intersection of neuropsychology and exercise leads to the notion of considering differences in the competitiveness, social components, and performance elements of physical activities, which may cause measurable changes in biomarker responses, or crucially, promote longitudinal adherence.

Facilitating Exercise Studies in Adults with DS

The current research describing the effects of exercise on neuropathology is encouraging. With the myriad of biomarkers available to yield data, consistent results across future trials can be obtained through rigorously designed randomized controlled trials. We propose a multidisciplinary approach to investigating the role of exercise, beginning with a proof of concept to determine the dose of exercise for people with DS. This includes precise exercise modality, intensity, duration, frequency, and environment.

The physical activity parameters must be treated as a prescription, and due to the inherent variability of each workout, must be designed with standards to promote quantifiable results. The type of physical activity is critical to consider as individuals with DS have high attrition with exercise programs (Aleksander-Szymanowicz et al., 2014; Eberhard et al., 1997; Jobling et al., 2006). Adherence to the program can be increased by utilizing interactive workout programs.

Difficulty with Methodological Rigor

Exercise protocols should be standardized with the same rigor as pharmacological treatments. Yet, it is challenging to quantify facets of exercise. For instance, the effort given in weightlifting can only be partially quantified by the number of repetitions completed; this measure lacks full insight into the exertion level of the participant. Achieving consistency with an outwardly subjective measure, such as exertion, can be done by favoring the upper boundaries of this measure. This contrasts with attempting to

standardize a 50% or 80% maximal repetition effort in an exercise protocol, which are common parameters in weightlifting and running regimens.

Yet, monitoring and enforcing exertion toward the upper bounds through human raters or digital feedback is impractical, especially with larger trials. As previously described, an increased effort of an exercise may neurologically strengthen anti-inflammatory responses in the short-term. This issue could be mitigated, for example, by using weights appropriate to each participant's baseline strength level or establishing baseline cardiovascular stamina to ensure the exertion is standard among participants. If omics-level precision of outcome measures is to be employed with AD-DS biomarker studies, the dose of exercise must be tightly controlled.

Standardization of Exercise Dosage Through Urgency in Training

Emerging concepts at the intersection of neuroscience and exercise physiology can lessen the difficulties of these trials and improve the potential to attain outcome measures. A way to close in on reaching the safe limits of effort can be through utilizing natural forces. Gravity provides a common challenge to humans, and maintaining equilibrium is a constant subconscious battle. The repercussions for not maximizing focus and stabilization are dire and unmistakable in sports such as surfing or gymnastics. In these high-stakes sports, rapid cerebellar adaptions in movement are required to adapt the body position seamlessly.

The physical demands likely increase catecholamine release in the brain and objectively requires greater muscle recruitment. This higher exertion has neurological

implications, possibly affecting the BDNF pathway, mitochondrial signaling or remodeling, or changes within oxidant conditions. Consistently responding to novel or consistently strong physical stressors may provide more precise results in a longitudinal trial.

The principles of intense sports can be extrapolated to exercise trials for individuals with DS, which do not necessitate such dire circumstances. For the average exerciser performing novel activities, such as a child learning to ride a bicycle or an adult learning to surf, the challenge of stability is brought to conscious awareness. Therefore, instead of stationary cycling, for example, researchers should exploit the minor urgency present in outdoor cycling that will motivate participants toward maximal effort and increase autonomic arousal.

An even safer instance to be utilized in exercise in DS trials may include activities like dance in a facility with cushioned floors. The proprioceptive feedback task is still imposed upon all participants, with maximized intrinsic exertion and less risk of injury or fear.

Strict regulation of exercise has not been accomplished across exercise in DS studies, and physiological changes can be measured to confirm optimization of workouts, including blood pressure, VO2 max, and body fat changes. These may serve as surrogate markers for rating the level of physical activity, as there are other subjective variables like the expertise of the exercise instructor. With the introduction of tight regulation on the exercise dosage, future trials could be run with concomitant treatments to study synergistic changes on AD biomarkers.

Martial Arts and Elements for a Successful Exercise Protocol

Martial arts styles often consist of a mix of mobility, flexibility, and practicality. The training of martial arts is somewhat akin to sports like American football, in which drills are frequently practiced, with the goal of enhancing a primary high-performance activity. In martial arts, drills include kicking and striking padded standing equipment or held by an instructor. The practice of maneuvers with partners also takes place. Classes typically take place on padded floormats. The coaching seen in most sports is also a primary component of martial arts, in which the instructor guides students in safely enhancing techniques.

The main activity in American football is the gameplay; in martial arts, it is either sparring or form performance. Sparring is typically a combative match between two participants comprising footwork, blocks, and strikes. Due to the competitive nature, the sparring opponent will force the participant to perform combinations of these movements. The consequences for failing to mitigate the opponent's advances results in the opponent striking or gaining a dominant position; this creates a sense of urgency.

Additionally, prediction and strategy become important tactics in advanced sparring. Form performance is a non-contact, individual or synchronized team demonstration of the above-mentioned movements. Urgency in movement to promote elevated levels of exertion can be coached by the instructor. Well-run martial arts programs consistently demand cognition, coordination, strength, and balance across training and performance.

Additionally, martial arts classes are generally organized in group settings. Training in groups may help in individuals with DS to overcome reduced exercise capacity through mental benefits as supported by evidence in the general population (Irwin et al., 2012; Wing & Jeffery, 1999). The social connections formed among practitioners also raise the interactivity in each class. It is also common for participants in the general population to train for years, and some individuals train for a majority of their lifetime.

The belt-rank system that most martial arts styles utilize may enhance long-term participation and combat the high rate of physical attrition rates observed in the population with DS. The stepwise goals that martial arts offers often range from white belt to black belt; each goal achieved leads to another more impactful and meaningful purpose. This intrinsic goal setting and reward element are unique to martial arts in comparison to other amateur sports.

The fact that practitioners enjoy the freedom to participate in riskier combative matches or the non-impact—yet still competitive—form performances may make martial arts appropriate for individuals with DS. The facilitation of exercise studies in this population can be modified to mostly include only the low-impact aspects of martial arts to avert major adverse events. Protocols that capture the valuable elements of martial arts across urgency in training, a goal-oriented and positive social environment, and safety aspects may prove highly rewarding to researchers studying exercise in the population with DS.

The Next Steps Linking Biomarkers and Exercise in People with DS

Aβ and tau approaches have clinically failed as effective therapeutic strategies; new routes must be taken. Neuroimaging of hallmark biomarkers such as AB, tau, and cortical matter in combination with examining the more recent classes of biomarkers pose a strategy. This can include the AB clearance pathways, anti-neuroinflammation induced by muscle or peripheral tissue, increases of innate antioxidants, mitophagy, and neurotrophins.

Exercise studies can additionally search to identify additional biomarkers. Some of these unidentified biomarkers may be therapeutic targets. Immunotherapeutic approaches in physical activity trials are also lacking research. Further trials to advance the field toward personalized solutions can enhance the potential for precision medicine. The cure for AD may require a combination of treatments targeting multiple pathways. Therefore, exercise-based omics approaches that span single molecules to pathway signatures can non-pharmacologically supply a systems biology-based approach to fight AD and enhance the health of the population with DS.

CONCLUSION

The curative approach to AD is unknown; however, it may involve a combination of treatments (Fessel, 2023). Therefore, the synergistic effects of combining exercise interventions with pharmacological therapies represent an additional gap that may yield novel strategies. Studying the hormetic effects of exercise can illuminate the underlying mechanisms that may lead to new interventions to forestall or cure pathophysiology.

Mechanistic understandings resulting from exercise studies may also inform advanced treatments on the horizon, such as precision medicine and omics-based strategies.

Combined measures of biomarkers such as Aβ and inflammatory molecules are strong predictors of prospective cognitive deterioration. Therefore, incorporating combinations of newly identified pathways that may mediate anti-inflammation, mitochondrial salvaging, and antioxidation are vital in this developing field. Studies within this framework serve as the foundation for future exercise-related studies in the population with DS, drawing upon AD-relevant biomarkers and biochemical mechanisms underlying the benefits of exercise. In this context, we must continue to investigate primary and secondary prevention avenues in people at the highest risk of AD. An avenue with great promise for primary and secondary prevention and symptomatic treatment is exercise.

REFERENCES

2021 Alzheimer's disease facts and figures. (2021). *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *17*(3), 327–406. https://doi.org/10.1002/alz.12328

Aagaard, P., & Andersen, J. L. (2010). Effects of strength training on endurance capacity in top-level endurance athletes. *Scandinavian Journal of Medicine & Science in Sports, 20 Suppl 2*, 39–47. https://doi.org/10.1111/j.1600-0838.2010.01197.x

Abd El-Kader, S. M., & Al-Jiffri, O. H. (2016). Aerobic exercise improves quality of life, psychological well-being and systemic inflammation in subjects with Alzheimer's disease. *African Health Sciences, 16*(4), 1045–1055. https://doi.org/10.4314/ahs.v16i4.22

Agudelo, L. Z., Femenía, T., Orhan, F., Porsmyr-Palmertz, M., Goiny, M., Martinez-Redondo, V., Correia, J. C., Izadi, M., Bhat, M., Schuppe-Koistinen, I., Pettersson, A. T., Ferreira, D. M. S., Krook, A., Barres, R., Zierath, J. R., Erhardt, S., Lindskog, M., & Ruas, J. L. (2014). Skeletal muscle PGC-1α1 modulates kynurenine metabolism and mediates resilience to stress-induced depression. *Cell*, *159*(1), 33–45. https://doi.org/10.1016/j.cell.2014.07.051

Aguiar, A. S., Tuon, T., Albuquerque, M. M., Rocha, G. S., Speck, A. E., Araújo, J. C., Dafré, A. L., Prediger, R. D. S., & Pinho, R. A. (2008). The exercise redox paradigm in the Down's syndrome: Improvements in motor function and increases in blood oxidative status in young adults. *Journal of Neural*

Transmission (Vienna, Austria: 1996), *115*(12), 1643–1650. https://doi.org/10.1007/s00702-008-0120-x

Ahmed, Md. M., Johnson, N. R., Boyd, T. D., Coughlan, C., Chial, H. J., & Potter, H. (2021). Innate Immune System Activation and Neuroinflammation in Down Syndrome and Neurodegeneration: Therapeutic Targets or Partners? *Frontiers in Aging Neuroscience*, *13*, 718426. https://doi.org/10.3389/fnagi.2021.718426

Alaama, J. Y., Ahmad, M. S., Damanhouri, S. A. and Z. A., Alaama, J. Y., Ahmad, M. S., & Damanhouri, S. A. and Z. A. (2015). Altered Metabolism in Down Syndrome. In *Health Problems in Down Syndrome*. IntechOpen. https://doi.org/10.5772/60638

Alberti, K. G., Johnston, D. G., Gill, A., Barnes, A. J., & Orskov, H. (1978). Hormonal regulation of ketone-body metabolism in man. *Biochemical Society Symposium*, *43*, 163–182.

Aleksander-Szymanowicz, P., Marchewka, A., Dabrowski, Z., Teleglow, A., Bac, A., & Glodzik, J. (2014). The influence of moderate-intensity physical effort on peripheral blood in adults with Down syndrome—A pilot study. *Journal of Physiology and Pharmacology: An Official Journal of the Polish Physiological Society*, *65*(5), 733–738.

Alesi, M., & Pepi, A. (2017). Physical Activity Engagement in Young People with Down Syndrome: Investigating Parental Beliefs. *Journal of Applied Research in Intellectual Disabilities: JARID*, *30*(1), 71–83. https://doi.org/10.1111/jar.12220

Alexander, M., Petri, H., Ding, Y., Wandel, C., Khwaja, O., & Foskett, N. (2016). Morbidity and medication in a large population of individuals with Down syndrome compared to the general population. *Developmental Medicine and Child Neurology*, *58*(3), 246–254. https://doi.org/10.1111/dmcn.12868

Alizaei Yousefabadi, H., Niyazi, A., Alaee, S., Fathi, M., & Mohammad Rahimi, G. R. (2021). Anti-Inflammatory Effects of Exercise on Metabolic Syndrome Patients: A Systematic Review and Meta-Analysis. *Biological Research for Nursing*, *23*(2), 280–292. https://doi.org/10.1177/1099800420958068

Alu, S. N., Los, E. A., Ford, G. A., & Stone, W. L. (2022). Oxidative Stress in Type 2 Diabetes: The Case for Future Pediatric Redoxomics Studies. *Antioxidants*, *11*(7), 1336. https://doi.org/10.3390/antiox11071336

Arbuzova, S., Hutchin, T., & Cuckle, H. (2002). Mitochondrial dysfunction and Down's syndrome. *BioEssays: News and Reviews in Molecular, Cellular and Developmental Biology*, *24*(8), 681–684. https://doi.org/10.1002/bies.10138

Arslan, J., Jamshed, H., & Qureshi, H. (2020). Early Detection and Prevention of Alzheimer's Disease: Role of Oxidative Markers and Natural Antioxidants. *Frontiers in Aging Neuroscience*, *12*, 231. https://doi.org/10.3389/fnagi.2020.00231

Atri, A. (2019). The Alzheimer's Disease Clinical Spectrum: Diagnosis and Management. *The Medical Clinics of North America*, *103*(2), 263–293. https://doi.org/10.1016/j.mcna.2018.10.009

Avansar, M. S. (2017). The Effects of Eight Weeks Interval Training and Curcumin Consumption on TNF-α and BDNF Levels in Men with Metabolic Syndrome. *Journal of Ardabil University of Medical Sciences*. https://www.semanticscholar.org/paper/The-Effects-of-Eight-Weeks-Interval-Training-and-on-Avansar/35c07c08f9e71d3bf8bd75adf54f10b017281a91

Baker, L. D., Bayer-Carter, J. L., Skinner, J., Montine, T. J., Cholerton, B. A., Callaghan, M., Leverenz, J. B., Walter, B. K., Tsai, E., Postupna, N., Lampe, J., & Craft, S. (2012). High-intensity physical activity modulates diet effects on cerebrospinal amyloid-β levels in normal aging and mild cognitive impairment. *Journal of Alzheimer's Disease: JAD*, *28*(1), 137–146. https://doi.org/10.3233/JAD-2011-111076

Baker, L. D., Frank, L. L., Foster-Schubert, K., Green, P. S., Wilkinson, C. W., McTiernan, A., Plymate, S. R., Fishel, M. A., Watson, G. S., Cholerton, B. A., Duncan, G. E., Mehta, P. D., & Craft, S. (2010). Effects of aerobic exercise on mild cognitive impairment: A controlled trial. *Archives of Neurology*, *67*(1), 71–79. https://doi.org/10.1001/archneurol.2009.307

Baker, L. D., Skinner, J. S., Craft, S., Sink, K. M., Montine, T., Hansen, A., Wilson, V. M., Jung, Y., Johnston, M., Cholerton, B., & Callaghan, M. (2015). O5-04-05: Aerobic exercise reduces phosphorylated tau protein in cerebrospinal fluid in older adults with mild cognitive impairment. *Alzheimer's & Dementia*, *11*(7S_Part_7), P324–P324. https://doi.org/10.1016/j.jalz.2015.07.467

Balic, M. G., Mateos, E. C., Blasco, C. G., & Fernhall, B. (2000). Physical Fitness Levels of Physically Active and Sedentary Adults with Down Syndrome. *Adapted Physical Activity Quarterly, 17*(3), 310–321. https://doi.org/10.1123/apaq.17.3.310

Balsamo, S., Willardson, J. M., Frederico, S. de S., Prestes, J., Balsamo, D. C., Dahan, da C. N., Dos Santos-Neto, L., & Nobrega, O. T. (2013). Effectiveness of exercise on cognitive impairment and Alzheimer's disease. *International Journal of General Medicine*, *6*, 387–391. https://doi.org/10.2147/IJGM.S35315

Banks, W. A., Kastin, A. J., & Gutierrez, E. G. (1994). Penetration of interleukin-6 across the murine blood-brain barrier. *Neuroscience Letters*, *179*(1–2), 53–56. https://doi.org/10.1016/0304-3940(94)90933-4

Barha, C. K., Hsiung, G.-Y. R., Best, J. R., Davis, J. C., Eng, J. J., Jacova, C., Lee, P. E., Munkacsy, M., Cheung, W., & Liu-Ambrose, T. (2017). Sex Difference in Aerobic Exercise Efficacy to Improve Cognition in Older Adults with Vascular Cognitive Impairment: Secondary Analysis of a Randomized Controlled Trial. *Journal of Alzheimer's Disease: JAD*, *60*(4), 1397–1410. https://doi.org/10.3233/JAD-170221

Barnard, M., Swanepoel, M., Ellapen, T. J., Paul, Y., & Hammill, H. V. (2019). The health benefits of exercise therapy for patients with Down syndrome: A systematic review. *African Journal of Disability*, *8*(1), 1–9. https://doi.org/10.4102/ajod.v8i0.576

Barnhart, R. C., & Connolly, B. (2007). Aging and Down syndrome: Implications for physical therapy. *Physical Therapy*, *87*(10), 1399–1406. https://doi.org/10.2522/ptj.20060334

Baynard, T., Pitetti, K. H., Guerra, M., & Fernhall, B. (2004). Heart rate variability at rest and during exercise in persons with Down syndrome. *Archives of Physical Medicine and Rehabilitation*, *85*(8), 1285–1290. https://doi.org/10.1016/j.apmr.2003.11.023

Berchtold, N. C., Castello, N., & Cotman, C. W. (2010). Exercise and time-dependent benefits to learning and memory. *Neuroscience*, *167*(3), 588–597. https://doi.org/10.1016/j.neuroscience.2010.02.050

Berchtold, N. C., Prieto, G. A., Phelan, M., Gillen, D. L., Baldi, P., Bennett, D. A., Buchman, A. S., & Cotman, C. W. (2019). Hippocampal gene expression patterns linked to late-life physical activity oppose age and AD-related transcriptional decline. *Neurobiology of Aging*, *78*, 142–154. https://doi.org/10.1016/j.neurobiolaging.2019.02.012

Berchtold, N., Chinn, G., Chou, M., Kesslak, J., & Cotman, C. W. (2005). Exercise primes a molecular memory for brain-derived neurotrophic factor protein induction in the rat hippocampus. *Neuroscience*, *133*, 853–861. https://doi.org/10.1016/j.neuroscience.2005.03.026

Bergholdt, R., Eising, S., Nerup, J., & Pociot, F. (2006). Increased prevalence of Down's syndrome in individuals with type 1 diabetes in Denmark: A nationwide

population-based study. *Diabetologia*, *49*(6), 1179–1182. https://doi.org/10.1007/s00125-006-0231-6

Bernardo, T. c., Marques-Aleixo, I., Beleza, J., Oliveira, P. j., Ascensão, A., & Magalhães, J. (2016). Physical Exercise and Brain Mitochondrial Fitness: The Possible Role Against Alzheimer's Disease. *Brain Pathology*, *26*(5), 648–663. https://doi.org/10.1111/bpa.12403

Bingel, U., Wanigasekera, V., Wiech, K., Ni Mhuircheartaigh, R., Lee, M. C., Ploner, M., & Tracey, I. (2011). The effect of treatment expectation on drug efficacy: Imaging the analgesic benefit of the opioid remifentanil. *Science Translational Medicine*, *3*(70), 70ra14. https://doi.org/10.1126/scitranslmed.3001244

Block, M. E. (1991). Motor Development in Children with Down Syndrome: A Review of the Literature. *Adapted Physical Activity Quarterly*, *8*(3), 179–209. https://doi.org/10.1123/apaq.8.3.179

Boer, P.-H., & de Beer, Z. (2019). The effect of aquatic exercises on the physical and functional fitness of adults with Down syndrome: A non-randomised controlled trial. *Journal of Intellectual Disability Research: JIDR*, *63*(12), 1453–1463. https://doi.org/10.1111/jir.12687

Bordi, M., Darji, S., Sato, Y., Mellén, M., Berg, M. J., Kumar, A., Jiang, Y., & Nixon, R. A. (2019). mTOR hyperactivation in Down Syndrome underlies deficits in autophagy induction, autophagosome formation, and mitophagy. *Cell Death & Disease*, *10*(8), Article 8. https://doi.org/10.1038/s41419-019-1752-5

Borg, G., Hassmén, P., & Lagerström, M. (1987). Perceived exertion related to heart rate and blood lactate during arm and leg exercise. *European Journal of Applied Physiology and Occupational Physiology*, *56*(6), 679–685. https://doi.org/10.1007/BF00424810

Bouzid, M. A., Hammouda, O., Matran, R., Robin, S., & Fabre, C. (2014). Changes in Oxidative Stress Markers and Biological Markers of Muscle Injury with Aging at Rest and in Response to an Exhaustive Exercise. *PLoS ONE*, *9*(3), e90420. https://doi.org/10.1371/journal.pone.0090420

Brás, A., Rodrigues, A. S., Gomes, B., & Rueff, J. (2018). Down syndrome and microRNAs. *Biomedical Reports*, *8*(1), 11–16. https://doi.org/10.3892/br.2017.1019

Brea, D., Sobrino, T., Rodríguez-Yáñez, M., Ramos-Cabrer, P., Agulla, J., Rodríguez-González, R., Campos, F., Blanco, M., & Castillo, J. (2011). Toll-like receptors 7 and 8 expression is associated with poor outcome and greater inflammatory response in acute ischemic stroke. *Clinical Immunology (Orlando, Fla.)*, *139*(2), 193–198. https://doi.org/10.1016/j.clim.2011.02.001

Buccellato, F. R., D'Anca, M., Tartaglia, G. M., Del Fabbro, M., Scarpini, E., & Galimberti, D. (2023). Treatment of Alzheimer's Disease: Beyond Symptomatic Therapies. *International Journal of Molecular Sciences*, *24*(18), Article 18. https://doi.org/10.3390/ijms241813900

Buchanan, M. M., Hutchinson, M., Watkins, L. R., & Yin, H. (2010). Toll-like Receptor 4 in CNS Pathologies. *Journal of Neurochemistry*, *114*(1), 13–27. https://doi.org/10.1111/j.1471-4159.2010.06736.x

Butterfield, D. A., Di Domenico, F., Swomley, A. M., Head, E., & Perluigi, M. (2014). Redox Proteomics Analysis to Decipher the Neurobiology of Alzheimer-like Neurodegeneration: Overlaps in Down Syndrome and Alzheimer Disease Brain. *The Biochemical Journal*, *463*(2), 177–189. https://doi.org/10.1042/BJ20140772

Butterfield, D. A., & Halliwell, B. (2019). Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease. *Nature Reviews. Neuroscience*, *20*(3), 148–160. https://doi.org/10.1038/s41583-019-0132-6

Butterfield, D. A., Poon, H. F., St. Clair, D., Keller, J. N., Pierce, W. M., Klein, J. B., & Markesbery, W. R. (2006). Redox proteomics identification of oxidatively modified hippocampal proteins in mild cognitive impairment: Insights into the development of Alzheimer's disease. *Neurobiology of Disease*, *22*(2), 223–232. https://doi.org/10.1016/j.nbd.2005.11.002

Cai, Y., An, S. S. A., & Kim, S. (2015). Mutations in presenilin 2 and its implications in Alzheimer's disease and other dementia-associated disorders. *Clinical Interventions in Aging*, *10*, 1163–1172. https://doi.org/10.2147/CIA.S85808

Caracausi, M., Ghini, V., Locatelli, C., Mericio, M., Piovesan, A., Antonaros, F., Pelleri, M. C., Vitale, L., Vacca, R. A., Bedetti, F., Mimmi, M. C., Luchinat, C., Turano, P., Strippoli, P., & Cocchi, G. (2018). Plasma and urinary metabolomic profiles of

Down syndrome correlate with alteration of mitochondrial metabolism. *Scientific Reports*, *8*, 2977. https://doi.org/10.1038/s41598-018-20834-y

Carter, H., Jones, A. M., Barstow, T. J., Burnley, M., Williams, C. A., & Doust, J. H. (2000). Oxygen uptake kinetics in treadmill running and cycle ergometry: A comparison. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, *89*(3), 899–907. https://doi.org/10.1152/jappl.2000.89.3.899

Carter, K., & Horvat, M. (2016). Effect of Taekwondo Training on Lower Body Strength and Balance in Young Adults with Down Syndrome. *Journal of Policy and Practice in Intellectual Disabilities*, *13*(2), 165–172. https://doi.org/10.1111/jppi.12164

Cervenka, I., Agudelo, L. Z., & Ruas, J. L. (2017). Kynurenines: Tryptophan's metabolites in exercise, inflammation, and mental health. *Science (New York, N.Y.)*, *357*(6349), eaaf9794. https://doi.org/10.1126/science.aaf9794

Chen, C.-C. J. J., Ringenbach, D. R. S., & Snow, M. (2014). Treadmill walking effects on grip strength in young men with Down syndrome. *Research in Developmental Disabilities*, *35*(2), 288–293. https://doi.org/10.1016/j.ridd.2013.10.032

Chen, C.-C. J. J., & Ringenbach, S. D. R. (2016). Dose-response relationship between intensity of exercise and cognitive performance in individuals with Down syndrome: A preliminary study. *Journal of Intellectual Disability Research: JIDR*, *60*(6), 606–614. https://doi.org/10.1111/jir.12258

Chen, C.-C. J. J., & Ringenbach, S. D. R. (2019). The effect of acute exercise on the performance of verbal fluency in adolescents and young adults with Down

syndrome: A pilot study. *Journal of Intellectual Disability Research: JIDR*, *63*(6), 614–623. https://doi.org/10.1111/jir.12603

Chen, C.-C. J. J., Ringenbach, S. D. R., Crews, D., Kulinna, P. H., & Amazeen, E. L. (2015). The association between a single bout of moderate physical activity and executive function in young adults with Down syndrome: A preliminary study. *Journal of Intellectual Disability Research: JIDR*, *59*(7), 589–598. https://doi.org/10.1111/jir.12163

Cheng, A., Wan, R., Yang, J.-L., Kamimura, N., Son, T. G., Ouyang, X., Luo, Y., Okun, E., & Mattson, M. P. (2012). Involvement of PGC-1α in the formation and maintenance of neuronal dendritic spines. *Nature Communications*, *3*, 1250. https://doi.org/10.1038/ncomms2238

Chew, H., Solomon, V. A., & Fonteh, A. N. (2020). Involvement of Lipids in Alzheimer's Disease Pathology and Potential Therapies. *Frontiers in Physiology*, *11*, 598. https://doi.org/10.3389/fphys.2020.00598

Chico, L., Simoncini, C., Lo Gerfo, A., Rocchi, A., Petrozzi, L., Carlesi, C., Volpi, L., Tognoni, G., Siciliano, G., & Bonuccelli, U. (2013). Oxidative stress and APO E polymorphisms in Alzheimer's disease and in mild cognitive impairment. *Free Radical Research*, *47*(8), 569–576. https://doi.org/10.3109/10715762.2013.804622

Coelho, F. G. de M., Vital, T. M., Stein, A. M., Arantes, F. J., Rueda, A. V., Camarini, R., Teodorov, E., & Santos-Galduróz, R. F. (2014). Acute aerobic exercise increases brain-derived neurotrophic factor levels in elderly with Alzheimer's

disease. *Journal of Alzheimer's Disease: JAD*, *39*(2), 401–408. https://doi.org/10.3233/JAD-131073

Coetsee, C., & Terblanche, E. (2017). Cerebral oxygenation during cortical activation: The differential influence of three exercise training modalities. A randomized controlled trial. *European Journal of Applied Physiology*, *117*(8), 1617–1627. https://doi.org/10.1007/s00421-017-3651-8

Coffey, V. G., & Hawley, J. A. (2017). Concurrent exercise training: Do opposites distract? *The Journal of Physiology*, *595*(9), 2883–2896. https://doi.org/10.1113/JP272270

Cojocaru, I. M., Cojocaru, M., Miu, G., & Sapira, V. (2011). Study of interleukin-6 production in Alzheimer's disease. *Romanian Journal of Internal Medicine = Revue Roumaine De Medecine Interne*, *49*(1), 55–58.

Colcombe, S. J., Erickson, K. I., Raz, N., Webb, A. G., Cohen, N. J., McAuley, E., & Kramer, A. F. (2003). Aerobic fitness reduces brain tissue loss in aging humans. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *58*(2), 176–180. https://doi.org/10.1093/gerona/58.2.m176

Colcombe, S. J., Erickson, K. I., Scalf, P. E., Kim, J. S., Prakash, R., McAuley, E., Elavsky, S., Marquez, D. X., Hu, L., & Kramer, A. F. (2006). Aerobic exercise training increases brain volume in aging humans. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *61*(11), 1166–1170. https://doi.org/10.1093/gerona/61.11.1166

Collao, N., Rada, I., Francaux, M., Deldicque, L., & Zbinden-Foncea, H. (2020). Anti-Inflammatory Effect of Exercise Mediated by Toll-Like Receptor Regulation in Innate Immune Cells—A Review. *International Reviews of Immunology*, *39*(2), 39–52. https://doi.org/10.1080/08830185.2019.1682569

Coskun, P. E., & Busciglio, J. (2012). Oxidative Stress and Mitochondrial Dysfunction in Down's Syndrome: Relevance to Aging and Dementia. *Current Gerontology and Geriatrics Research*, *2012*, 383170. https://doi.org/10.1155/2012/383170

Coskun, P. E., Wyrembak, J., Derbereva, O., Melkonian, G., Doran, E., Lott, I. T., Head, E., Cotman, C. W., & Wallace, D. C. (2010). Systemic mitochondrial dysfunction and the etiology of Alzheimer's disease and down syndrome dementia. *Journal of Alzheimer's Disease: JAD*, *20 Suppl 2*(0 2), S293-310. https://doi.org/10.3233/JAD-2010-100351

Cui, M. Y., Lin, Y., Sheng, J. Y., Zhang, X., & Cui, R. J. (2018). Exercise Intervention Associated with Cognitive Improvement in Alzheimer's Disease. *Neural Plasticity*, *2018*, 9234105. https://doi.org/10.1155/2018/9234105

D'Acunzo, P., Pérez-González, R., Kim, Y., Hargash, T., Miller, C., Alldred, M. J., Erdjument-Bromage, H., Penikalapati, S. C., Pawlik, M., Saito, M., Saito, M., Ginsberg, S. D., Neubert, T. A., Goulbourne, C. N., & Levy, E. (2021). Mitovesicles are a novel population of extracellular vesicles of mitochondrial origin altered in Down syndrome. *Science Advances*, *7*(7), eabe5085. https://doi.org/10.1126/sciadv.abe5085

De Miguel, Z., Khoury, N., Betley, M. J., Lehallier, B., Willoughby, D., Olsson, N., Yang, A. C., Hahn, O., Lu, N., Vest, R. T., Bonanno, L. N., Yerra, L., Zhang, L., Saw, N. L., Fairchild, J. K., Lee, D., Zhang, H., McAlpine, P. L., Contrepois, K., … Wyss-Coray, T. (2021). Exercise plasma boosts memory and dampens brain inflammation via clusterin. *Nature*, *600*(7889), 494–499. https://doi.org/10.1038/s41586-021-04183-x

Dienstbier, R. A. (1989). Arousal and physiological toughness: Implications for mental and physical health. *Psychological Review*, *96*(1), 84–100. https://doi.org/10.1037/0033-295x.96.1.84

Ding, Q., Markesbery, W. R., Chen, Q., Li, F., & Keller, J. N. (2005). Ribosome dysfunction is an early event in Alzheimer's disease. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *25*(40), 9171–9175. https://doi.org/10.1523/JNEUROSCI.3040-05.2005

Dodd, K. J., & Shields, N. (2005). A Systematic Review of the Outcomes of Cardiovascular Exercise Programs for People With Down Syndrome. *Archives of Physical Medicine and Rehabilitation*, *86*(10), 2051–2058. https://doi.org/10.1016/j.apmr.2005.06.003

Dogliotti, G., Galliera, E., Licastro, F., & Corsi, M. M. (2010). Age-related changes in plasma levels of BDNF in Down syndrome patients. *Immunity & Ageing: I & A*, *7*, 2. https://doi.org/10.1186/1742-4933-7-2

dos Santos, J. A. C., Veras, A. S. C., Batista, V. R. G., Tavares, M. E. A., Correia, R. R., Suggett, C. B., & Teixeira, G. R. (2022). Physical exercise and the functions of

microRNAs. *Life Sciences*, *304*, 120723. https://doi.org/10.1016/j.lfs.2022.120723

Ďuračková, Z. (2010). Some current insights into oxidative stress. *Physiological Research*, *59*(4), 459–469. https://doi.org/10.33549/physiolres.931844

Eberhard, Y., Eterradossi, J., & Debû, B. (1997). Biological Changes Induced by Physical Activity in Individuals with Down's Syndrome. *Adapted Physical Activity Quarterly*, *14*(2), 166–175. https://doi.org/10.1123/apaq.14.2.166

Edwards, D. G., Schofield, R. S., Lennon, S. L., Pierce, G. L., Nichols, W. W., & Braith, R. W. (2004). Effect of exercise training on endothelial function in men with coronary artery disease. *The American Journal of Cardiology*, *93*(5), 617–620. https://doi.org/10.1016/j.amjcard.2003.11.032

Eisenberger, N. I., Master, S. L., Inagaki, T. K., Taylor, S. E., Shirinyan, D., Lieberman, M. D., & Naliboff, B. D. (2011). Attachment figures activate a safety signal-related neural region and reduce pain experience. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(28), 11721–11726. https://doi.org/10.1073/pnas.1108239108

Endres, M., Gertz, K., Lindauer, U., Katchanov, J., Schultze, J., Schröck, H., Nickenig, G., Kuschinsky, W., Dirnagl, U., & Laufs, U. (2003). Mechanisms of stroke protection by physical activity. *Annals of Neurology*, *54*(5), 582–590. https://doi.org/10.1002/ana.10722

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., Kim, J. S., Heo, S., Alves, H., White, S. M., Wojcicki, T. R., Mailey, E., Vieira, V. J.,

Martin, S. A., Pence, B. D., Woods, J. A., McAuley, E., & Kramer, A. F. (2011). Exercise training increases size of hippocampus and improves memory. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(7), 3017–3022. https://doi.org/10.1073/pnas.1015950108

Fareed, M. M., Qasmi, M., Aziz, S., Völker, E., Förster, C. Y., & Shityakov, S. (2022). The Role of Clusterin Transporter in the Pathogenesis of Alzheimer's Disease at the Blood–Brain Barrier Interface: A Systematic Review. *Biomolecules*, *12*(10), 1452. https://doi.org/10.3390/biom12101452

Farina, N., Rusted, J., & Tabet, N. (2014). The effect of exercise interventions on cognitive outcome in Alzheimer's disease: A systematic review. *International Psychogeriatrics*, *26*(1), 9–18. https://doi.org/10.1017/S1041610213001385

Fernhall, B. (1993). Physical fitness and exercise training of individuals with mental retardation. *Medicine and Science in Sports and Exercise*, *25*(4), 442–450.

Fernhall, B., Millar, L., Tymeson, G., & Burkett, L. (1989). Cardiovascular Fitness Testing and Fitness Levels of Adolescents and Adults with Mental Retardation Including Down Syndrome. *Education and Training in Mental Retardation*, *24*(2), 133–138.

Féry, F., & Balasse, E. O. (1986). Response of ketone body metabolism to exercise during transition from postabsorptive to fasted state. *The American Journal of Physiology*, *250*(5 Pt 1), E495-501. https://doi.org/10.1152/ajpendo.1986.250.5.E495

Féry, F., & Balasse, E. O. (1988). Effect of exercise on the disposal of infused ketone bodies in humans. *The Journal of Clinical Endocrinology and Metabolism*, *67*(2), 245–250. https://doi.org/10.1210/jcem-67-2-245

Fessel, J. (2023). The several ways to authentically cure Alzheimer's dementia. *Ageing Research Reviews*, *92*, 102093. https://doi.org/10.1016/j.arr.2023.102093

Firth, J., Carney, R., French, P., Elliott, R., Cotter, J., & Yung, A. R. (2018). Long-term maintenance and effects of exercise in early psychosis. *Early Intervention in Psychiatry*, *12*(4), 578–585. https://doi.org/10.1111/eip.12365

Fleig, L., Lippke, S., Pomp, S., & Schwarzer, R. (2011). Exercise maintenance after rehabilitation: How experience can make a difference. *Psychology of Sport and Exercise - PSYCHOL SPORT EXERC*, *12*, 293–299. https://doi.org/10.1016/j.psychsport.2011.01.003

Fleming, V., Piro-Gambetti, B., Patrick, A., Zammit, M., Alexander, A., Christian, B. T., Handen, B., Cohen, A., Klunk, W., Laymon, C., Ances, B. M., Plante, D. T., Okonkwo, O., & Hartley, S. L. (2021). Physical activity and cognitive and imaging biomarkers of Alzheimer's disease in down syndrome. *Neurobiology of Aging*, *107*, 118–127. https://doi.org/10.1016/j.neurobiolaging.2021.07.016

Flores-Aguilar, L., Iulita, M. F., Kovecses, O., Torres, M. D., Levi, S. M., Zhang, Y., Askenazi, M., Wisniewski, T., Busciglio, J., & Cuello, A. C. (2020). Evolution of neuroinflammation across the lifespan of individuals with Down syndrome. *Brain: A Journal of Neurology*, *143*(12), 3653–3671. https://doi.org/10.1093/brain/awaa326

Fote, G., Wu, J., Mapstone, M., Macciardi, F., Fiandaca, M. S., & Federoff, H. J. (2021). Plasma Sphingomyelins in Late-Onset Alzheimer's Disease. *Journal of Alzheimer's Disease : JAD*, *83*(3), 1161–1171. https://doi.org/10.3233/JAD-200871

Francisco Javier, O., Manuel, R., & Manuel, R.-R. (2006). Regular physical activity increases glutathione peroxidase activity in adolescents with Down syndrome. *Clinical Journal of Sport Medicine: Official Journal of the Canadian Academy of Sport Medicine*, *16*(4), 355–356. https://doi.org/10.1097/00042752-200607000-00013

Gao, W., Xiong, Y., Li, Q., & Yang, H. (2017). Inhibition of Toll-Like Receptor Signaling as a Promising Therapy for Inflammatory Diseases: A Journey from Molecular to Nano Therapeutics. *Frontiers in Physiology*, *8*, 508. https://doi.org/10.3389/fphys.2017.00508

Geffken, D. F., Cushman, M., Burke, G. L., Polak, J. F., Sakkinen, P. A., & Tracy, R. P. (2001). Association between physical activity and markers of inflammation in a healthy elderly population. *American Journal of Epidemiology*, *153*(3), 242–250. https://doi.org/10.1093/aje/153.3.242

Giagkoudaki, F., Dimitros, E., Kouidi, E., & Deligiannis, A. (2010). Effects of exercise training on heart-rate-variability indices in individuals with Down Syndrome. *Journal of Sport Rehabilitation*, *19*(2), 173–183. https://doi.org/10.1123/jsr.19.2.173

Gleeson, M., McFarlin, B., & Flynn, M. (2006). Exercise and Toll-like receptors. *Exercise Immunology Review*, *12*, 34–53.

Glynn, E. L., Lujan, H. L., Kramer, V. J., Drummond, M. J., DiCarlo, S. E., & Rasmussen, B. B. (2008). A chronic increase in physical activity inhibits fed-state mTOR/S6K1 signaling and reduces IRS-1 serine phosphorylation in rat skeletal muscle. *Applied Physiology, Nutrition, and Metabolism = Physiologie Appliquee, Nutrition Et Metabolisme*, *33*(1), 93–101. https://doi.org/10.1139/H07-149

Goldberg, M., Islam, M. R., Kerimoglu, C., Lancelin, C., Gisa, V., Burkhardt, S., Krüger, D. M., Marquardt, T., Malchow, B., Schmitt, A., Falkai, P., Sananbenesi, F., & Fischer, A. (2021). Exercise as a model to identify microRNAs linked to human cognition: A role for microRNA-409 and microRNA-501. *Translational Psychiatry*, *11*(1), Article 1. https://doi.org/10.1038/s41398-021-01627-w

González-Agüero, A., Vicente-Rodríguez, G., Ara, I., Moreno, L. A., & Casajús, J. A. (2011). Accuracy of prediction equations to assess percentage of body fat in children and adolescents with Down syndrome compared to air displacement plethysmography. *Research in Developmental Disabilities*, *32*(5), 1764–1769. https://doi.org/10.1016/j.ridd.2011.03.006

González-Agüero, A., Vicente-Rodríguez, G., Moreno, L. A., Guerra-Balic, M., Ara, I., & Casajús, J. A. (2010). Health-related physical fitness in children and adolescents with Down syndrome and response to training. *Scandinavian Journal of Medicine & Science in Sports*, *20*(5), 716–724. https://doi.org/10.1111/j.1600-0838.2010.01120.x

Grammatikopoulou, M. G., Manai, A., Tsigga, M., Tsiligiroglou-Fachantidou, A., Galli-Tsinopoulou, A., & Zakas, A. (2008). Nutrient intake and anthropometry in children and adolescents with Down syndrome—A preliminary study. *Developmental Neurorehabilitation*, *11*(4), 260–267. https://doi.org/10.1080/17518420802525526

Green, Z. D., John, C. S., Kueck, P. J., Burns, J. M., Perry, M., Donald, J., Mahnken, J. D., Honea, R. A., Vidoni, E. D., & Morris, J. K. (2021). Rationale and methods to characterize the acute exercise response in aging and Alzheimer's Disease: The AEROBIC pilot study. *Contemporary Clinical Trials*, *107*, 106457. https://doi.org/10.1016/j.cct.2021.106457

Gross, T. J., Doran, E., Cheema, A. K., Head, E., Lott, I. T., & Mapstone, M. (2019). Plasma metabolites related to cellular energy metabolism are altered in adults with Down syndrome and Alzheimer's disease. *Developmental Neurobiology*, *79*(7), 622–638. https://doi.org/10.1002/dneu.22716

Gutierrez-Hervas, A., Gómez-Martínez, S., Izquierdo-Gómez, R., Veiga, O. L., Perez-Bey, A., Castro-Piñero, J., & Marcos, A. (2020). Inflammation and fatness in adolescents with and without Down syndrome: UP & DOWN study. *Journal of Intellectual Disability Research: JIDR*, *64*(2), 170–179. https://doi.org/10.1111/jir.12697

Head, E., Lott, I. T., Patterson, D., Doran, E., & Haier, R. J. (2007). Possible Compensatory Events in Adult Down Syndrome Brain Prior to the Development of Alzheimer Disease Neuropathology: Targets for Nonpharmacological

Intervention. *Journal of Alzheimer's Disease*, *11*(1), 61–76. https://doi.org/10.3233/JAD-2007-11110

Head, E., Lott, I. T., Wilcock, D. M., & Lemere, C. A. (2016). Aging in Down Syndrome and the Development of Alzheimer's Disease Neuropathology. *Current Alzheimer Research*, *13*(1), 18–29. https://doi.org/10.2174/1567205012666151020114607

Hegazy, S. H., Thomassen, J. Q., Rasmussen, I. J., Nordestgaard, B. G., Tybjærg-Hansen, A., & Frikke-Schmidt, R. (2022). C-reactive protein levels and risk of dementia—Observational and genetic studies of 111,242 individuals from the general population. *Alzheimer's & Dementia*, *18*(11), 2262–2271. https://doi.org/10.1002/alz.12568

Helguera, P., Seiglie, J., Rodriguez, J., Hanna, M., Helguera, G., & Busciglio, J. (2013). Adaptive Downregulation of Mitochondrial Function in Down Syndrome. *Cell Metabolism*, *17*(1), 132–140. https://doi.org/10.1016/j.cmet.2012.12.005

Hoffmann, K., Sobol, N. A., Frederiksen, K. S., Beyer, N., Vogel, A., Vestergaard, K., Brændgaard, H., Gottrup, H., Lolk, A., Wermuth, L., Jacobsen, S., Laugesen, L. P., Gergelyffy, R. G., Høgh, P., Bjerregaard, E., Andersen, B. B., Siersma, V., Johannsen, P., Cotman, C. W., … Hasselbalch, S. G. (2016). Moderate-to-High Intensity Physical Exercise in Patients with Alzheimer's Disease: A Randomized Controlled Trial. *Journal of Alzheimer's Disease: JAD*, *50*(2), 443–453. https://doi.org/10.3233/JAD-150817

Hojlo, M. A., Milliken, A. L., Baumer, N. T., & Davidson, E. J. (2022). DSFit: A feasibility pilot study of a group exercise programme for adolescents with Down

syndrome. *Journal of Intellectual Disability Research: JIDR*, *66*(12), 952–966. https://doi.org/10.1111/jir.12977

Hu, E., Du, H., Zhu, X., Wang, L., Shang, S., Wu, X., Lu, H., & Lu, X. (2018). Beta-hydroxybutyrate Promotes the Expression of BDNF in Hippocampal Neurons under Adequate Glucose Supply. *Neuroscience*, *386*, 315–325. https://doi.org/10.1016/j.neuroscience.2018.06.036

Hughes, D. C., Ellefsen, S., & Baar, K. (2018). Adaptations to Endurance and Strength Training. *Cold Spring Harbor Perspectives in Medicine*, *8*(6), a029769. https://doi.org/10.1101/cshperspect.a029769

Huynh, Q.-S., Elangovan, S., & Holsinger, R. M. D. (2022). Non-Pharmacological Therapeutic Options for the Treatment of Alzheimer's Disease. *International Journal of Molecular Sciences*, *23*(19), Article 19. https://doi.org/10.3390/ijms231911037

Improta-Caria, A. C., Nonaka, C. K. V., Cavalcante, B. R. R., De Sousa, R. A. L., Aras Júnior, R., & Souza, B. S. de F. (2020). Modulation of MicroRNAs as a Potential Molecular Mechanism Involved in the Beneficial Actions of Physical Exercise in Alzheimer Disease. *International Journal of Molecular Sciences*, *21*(14), Article 14. https://doi.org/10.3390/ijms21144977

Ionescu-Tucker, A., & Cotman, C. W. (2021). Emerging roles of oxidative stress in brain aging and Alzheimer's disease. *Neurobiology of Aging*, *107*, 86–95. https://doi.org/10.1016/j.neurobiolaging.2021.07.014

Irwin, B. C., Scorniaenchi, J., Kerr, N. L., Eisenmann, J. C., & Feltz, D. L. (2012). Aerobic exercise is promoted when individual performance affects the group: A test of the Kohler motivation gain effect. *Annals of Behavioral Medicine: A Publication of the Society of Behavioral Medicine*, *44*(2), 151–159. https://doi.org/10.1007/s12160-012-9367-4

Ismail, R., Parbo, P., Madsen, L. S., Hansen, A. K., Hansen, K. V., Schaldemose, J. L., Kjeldsen, P. L., Stokholm, M. G., Gottrup, H., Eskildsen, S. F., & Brooks, D. J. (2020). The relationships between neuroinflammation, beta-amyloid and tau deposition in Alzheimer's disease: A longitudinal PET study. *Journal of Neuroinflammation*, *17*(1), 151. https://doi.org/10.1186/s12974-020-01820-6

Iulita, M. F., Ower, A., Barone, C., Pentz, R., Gubert, P., Romano, C., Cantarella, R. A., Elia, F., Buono, S., Recupero, M., Romano, C., Castellano, S., Bosco, P., Di Nuovo, S., Drago, F., Caraci, F., & Cuello, A. C. (2016). An inflammatory and trophic disconnect biomarker profile revealed in Down syndrome plasma: Relation to cognitive decline and longitudinal evaluation. *Alzheimer's & Dementia*, *12*(11), 1132–1148. https://doi.org/10.1016/j.jalz.2016.05.001

Janmohammadi, A., & Moghadasi, M. (2021). Effect of eight weeks SPARK program on malondialdehyde and brain-derived neurotrophic factor in boys with Down syndrome. *Journal of Applied Exercise Physiology*, *17*(34), 47–60. https://doi.org/10.22080/jaep.2021.21963.2053

Jensen, C. S., Bahl, J. M., Østergaard, L. B., Høgh, P., Wermuth, L., Heslegrave, A., Zetterberg, H., Heegaard, N. H. H., Hasselbalch, S. G., & Simonsen, A. H.

(2019). Exercise as a potential modulator of inflammation in patients with Alzheimer's disease measured in cerebrospinal fluid and plasma. *Experimental Gerontology*, *121*, 91–98. https://doi.org/10.1016/j.exger.2019.04.003

Jiang, S., Xia, R., Jiang, Y., Wang, L., & Gao, F. (2014). Vascular Endothelial Growth Factors Enhance the Permeability of the Mouse Blood-brain Barrier. *PLoS ONE*, *9*(2), e86407. https://doi.org/10.1371/journal.pone.0086407

Jobling, A., Virji-Babul, N., & Nichols, D. (2006). Children with Down Syndrome: Discovering the Joy of Movement. *Journal of Physical Education, Recreation & Dance*, *77*(6), 34–54. https://doi.org/10.1080/07303084.2006.10597892

Johnson, M. B., De Franco, E., Greeley, S. A. W., Letourneau, L. R., Gillespie, K. M., Wakeling, M. N., Ellard, S., Flanagan, S. E., Patel, K. A., & Hattersley, A. T. (2019). Trisomy 21 Is a Cause of Permanent Neonatal Diabetes That Is Autoimmune but Not HLA Associated. *Diabetes*, *68*(7), 1528–1535. https://doi.org/10.2337/db19-0045

Jordan, J. L., Holden, M. A., Mason, E. E., & Foster, N. E. (2010). Interventions to improve adherence to exercise for chronic musculoskeletal pain in adults. *The Cochrane Database of Systematic Reviews*, *2010*(1), CD005956. https://doi.org/10.1002/14651858.CD005956.pub2

Kálmán, J., Juhász, A., Laird, G., Dickens, P., Járdánházy, T., Rimanóczy, A., Boncz, I., Parry-Jones, W. L., & Janka, Z. (1997). Serum interleukin-6 levels correlate with the severity of dementia in Down syndrome and in Alzheimer's disease. *Acta*

Neurologica Scandinavica, *96*(4), 236–240. https://doi.org/10.1111/j.1600-0404.1997.tb00275.x

Kelly, S. A., & Pomp, D. (2013). Genetic determinants of voluntary exercise. *Trends in Genetics : TIG*, *29*(6), 348–357. https://doi.org/10.1016/j.tig.2012.12.007

Kerstiens, R., & Green, M. (2015). Exercise in Individuals with Down Syndrome: A Brief Review. *International Journal of Exercise Science*, *8*(2). https://digitalcommons.wku.edu/ijes/vol8/iss2/10

Khokhar, M., Tomo, S., Gadwal, A., & Purohit, P. (2022). Multi-omics integration and interactomics reveals molecular networks and regulators of the beneficial effect of yoga and exercise. *International Journal of Yoga*, *15*(1), 25–39. https://doi.org/10.4103/ijoy.ijoy_146_21

Kim, S. H., Vlkolinsky, R., Cairns, N., & Lubec, G. (2000). Decreased levels of complex III core protein 1 and complex V beta chain in brains from patients with Alzheimer's disease and Down syndrome. *Cellular and Molecular Life Sciences: CMLS*, *57*(12), 1810–1816. https://doi.org/10.1007/pl00000661

King, D. E., Carek, P., Mainous, A. G., & Pearson, W. S. (2003). Inflammatory markers and exercise: Differences related to exercise type. *Medicine and Science in Sports and Exercise*, *35*(4), 575–581. https://doi.org/10.1249/01.MSS.0000058440.28108.CC

Knechtle, B., & Nikolaidis, P. T. (2018). Physiology and Pathophysiology in Ultra-Marathon Running. *Frontiers in Physiology*, *9*, 634. https://doi.org/10.3389/fphys.2018.00634

Konings, C. H., van Trotsenburg, A. S., Ris-Stalpers, C., Vulsma, T., Wiedijk, B. M., & de Vijlder, J. J. (2001). Plasma thyrotropin bioactivity in Down's syndrome children with subclinical hypothyroidism. *European Journal of Endocrinology, 144*(1), 1–4. https://doi.org/10.1530/eje.0.1440001

Korenberg, J. R., Kawashima, H., Pulst, S. M., Ikeuchi, T., Ogasawara, N., Yamamoto, K., Schonberg, S. A., West, R., Allen, L., & Magenis, E. (1990). Molecular definition of a region of chromosome 21 that causes features of the Down syndrome phenotype. *American Journal of Human Genetics, 47*(2), 236–246.

Kou, X., Chen, D., & Chen, N. (2019). Physical Activity Alleviates Cognitive Dysfunction of Alzheimer's Disease through Regulating the mTOR Signaling Pathway. *International Journal of Molecular Sciences*, *20*(7), 1591. https://doi.org/10.3390/ijms20071591

Kowalska, M., Piekut, T., Prendecki, M., Sodel, A., Kozubski, W., & Dorszewska, J. (2020). Mitochondrial and Nuclear DNA Oxidative Damage in Physiological and Pathological Aging. *DNA and Cell Biology*, *39*(8), 1410–1420. https://doi.org/10.1089/dna.2019.5347

Kozakiewicz, M., Rowiński, R., Kornatowski, M., Dąbrowski, A., Kędziora-Kornatowska, K., & Strachecka, A. (2019). Relation of Moderate Physical Activity to Blood Markers of Oxidative Stress and Antioxidant Defense in the Elderly. *Oxidative Medicine and Cellular Longevity*, *2019*, 5123628. https://doi.org/10.1155/2019/5123628

Kraus, R. M., Stallings, H. W., Yeager, R. C., & Gavin, T. P. (2004). Circulating plasma VEGF response to exercise in sedentary and endurance-trained men. *Journal of Applied Physiology*, *96*(4), 1445–1450. https://doi.org/10.1152/japplphysiol.01031.2003

Lan, Y., Huang, Z., Jiang, Y., Zhou, X., Zhang, J., Zhang, D., Wang, B., & Hou, G. (2018). Strength exercise weakens aerobic exercise-induced cognitive improvements in rats. *PLOS ONE*, *13*(10), e0205562. https://doi.org/10.1371/journal.pone.0205562

Lancaster, G. I., Khan, Q., Drysdale, P., Wallace, F., Jeukendrup, A. E., Drayson, M. T., & Gleeson, M. (2005). The physiological regulation of toll-like receptor expression and function in humans. *The Journal of Physiology*, *563*(Pt 3), 945–955. https://doi.org/10.1113/jphysiol.2004.081224

Landreth, G. E., & Reed-Geaghan, E. G. (2009). Toll-like receptors in Alzheimer's disease. *Current Topics in Microbiology and Immunology*, *336*, 137–153. https://doi.org/10.1007/978-3-642-00549-7_8

Laufs, U., Wassmann, S., Czech, T., Münzel, T., Eisenhauer, M., Böhm, M., & Nickenig, G. (2005). Physical inactivity increases oxidative stress, endothelial dysfunction, and atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *25*(4), 809–814. https://doi.org/10.1161/01.ATV.0000158311.24443.af

Lautenschlager, N. T., Cox, K. L., Flicker, L., Foster, J. K., van Bockxmeer, F. M., Xiao, J., Greenop, K. R., & Almeida, O. P. (2008). Effect of physical activity on

cognitive function in older adults at risk for Alzheimer disease: A randomized trial. *JAMA*, *300*(9), 1027–1037. https://doi.org/10.1001/jama.300.9.1027

Lebus, D. K., Casazza, G. A., Hoffman, M. D., & Van Loan, M. D. (2010). Can changes in body mass and total body water accurately predict hyponatremia after a 161-km running race? *Clinical Journal of Sport Medicine: Official Journal of the Canadian Academy of Sport Medicine*, *20*(3), 193–199. https://doi.org/10.1097/JSM.0b013e3181da53ea

Lee, S. H., Lee, S., Jun, H. S., Jeong, H. J., Cha, W. T., Cho, Y. S., Kim, J. H., Ku, S. Y., & Cha, K. Y. (2003). Expression of the mitochondrial ATPase6 gene and Tfam in Down syndrome. *Molecules and Cells*, *15*(2), 181–185.

Lepers, R., Rüst, C. A., Stapley, P. J., & Knechtle, B. (2013). Relative improvements in endurance performance with age: Evidence from 25 years of Hawaii Ironman racing. *Age (Dordrecht, Netherlands)*, *35*(3), 953–962. https://doi.org/10.1007/s11357-012-9392-z

Lepers, R., & Stapley, P. J. (2016). Master Athletes Are Extending the Limits of Human Endurance. *Frontiers in Physiology*, *7*, 613. https://doi.org/10.3389/fphys.2016.00613

Li, Y.-Q., Zhang, F., Yu, L.-P., Mu, J.-K., Yang, Y.-Q., Yu, J., & Yang, X.-X. (2021). Targeting PINK1 Using Natural Products for the Treatment of Human Diseases. *BioMed Research International*, *2021*, 4045819. https://doi.org/10.1155/2021/4045819

Liang, K. Y., Mintun, M. A., Fagan, A. M., Goate, A. M., Bugg, J. M., Holtzman, D. M., Morris, J. C., & Head, D. (2010). Exercise and Alzheimer's disease biomarkers in cognitively normal older adults. *Annals of Neurology*, *68*(3), 311–318. https://doi.org/10.1002/ana.22096

Liberman, K., Forti, L. N., Beyer, I., & Bautmans, I. (2017). The effects of exercise on muscle strength, body composition, physical functioning and the inflammatory profile of older adults: A systematic review. *Current Opinion in Clinical Nutrition and Metabolic Care*, *20*(1), 30–53. https://doi.org/10.1097/MCO.0000000000000335

Liu, H., Zhao, G., Cai, K., Zhao, H., & Shi, L. (2011). Treadmill exercise prevents decline in spatial learning and memory in APP/PS1 transgenic mice through improvement of hippocampal long-term potentiation. *Behavioural Brain Research*, *218*(2), 308–314. https://doi.org/10.1016/j.bbr.2010.12.030

Liu, Y. F., Chen, H. ing, Yu, L., Kuo, Y. M., Wu, F. S., Chuang, J. I., Liao, P. C., & Jen, C. J. (2008). Upregulation of hippocampal TrkB and synaptotagmin is involved in treadmill exercise-enhanced aversive memory in mice. *Neurobiology of Learning and Memory*, *90*(1), 81–89. https://doi.org/10.1016/j.nlm.2008.02.005

Lockrow, J. P., Fortress, A. M., & Granholm, A.-C. E. (2012). Age-related neurodegeneration and memory loss in down syndrome. *Current Gerontology and Geriatrics Research*, *2012*, 463909. https://doi.org/10.1155/2012/463909

López-Ortiz, S., Pinto-Fraga, J., Valenzuela, P. L., Martín-Hernández, J., Seisdedos, M. M., García-López, O., Toschi, N., Di Giuliano, F., Garaci, F., Mercuri, N. B.,

Nisticò, R., Emanuele, E., Lista, S., Lucia, A., & Santos-Lozano, A. (2021). Physical Exercise and Alzheimer's Disease: Effects on Pathophysiological Molecular Pathways of the Disease. *International Journal of Molecular Sciences*, *22*(6), Article 6. https://doi.org/10.3390/ijms22062897

Loprinzi, P. D. (2019). The role of astrocytes on the effects of exercise on episodic memory function. *Physiology International*, *106*(1), 21–28. https://doi.org/10.1556/2060.106.2019.04

Lott, I. T., Doran, E., Nguyen, V. Q., Tournay, A., Head, E., & Gillen, D. L. (2011). Down Syndrome and Dementia: A Randomized, Controlled Trial of Antioxidant Supplementation. *American Journal of Medical Genetics. Part A*, *155A*(8), 1939–1948. https://doi.org/10.1002/ajmg.a.34114

Lott, I. T., & Head, E. (2019). Dementia in Down syndrome: Unique insights for Alzheimer disease research. *Nature Reviews. Neurology*, *15*(3), 135–147. https://doi.org/10.1038/s41582-018-0132-6

Lott, I. T., Head, E., Doran, E., & Busciglio, J. (2006). Beta-amyloid, oxidative stress and down syndrome. *Current Alzheimer Research*, *3*(5), 521–528. https://doi.org/10.2174/156720506779025305

Loveday, S. J., Thompson, J. M. D., & Mitchell, E. A. (2012). Bioelectrical impedance for measuring percentage body fat in young persons with Down syndrome: Validation with dual-energy absorptiometry. *Acta Paediatrica (Oslo, Norway: 1992)*, *101*(11), e491-495. https://doi.org/10.1111/j.1651-2227.2012.02821.x

Luca, M., & Luca, A. (2019). Oxidative Stress-Related Endothelial Damage in Vascular Depression and Vascular Cognitive Impairment: Beneficial Effects of Aerobic Physical Exercise. *Oxidative Medicine and Cellular Longevity, 2019*, 8067045. https://doi.org/10.1155/2019/8067045

Manna, C., Officioso, A., Trojsi, F., Tedeschi, G., Leoncini, S., Signorini, C., Ciccoli, L., & De Felice, C. (2016). Increased non-protein bound iron in Down syndrome: Contribution to lipid peroxidation and cognitive decline. *Free Radical Research*, *50*(12), 1422–1431. https://doi.org/10.1080/10715762.2016.1253833

Mapstone, M., Gross, T. J., Macciardi, F., Cheema, A. K., Petersen, M., Head, E., Handen, B. L., Klunk, W. E., Christian, B. T., Silverman, W., Lott, I. T., & Schupf, N. (2020). Metabolic correlates of prevalent mild cognitive impairment and Alzheimer's disease in adults with Down syndrome. *Alzheimer's & Dementia : Diagnosis, Assessment & Disease Monitoring*, *12*(1), e12028. https://doi.org/10.1002/dad2.12028

Margallo-Lana, M., Morris, C. M., Gibson, A. M., Tan, A. L., Kay, D. W. K., Tyrer, S. P., Moore, B. P., & Ballard, C. G. (2004). Influence of the amyloid precursor protein locus on dementia in Down syndrome. *Neurology*, *62*(11), 1996–1998. https://doi.org/10.1212/01.wnl.0000129275.13169.be

Markesbery, W. R., & Carney, J. M. (1999). Oxidative alterations in Alzheimer's disease. *Brain Pathology (Zurich, Switzerland)*, *9*(1), 133–146. https://doi.org/10.1111/j.1750-3639.1999.tb00215.x

Matthews, V. B., Aström, M.-B., Chan, M. H. S., Bruce, C. R., Krabbe, K. S., Prelovsek, O., Akerström, T., Yfanti, C., Broholm, C., Mortensen, O. H., Penkowa, M., Hojman, P., Zankari, A., Watt, M. J., Bruunsgaard, H., Pedersen, B. K., & Febbraio, M. A. (2009). Brain-derived neurotrophic factor is produced by skeletal muscle cells in response to contraction and enhances fat oxidation via activation of AMP-activated protein kinase. *Diabetologia*, *52*(7), 1409–1418. https://doi.org/10.1007/s00125-009-1364-1

McGeer, P. L., & McGeer, E. G. (1995). The inflammatory response system of brain: Implications for therapy of Alzheimer and other neurodegenerative diseases. *Brain Research. Brain Research Reviews*, *21*(2), 195–218. https://doi.org/10.1016/0165-0173(95)00011-9

McMorris, T., Tomporowski, P. D., & Audiffren, M. (Eds.). (2009). *Exercise and cognitive function*. Wiley.

Meeusen, R., Piacentini, M. F., & De Meirleir, K. (2001). Brain microdialysis in exercise research. *Sports Medicine (Auckland, N.Z.)*, *31*(14), 965–983. https://doi.org/10.2165/00007256-200131140-00002

Meeusen, R., Smolders, I., Sarre, S., de Meirleir, K., Keizer, H., Serneels, M., Ebinger, G., & Michotte, Y. (1997). Endurance training effects on neurotransmitter release in rat striatum: An in vivo microdialysis study. *Acta Physiologica Scandinavica*, *159*(4), 335–341. https://doi.org/10.1046/j.1365-201X.1997.00118.x

Meguid, N. A., Eltohamy, A. M., Anwar, M., Hashish, A. F., & Elnahry, A. (2014). Efficacy of selected treadmill training programme on oxidative stress in

adolescents with Down syndrome. *Eastern Mediterranean Health Journal = La Revue De Sante De La Mediterranee Orientale = Al-Majallah Al-Sihhiyah Li-Sharq Al-Mutawassit*, *19 Suppl 3*, S131-137.

Mehta, P. D., Capone, G., Jewell, A., & Freedland, R. L. (2007). Increased amyloid beta protein levels in children and adolescents with Down syndrome. *Journal of the Neurological Sciences*, *254*(1–2), 22–27. https://doi.org/10.1016/j.jns.2006.12.010

Mendonca, G. V., Pereira, F. D., & Fernhall, B. (2011). Effects of combined aerobic and resistance exercise training in adults with and without Down syndrome. *Archives of Physical Medicine and Rehabilitation*, *92*(1), 37–45. https://doi.org/10.1016/j.apmr.2010.09.015

Mendonca, G. V., Pereira, F. D., & Fernhall, B. (2013). Heart rate recovery and variability following combined aerobic and resistance exercise training in adults with and without Down syndrome. *Research in Developmental Disabilities*, *34*(1), 353–361. https://doi.org/10.1016/j.ridd.2012.08.023

Menzel, A., Samouda, H., Dohet, F., Loap, S., Ellulu, M. S., & Bohn, T. (2021). Common and Novel Markers for Measuring Inflammation and Oxidative Stress Ex Vivo in Research and Clinical Practice-Which to Use Regarding Disease Outcomes? *Antioxidants (Basel, Switzerland)*, *10*(3), 414. https://doi.org/10.3390/antiox10030414

Miles, L. K., Nind, L. K., Henderson, Z., & Macrae, C. N. (2010). Moving memories: Behavioral synchrony and memory for self and others. *Journal of Experimental Social Psychology*, *46*(2), 457–460. https://doi.org/10.1016/j.jesp.2009.12.006

Minoretti, P., Gazzaruso, C., Vito, C. D., Emanuele, E., Bianchi, M., Coen, E., Reino, M., & Geroldi, D. (2006). Effect of the functional toll-like receptor 4 Asp299Gly polymorphism on susceptibility to late-onset Alzheimer's disease. *Neuroscience Letters*, *391*(3), 147–149. https://doi.org/10.1016/j.neulet.2005.08.047

Mithaiwala, M. N., Santana-Coelho, D., Porter, G. A., & O'Connor, J. C. (2021). Neuroinflammation and the Kynurenine Pathway in CNS Disease: Molecular Mechanisms and Therapeutic Implications. *Cells*, *10*(6), 1548. https://doi.org/10.3390/cells10061548

Mollo, N., Cicatiello, R., Aurilia, M., Scognamiglio, R., Genesio, R., Charalambous, M., Paladino, S., Conti, A., Nitsch, L., & Izzo, A. (2020). Targeting Mitochondrial Network Architecture in Down Syndrome and Aging. *International Journal of Molecular Sciences*, *21*(9), 3134. https://doi.org/10.3390/ijms21093134

Monteiro-Junior, R. S., de Tarso Maciel-Pinheiro, P., da Matta Mello Portugal, E., da Silva Figueiredo, L. F., Terra, R., Carneiro, L. S. F., Rodrigues, V. D., Nascimento, O. J. M., Deslandes, A. C., & Laks, J. (2018). Effect of Exercise on Inflammatory Profile of Older Persons: Systematic Review and Meta-Analyses. *Journal of Physical Activity & Health*, *15*(1), 64–71. https://doi.org/10.1123/jpah.2016-0735

Moon, H. Y., Becke, A., Berron, D., Becker, B., Sah, N., Benoni, G., Janke, E., Lubejko, S., Greig, N., Mattison, J. A., Duzel, E., & van Praag, H. (2016). Running-Induced Systemic Cathepsin B Secretion Is Associated with Memory Function. *Cell Metabolism*, *24*. https://doi.org/10.1016/j.cmet.2016.05.025

Moreira, O. C., Estébanez, B., Martínez-Florez, S., de Paz, J. A., Cuevas, M. J., & González-Gallego, J. (2017). Mitochondrial Function and Mitophagy in the Elderly: Effects of Exercise. *Oxidative Medicine and Cellular Longevity*, *2017*, 2012798. https://doi.org/10.1155/2017/2012798

Muchová, J., Žitňanová, I., & Ďuračková, Z. (2014). Oxidative stress and Down syndrome. Do antioxidants play a role in therapy? *Physiological Research*, *63*(5), 535–542. https://doi.org/10.33549/physiolres.932722

Mujica-Parodi, L. R., Amgalan, A., Sultan, S. F., Antal, B., Sun, X., Skiena, S., Lithen, A., Adra, N., Ratai, E.-M., Weistuch, C., Govindarajan, S. T., Strey, H. H., Dill, K. A., Stufflebeam, S. M., Veech, R. L., & Clarke, K. (2020). Diet modulates brain network stability, a biomarker for brain aging, in young adults. *Proceedings of the National Academy of Sciences*, *117*(11), 6170–6177. https://doi.org/10.1073/pnas.1913042117

Muñoz-Cánoves, P., Scheele, C., Pedersen, B. K., & Serrano, A. L. (2013). Interleukin-6 myokine signaling in skeletal muscle: A double-edged sword? *The FEBS Journal*, *280*(17), 4131–4148. https://doi.org/10.1111/febs.12338

Murray, J., & Ryan-Krause, P. (2010). Obesity in children with Down syndrome: Background and recommendations for management. *Pediatric Nursing*, *36*(6), 314–319.

Nascimento, C. M. C., Pereira, J. R., de Andrade, L. P., Garuffi, M., Talib, L. L., Forlenza, O. V., Cancela, J. M., Cominetti, M. R., & Stella, F. (2014). Physical exercise in MCI elderly promotes reduction of pro-inflammatory cytokines and improvements on cognition and BDNF peripheral levels. *Current Alzheimer Research*, *11*(8), 799–805. https://doi.org/10.2174/1567205011081409101228 49

Nay, K., Smiles, W. J., Kaiser, J., McAloon, L. M., Loh, K., Galic, S., Oakhill, J. S., Gundlach, A. L., & Scott, J. W. (2021). Molecular Mechanisms Underlying the Beneficial Effects of Exercise on Brain Function and Neurological Disorders. *International Journal of Molecular Sciences*, *22*(8), 4052. https://doi.org/10.3390/ijms22084052

Nichol, K., Deeny, S. P., Seif, J., Camaclang, K., & Cotman, C. W. (2009). Exercise improves cognition and hippocampal plasticity in APOE epsilon4 mice. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *5*(4), 287–294. https://doi.org/10.1016/j.jalz.2009.02.006

Nieman, D. C., Luo, B., Dréau, D., Henson, D. A., Shanely, R. A., Dew, D., & Meaney, M. P. (2014). Immune and inflammation responses to a 3-day period of intensified running versus cycling. *Brain, Behavior, and Immunity*, *39*, 180–185. https://doi.org/10.1016/j.bbi.2013.09.004

Nokia, M. S., Lensu, S., Ahtiainen, J. P., Johansson, P. P., Koch, L. G., Britton, S. L., & Kainulainen, H. (2016). Physical exercise increases adult hippocampal neurogenesis in male rats provided it is aerobic and sustained. *The Journal of Physiology*, *594*(7), 1855–1873. https://doi.org/10.1113/JP271552

Norton, S., Matthews, F. E., Barnes, D. E., Yaffe, K., & Brayne, C. (2014). Potential for primary prevention of Alzheimer's disease: An analysis of population-based data. *The Lancet Neurology*, *13*(8), 788–794. https://doi.org/10.1016/S1474-4422(14)70136-X

Nunomura, A., Perry, G., Aliev, G., Hirai, K., Takeda, A., Balraj, E. K., Jones, P. K., Ghanbari, H., Wataya, T., Shimohama, S., Chiba, S., Atwood, C. S., Petersen, R. B., & Smith, M. A. (2001). Oxidative damage is the earliest event in Alzheimer disease. *Journal of Neuropathology and Experimental Neurology*, *60*(8), 759–767. https://doi.org/10.1093/jnen/60.8.759

O'Connell, R. M., Taganov, K. D., Boldin, M. P., Cheng, G., & Baltimore, D. (2007). MicroRNA-155 is induced during the macrophage inflammatory response. *Proceedings of the National Academy of Sciences*, *104*(5), 1604–1609. https://doi.org/10.1073/pnas.0610731104

Ordonez, F. J., Rosety, I., Rosety, M. A., Camacho-Molina, A., Fornieles, G., Rosety, M., & Rosety-Rodriguez, M. (2012). Aerobic training at moderate intensity reduced protein oxidation in adolescents with Down syndrome. *Scandinavian Journal of Medicine & Science in Sports*, *22*(1), 91–94. https://doi.org/10.1111/j.1600-0838.2010.01153.x

Ostrowski, K., Rohde, T., Asp, S., Schjerling, P., & Pedersen, B. K. (1999). Pro- and anti-inflammatory cytokine balance in strenuous exercise in humans. *The Journal of Physiology*, *515*(Pt 1), 287–291. https://doi.org/10.1111/j.1469-7793.1999.287ad.x

Ostrowski, K., Schjerling, P., & Pedersen, B. K. (2000). Physical activity and plasma interleukin-6 in humans—Effect of intensity of exercise. *European Journal of Applied Physiology*, *83*(6), 512–515. https://doi.org/10.1007/s004210000312

Panagaki, T., Randi, E. B., Augsburger, F., & Szabo, C. (2019). Overproduction of H2S, generated by CBS, inhibits mitochondrial Complex IV and suppresses oxidative phosphorylation in Down syndrome. *Proceedings of the National Academy of Sciences of the United States of America*, *116*(38), 18769–18771. https://doi.org/10.1073/pnas.1911895116

Pape, S. E., Baksh, R. A., Startin, C., Hamburg, S., Hithersay, R., & Strydom, A. (2021). The Association between Physical Activity and CAMDEX-DS Changes Prior to the Onset of Alzheimer's Disease in Down Syndrome. *Journal of Clinical Medicine*, *10*(9), Article 9. https://doi.org/10.3390/jcm10091882

Parrini, M., Ghezzi, D., Deidda, G., Medrihan, L., Castroflorio, E., Alberti, M., Baldelli, P., Cancedda, L., & Contestabile, A. (2017). Aerobic exercise and a BDNF-mimetic therapy rescue learning and memory in a mouse model of Down syndrome. *Scientific Reports*, *7*, 16825. https://doi.org/10.1038/s41598-017-17201-8

Pastula, R. M., Stopka, C. B., Delisle, A. T., & Hass, C. J. (2012). Effect of moderate-intensity exercise training on the cognitive function of young adults with intellectual disabilities. *Journal of Strength and Conditioning Research*, *26*(12), 3441–3448. https://doi.org/10.1519/JSC.0b013e318270fc83

Patterson, D. (2009). Molecular genetic analysis of Down syndrome. *Human Genetics*, *126*(1), 195–214. https://doi.org/10.1007/s00439-009-0696-8

Pecze, L., Randi, E. B., & Szabo, C. (2020). Meta-analysis of metabolites involved in bioenergetic pathways reveals a pseudohypoxic state in Down syndrome. *Molecular Medicine*, *26*(1), 102. https://doi.org/10.1186/s10020-020-00225-8

Pedersen, B. K., & Fischer, C. P. (2007). Beneficial health effects of exercise—The role of IL-6 as a myokine. *Trends in Pharmacological Sciences*, *28*(4), 152–156. https://doi.org/10.1016/j.tips.2007.02.002

Peña-Bautista, C., Álvarez-Sánchez, L., Ferrer, I., López-Nogueroles, M., Cañada-Martínez, A. J., Oger, C., Galano, J.-M., Durand, T., Baquero, M., & Cháfer-Pericás, C. (2021). Lipid Peroxidation Assessment in Preclinical Alzheimer Disease Diagnosis. *Antioxidants*, *10*(7), 1043. https://doi.org/10.3390/antiox10071043

Peña-Bautista, C., Baquero, M., Vento, M., & Cháfer-Pericás, C. (2019). Free radicals in Alzheimer's disease: Lipid peroxidation biomarkers. *Clinica Chimica Acta*, *491*, 85–90. https://doi.org/10.1016/j.cca.2019.01.021

Peng, S., Wuu, J., Mufson, E. J., & Fahnestock, M. (2005). Precursor form of brain-derived neurotrophic factor and mature brain-derived neurotrophic factor are

decreased in the pre-clinical stages of Alzheimer's disease. *Journal of Neurochemistry*, *93*(6), 1412–1421. https://doi.org/10.1111/j.1471-4159.2005.03135.x

Perić, D. B., Milićević-Marinković, B., & Djurović, D. (2022). The effect of the adapted soccer programme on motor learning and psychosocial behaviour in adolescents with Down syndrome. *Journal of Intellectual Disability Research: JIDR*, *66*(6), 533–544. https://doi.org/10.1111/jir.12881

Perluigi, M., & Butterfield, D. A. (2012). Oxidative Stress and Down Syndrome: A Route toward Alzheimer-Like Dementia. *Current Gerontology and Geriatrics Research*, *2012*, 724904. https://doi.org/10.1155/2012/724904

Peven, J. C., Handen, B. L., Laymon, C. M., Fleming, V., Piro-Gambetti, B., Christian, B. T., Klunk, W., Cohen, A. D., Okonkwo, O., & Hartley, S. L. (2022). Physical activity, memory function, and hippocampal volume in adults with Down syndrome. *Frontiers in Integrative Neuroscience*, *16*. https://www.frontiersin.org/articles/10.3389/fnint.2022.919711

Phillips, A. C., & Holland, A. J. (2011). Assessment of objectively measured physical activity levels in individuals with intellectual disabilities with and without Down's syndrome. *PloS One*, *6*(12), e28618. https://doi.org/10.1371/journal.pone.0028618

Piccoli, C., Izzo, A., Scrima, R., Bonfiglio, F., Manco, R., Negri, R., Quarato, G., Cela, O., Ripoli, M., Prisco, M., Gentile, F., Calì, G., Pinton, P., Conti, A., Nitsch, L., & Capitanio, N. (2013). Chronic pro-oxidative state and mitochondrial

dysfunctions are more pronounced in fibroblasts from Down syndrome foeti with congenital heart defects. *Human Molecular Genetics*, *22*(6), 1218–1232. https://doi.org/10.1093/hmg/dds529

Powers, S. K., Talbert, E. E., & Adhihetty, P. J. (2011). Reactive oxygen and nitrogen species as intracellular signals in skeletal muscle. *The Journal of Physiology*, *589*(Pt 9), 2129–2138. https://doi.org/10.1113/jphysiol.2010.201327

Prasad, K. N. (2017). Oxidative stress and pro-inflammatory cytokines may act as one of the signals for regulating microRNAs expression in Alzheimer's disease. *Mechanisms of Ageing and Development*, *162*, 63–71. https://doi.org/10.1016/j.mad.2016.12.003

Ptomey, L. T., Szabo, A. N., Willis, E. A., Gorczyca, A. M., Greene, J. L., Danon, J. C., & Donnelly, J. E. (2018). Changes in cognitive function after a 12-week exercise intervention in adults with Down syndrome. *Disability and Health Journal*, *11*(3), 486–490. https://doi.org/10.1016/j.dhjo.2018.02.003

Puertas, M. C., Martínez-Martos, J. M., Cobo, M. P., Carrera, M. P., Mayas, M. D., & Ramírez-Expósito, M. J. (2012). Plasma oxidative stress parameters in men and women with early stage Alzheimer type dementia. *Experimental Gerontology*, *47*(8), 625–630. https://doi.org/10.1016/j.exger.2012.05.019

Radak, Z., Hart, N., Sarga, L., Koltai, E., Atalay, M., Ohno, H., & Boldogh, I. (2010). Exercise plays a preventive role against Alzheimer's disease. *Journal of Alzheimer's Disease: JAD*, *20*(3), 777–783. https://doi.org/10.3233/JAD-2010-091531

Radom-Aizik, S., & Cooper, D. M. (2016). Bridging the Gaps: The Promise of Omics Studies in Pediatric Exercise Research. *Pediatric Exercise Science*, *28*(2), 194–201. https://doi.org/10.1123/pes.2015-0270

Rani, V., Verma, R., Kumar, K., & Chawla, R. (2022). Role of pro-inflammatory cytokines in Alzheimer's disease and neuroprotective effects of pegylated self-assembled nanoscaffolds. *Current Research in Pharmacology and Drug Discovery*, *4*, 100149. https://doi.org/10.1016/j.crphar.2022.100149

Rasmussen, P., Brassard, P., Adser, H., Pedersen, M. V., Leick, L., Hart, E., Secher, N. H., Pedersen, B. K., & Pilegaard, H. (2009). Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. *Experimental Physiology*, *94*(10), 1062–1069. https://doi.org/10.1113/expphysiol.2009.048512

Ravančić, M. E., Obradović, V., Ravančić, M. E., & Obradović, V. (2022). Supplements and Down Syndrome. In *Dietary Supplements—Challenges and Future Research*. IntechOpen. https://doi.org/10.5772/intechopen.106655

Ribarič, S. (2022). Physical Exercise, a Potential Non-Pharmacological Intervention for Attenuating Neuroinflammation and Cognitive Decline in Alzheimer's Disease Patients. *International Journal of Molecular Sciences*, *23*(6), Article 6. https://doi.org/10.3390/ijms23063245

Rimmer, J. H., Heller, T., Wang, E., & Valerio, I. (2004). Improvements in physical fitness in adults with Down syndrome. *American Journal of Mental Retardation: AJMR*, *109*(2), 165–174. https://doi.org/10.1352/0895-8017(2004)109<165:IIPFIA>2.0.CO;2

Ringenbach, S., Arnold, N., Myer, B., Hayes, C., Nam, K., & Chen, C.-C. (2021). Executive Function Improves Following Acute Exercise in Adults with Down Syndrome. *Brain Sciences*, *11*(5), Article 5. https://doi.org/10.3390/brainsci11050620

Roat, E., Prada, N., Ferraresi, R., Giovenzana, C., Nasi, M., Troiano, L., Pinti, M., Nemes, E., Lugli, E., Biagioni, O., Mariotti, M., Ciacci, L., Consolo, U., Balli, F., & Cossarizza, A. (2007). Mitochondrial alterations and tendency to apoptosis in peripheral blood cells from children with Down syndrome. *FEBS Letters*, *581*(3), 521–525. https://doi.org/10.1016/j.febslet.2006.12.058

Robinson, M. M., Lowe, V. J., & Nair, K. S. (2018). Increased Brain Glucose Uptake After 12 Weeks of Aerobic High-Intensity Interval Training in Young and Older Adults. *The Journal of Clinical Endocrinology and Metabolism*, *103*(1), 221–227. https://doi.org/10.1210/jc.2017-01571

Rohn, T. T., McCarty, K. L., Love, J. E., & Head, E. (2014). Is Apolipoprotein E4 an Important Risk Factor for Dementia in Persons with Down Syndrome? *Journal of Parkinson's Disease and Alzheimer's Disease*, *1*(1), 7.

Rosety-Rodriguez, M., Bernardi, M., Elosegui, S., Rosety, I., Diaz, A. J., Rosety, M. A., Brenes, F., Oliva-Pascual-Vaca, A., Alvero-Cruz, J. R., & Ordonez, F. J. (2021). A Short-Term Resistance Training Circuit Improved Antioxidants in Sedentary Adults with Down Syndrome. *Oxidative Medicine and Cellular Longevity*, *2021*, e8811153. https://doi.org/10.1155/2021/8811153

Rosety-Rodriguez, M., Camacho, A., Rosety, I., Fornieles, G., Rosety, M. A., Diaz, A. J., Rosety, M., & Ordonez, F. J. (2013). Resistance circuit training reduced inflammatory cytokines in a cohort of male adults with Down syndrome. *Medical Science Monitor : International Medical Journal of Experimental and Clinical Research*, *19*, 949–953. https://doi.org/10.12659/MSM.889362

Rosety-Rodriguez, M., Rosety, I., Fornieles-Gonzalez, G., Diaz, A., Rosety, M., & Ordonez, F. J. (2010). A 12-week aerobic training programme reduced plasmatic allantoin in adolescents with Down syndrome. *British Journal of Sports Medicine*, *44*(9), 685–687. https://doi.org/10.1136/bjsm.2008.052530

Rothaug, M., Becker-Pauly, C., & Rose-John, S. (2016). The role of interleukin-6 signaling in nervous tissue. *Biochimica Et Biophysica Acta*, *1863*(6 Pt A), 1218–1227. https://doi.org/10.1016/j.bbamcr.2016.03.018

Rotta, K., Raaymakers, A., & Poling, A. (2023). Using Positive Reinforcement to Increase the Physical Activity of Individuals with Developmental Disabilities: A Review. *Journal of Developmental and Physical Disabilities*, *35*(4), 551–575. https://doi.org/10.1007/s10882-022-09873-6

Safieh, M., Korczyn, A. D., & Michaelson, D. M. (2019). ApoE4: An emerging therapeutic target for Alzheimer's disease. *BMC Medicine*, *17*(1), 64. https://doi.org/10.1186/s12916-019-1299-4

Santos, R. X., Correia, S. C., Zhu, X., Lee, H.-G., Petersen, R. B., Nunomura, A., Smith, M. A., Perry, G., & Moreira, P. I. (2012). Nuclear and mitochondrial DNA

oxidation in Alzheimer's disease. *Free Radical Research*, *46*(4), 565–576. https://doi.org/10.3109/10715762.2011.648188

Sawa, M., Overk, C., Becker, A., Derse, D., Albay, R., Weldy, K., Salehi, A., Beach, T. G., Doran, E., Head, E., Yu, Y. E., & Mobley, W. C. (2022). Impact of increased APP gene dose in Down syndrome and the Dp16 mouse model. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *18*(6), 1203–1234. https://doi.org/10.1002/alz.12463

Sawyer, B. J., Stokes, D. G., Womack, C. J., Morton, R. H., Weltman, A., & Gaesser, G. A. (2014). Strength training increases endurance time to exhaustion during high-intensity exercise despite no change in critical power. *Journal of Strength and Conditioning Research*, *28*(3), 601–609. https://doi.org/10.1519/JSC.0b013e31829e113b

Scheller, J., Chalaris, A., Schmidt-Arras, D., & Rose-John, S. (2011). The pro- and anti-inflammatory properties of the cytokine interleukin-6. *Biochimica Et Biophysica Acta*, *1813*(5), 878–888. https://doi.org/10.1016/j.bbamcr.2011.01.034

Seifert, T., Brassard, P., Wissenberg, M., Rasmussen, P., Nordby, P., Stallknecht, B., Adser, H., Jakobsen, A. H., Pilegaard, H., Nielsen, H. B., & Secher, N. H. (2010). Endurance training enhances BDNF release from the human brain. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, *298*(2), R372-377. https://doi.org/10.1152/ajpregu.00525.2009

Seron, B. B., Silva, R. A. C., & Greguol, M. (2014). Effects of two programs of exercise on body composition of adolescents with Down syndrome. *Revista Paulista de Pediatria*, *32*, 92–98. https://doi.org/10.1590/S0103-05822014000100015

Sharma, A., Fernandes, D. C., Reis, R. L., Gołubczyk, D., Neumann, S., Lukomska, B., Janowski, M., Kortylewski, M., Walczak, P., Oliveira, J. M., & Maciaczyk, J. (2023). Cutting-edge advances in modeling the blood–brain barrier and tools for its reversible permeabilization for enhanced drug delivery into the brain. *Cell & Bioscience*, *13*, 137. https://doi.org/10.1186/s13578-023-01079-3

Sheedy, F. J., Palsson-McDermott, E., Hennessy, E. J., Martin, C., O'Leary, J. J., Ruan, Q., Johnson, D. S., Chen, Y., & O'Neill, L. A. J. (2010). Negative regulation of TLR4 via targeting of the proinflammatory tumor suppressor PDCD4 by the microRNA miR-21. *Nature Immunology*, *11*(2), 141–147. https://doi.org/10.1038/ni.1828

Shields, N., Downs, J., de Haan, J. B., Taylor, N. F., Torr, J., Fernhall, B., Kingsley, M., Mnatzaganian, G., & Leonard, H. (2018). What effect does regular exercise have on oxidative stress in people with Down syndrome? A systematic review with meta-analyses. *Journal of Science and Medicine in Sport*, *21*(6), 596–603. https://doi.org/10.1016/j.jsams.2017.10.015

Shields, N., Mizzi, N., Buhlert-Smith, K., Strydom, A., Prendergast, L., & Hocking, D. R. (2022). A 12-week exercise programme has a positive effect on everyday executive function in young people with Down syndrome: A pilot non-

randomised controlled trial. *Journal of Intellectual Disability Research*, *66*(12), 924–938. https://doi.org/10.1111/jir.12979

Shono, N., Urata, H., Saltin, B., Mizuno, M., Harada, T., Shindo, M., & Tanaka, H. (2002). Effects of low intensity aerobic training on skeletal muscle capillary and blood lipoprotein profiles. *Journal of Atherosclerosis and Thrombosis*, *9*(1), 78–85. https://doi.org/10.5551/jat.9.78

Shukkur, E. A., Shimohata, A., Akagi, T., Yu, W., Yamaguchi, M., Murayama, M., Chui, D., Takeuchi, T., Amano, K., Subramhanya, K. H., Hashikawa, T., Sago, H., Epstein, C. J., Takashima, A., & Yamakawa, K. (2006). Mitochondrial dysfunction and tau hyperphosphorylation in Ts1Cje, a mouse model for Down syndrome. *Human Molecular Genetics*, *15*(18), 2752–2762. https://doi.org/10.1093/hmg/ddl211

Simpson, R. J., McFarlin, B. K., McSporran, C., Spielmann, G., ó Hartaigh, B., & Guy, K. (2009). Toll-like receptor expression on classic and pro-inflammatory blood monocytes after acute exercise in humans. *Brain, Behavior, and Immunity*, *23*(2), 232–239. https://doi.org/10.1016/j.bbi.2008.09.013

Sinet, P. M. (1982). Metabolism of Oxygen Derivatives in Down's Syndrome*. *Annals of the New York Academy of Sciences*, *396*(1), 83–94. https://doi.org/10.1111/j.1749-6632.1982.tb26845.x

Sleiman, S. F., Henry, J., Al-Haddad, R., El Hayek, L., Abou Haidar, E., Stringer, T., Ulja, D., Karuppagounder, S. S., Holson, E. B., Ratan, R. R., Ninan, I., & Chao, M. V. (2016). Exercise promotes the expression of brain derived neurotrophic

factor (BDNF) through the action of the ketone body β-hydroxybutyrate. *eLife*, *5*, e15092. https://doi.org/10.7554/eLife.15092

Snyder, A. C., O'Hagan, K. P., Clifford, P. S., Hoffman, M. D., & Foster, C. (1993). Exercise responses to in-line skating: Comparisons to running and cycling. *International Journal of Sports Medicine*, *14*(1), 38–42. https://doi.org/10.1055/s-2007-1021143

Sobol, N. A., Hoffmann, K., Frederiksen, K. S., Vogel, A., Vestergaard, K., Brændgaard, H., Gottrup, H., Lolk, A., Wermuth, L., Jakobsen, S., Laugesen, L., Gergelyffy, R., Høgh, P., Bjerregaard, E., Siersma, V., Andersen, B. B., Johannsen, P., Waldemar, G., Hasselbalch, S. G., & Beyer, N. (2016). Effect of aerobic exercise on physical performance in patients with Alzheimer's disease. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *12*(12), 1207–1215. https://doi.org/10.1016/j.jalz.2016.05.004

Stein, A. M., da Silva, T. M. V., Coelho, F. G. de M., Rueda, A. V., Camarini, R., & Galduróz, R. F. S. (2021). Acute exercise increases circulating IGF-1 in Alzheimer's disease patients, but not in older adults without dementia. *Behavioural Brain Research*, *396*, 112903. https://doi.org/10.1016/j.bbr.2020.112903

Stewart, L. K., Flynn, M. G., Campbell, W. W., Craig, B. A., Robinson, J. P., McFarlin, B. K., Timmerman, K. L., Coen, P. M., Felker, J., & Talbert, E. (2005). Influence of exercise training and age on CD14+ cell-surface expression of toll-like receptor

2 and 4. *Brain, Behavior, and Immunity*, *19*(5), 389–397. https://doi.org/10.1016/j.bbi.2005.04.003

Stocker, H., Nabers, A., Perna, L., Möllers, T., Rujescu, D., Hartmann, A., Holleczek, B., Schöttker, B., Gerwert, K., & Brenner, H. (2020). Prediction of Alzheimer's disease diagnosis within 14 years through Aβ misfolding in blood plasma compared to APOE4 status, and other risk factors. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *16*(2), 283–291. https://doi.org/10.1016/j.jalz.2019.08.189

Ströhle, A., Schmidt, D. K., Schultz, F., Fricke, N., Staden, T., Hellweg, R., Priller, J., Rapp, M. A., & Rieckmann, N. (2015). Drug and Exercise Treatment of Alzheimer Disease and Mild Cognitive Impairment: A Systematic Review and Meta-Analysis of Effects on Cognition in Randomized Controlled Trials. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *23*(12), 1234–1249. https://doi.org/10.1016/j.jagp.2015.07.007

Strydom, A., Dickinson, M. J., Shende, S., Pratico, D., & Walker, Z. (2009). Oxidative stress and cognitive ability in adults with Down syndrome. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *33*(1), 76–80. https://doi.org/10.1016/j.pnpbp.2008.10.006

Stults-Kolehmainen, M. A., & Sinha, R. (2014). The effects of stress on physical activity and exercise. *Sports Medicine (Auckland, N.Z.)*, *44*(1), 81–121. https://doi.org/10.1007/s40279-013-0090-5

Sullivan, K. D., Evans, D., Pandey, A., Hraha, T. H., Smith, K. P., Markham, N., Rachubinski, A. L., Wolter-Warmerdam, K., Hickey, F., Espinosa, J. M., & Blumenthal, T. (2017). Trisomy 21 causes changes in the circulating proteome indicative of chronic autoinflammation. *Scientific Reports*, *7*(1), 14818. https://doi.org/10.1038/s41598-017-13858-3

Sungkarat, S., Boripuntakul, S., Kumfu, S., Lord, S. R., & Chattipakorn, N. (2018). Tai Chi Improves Cognition and Plasma BDNF in Older Adults With Mild Cognitive Impairment: A Randomized Controlled Trial. *Neurorehabilitation and Neural Repair*, *32*(2), 142–149. https://doi.org/10.1177/1545968317753682

Suzuki, K. (2018). Cytokine Response to Exercise and Its Modulation. *Antioxidants*, *7*(1), 17. https://doi.org/10.3390/antiox7010017

Suzuki, T., Shimada, H., Makizako, H., Doi, T., Yoshida, D., Ito, K., Shimokata, H., Washimi, Y., Endo, H., & Kato, T. (2013). A randomized controlled trial of multicomponent exercise in older adults with mild cognitive impairment. *PloS One*, *8*(4), e61483. https://doi.org/10.1371/journal.pone.0061483

Swain, R. A., Harris, A. B., Wiener, E. C., Dutka, M. V., Morris, H. D., Theien, B. E., Konda, S., Engberg, K., Lauterbur, P. C., & Greenough, W. T. (2003). Prolonged exercise induces angiogenesis and increases cerebral blood volume in primary motor cortex of the rat. *Neuroscience*, *117*(4), 1037–1046. https://doi.org/10.1016/s0306-4522(02)00664-4

Szabo, C. (2020). The re-emerging pathophysiological role of the cystathionine-β-synthase—Hydrogen sulfide system in Down syndrome. *The FEBS Journal*, *287*(15), 3150–3160. https://doi.org/10.1111/febs.15214

Szuhany, K. L., Bugatti, M., & Otto, M. W. (2015). A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor. *Journal of Psychiatric Research*, *60*, 56–64. https://doi.org/10.1016/j.jpsychires.2014.10.003

Tan, K.-L., Lee, H.-C., Cheah, P.-S., & Ling, K.-H. (2023). Mitochondrial Dysfunction in Down Syndrome: From Pathology to Therapy. *Neuroscience*, *511*, 1–12. https://doi.org/10.1016/j.neuroscience.2022.12.003

Terada, T., Obi, T., Bunai, T., Matsudaira, T., Yoshikawa, E., Ando, I., Futatsubashi, M., Tsukada, H., & Ouchi, Y. (2020). In vivo mitochondrial and glycolytic impairments in patients with Alzheimer disease. *Neurology*, *94*(15), e1592–e1604. https://doi.org/10.1212/WNL.0000000000009249

Tokgöz, S., & Claassen, J. A. H. R. (2021). Exercise as Potential Therapeutic Target to Modulate Alzheimer's Disease Pathology in APOE ε4 Carriers: A Systematic Review. *Cardiology and Therapy*, *10*(1), 67–88. https://doi.org/10.1007/s40119-020-00209-z

Tomporowski, P. (1997). The Effects of Physical and Mental Training on the Mental Abilities of Older Adults. *Journal of Aging and Physical Activity*, *5*, 9–26. https://doi.org/10.1123/japa.5.1.9

Torres, L. L., Quaglio, N. B., de Souza, G. T., Garcia, R. T., Dati, L. M. M., Moreira, W. L., Loureiro, A. P. de M., de Souza-Talarico, J. N., Smid, J., Porto, C. S., Bottino,

C. M. de C., Nitrini, R., Barros, S. B. de M., Camarini, R., & Marcourakis, T. (2011). Peripheral oxidative stress biomarkers in mild cognitive impairment and Alzheimer's disease. *Journal of Alzheimer's Disease: JAD*, *26*(1), 59–68. https://doi.org/10.3233/JAD-2011-110284

Tsimaras, V., Giagazoglou, P., Fotiadou, E., Christoulas, K., & Angelopoulou, N. (2003). Jog-walk training in cardiorespiratory fitness of adults with Down syndrome. *Perceptual and Motor Skills*, *96*(3 Pt 2), 1239–1251. https://doi.org/10.2466/pms.2003.96.3c.1239

Tsimaras, V. K., & Fotiadou, E. G. (2004). Effect of training on the muscle strength and dynamic balance ability of adults with down syndrome. *Journal of Strength and Conditioning Research*, *18*(2), 343–347. https://doi.org/10.1519/R-12832.1

Tsukiyama, Y., Ito, T., Nagaoka, K., Eguchi, E., & Ogino, K. (2017). Effects of exercise training on nitric oxide, blood pressure and antioxidant enzymes. *Journal of Clinical Biochemistry and Nutrition*, *60*(3), 180–186. https://doi.org/10.3164/jcbn.16-108

Valente-Silva, P., & Ruas, J. L. (2017). Tryptophan-Kynurenine Metabolites in Exercise and Mental Health. In B. Spiegelman (Ed.), *Hormones, Metabolism and the Benefits of Exercise*. Springer. http://www.ncbi.nlm.nih.gov/books/NBK543788/

Valenti, D., Braidy, N., De Rasmo, D., Signorile, A., Rossi, L., Atanasov, A. G., Volpicella, M., Henrion-Caude, A., Nabavi, S. M., & Vacca, R. A. (2018). Mitochondria as pharmacological targets in Down syndrome. *Free Radical*

Biology & Medicine, *114*, 69–83. https://doi.org/10.1016/j.freeradbiomed.2017.08.014

Valenti, D., Manente, G. A., Moro, L., Marra, E., & Vacca, R. A. (2011). Deficit of complex I activity in human skin fibroblasts with chromosome 21 trisomy and overproduction of reactive oxygen species by mitochondria: Involvement of the cAMP/PKA signalling pathway. *Biochemical Journal*, *435*(3), 679–688. https://doi.org/10.1042/BJ20101908

Valenti, D., Tullo, A., Caratozzolo, M. F., Merafina, R. S., Scartezzini, P., Marra, E., & Vacca, R. A. (2010). Impairment of F1F0-ATPase, adenine nucleotide translocator and adenylate kinase causes mitochondrial energy deficit in human skin fibroblasts with chromosome 21 trisomy. *Biochemical Journal*, *431*(2), 299–310. https://doi.org/10.1042/BJ20100581

Valenzuela, P. L., Castillo-García, A., Morales, J. S., de la Villa, P., Hampel, H., Emanuele, E., Lista, S., & Lucia, A. (2020). Exercise benefits on Alzheimer's disease: State-of-the-science. *Ageing Research Reviews*, *62*, 101108. https://doi.org/10.1016/j.arr.2020.101108

Varela, A. M., Sardinha, L. B., & Pitetti, K. H. (2001). Effects of an aerobic rowing training regimen in young adults with Down syndrome. *American Journal of Mental Retardation: AJMR*, *106*(2), 135–144. https://doi.org/10.1352/0895-8017(2001)106<0135:EOAART>2.0.CO;2

Vassalle, C., Del Turco, S., Sabatino, L., Basta, G., Maltinti, M., Sbrana, F., Ndreu, R., Mastorci, F., & Pingitore, A. (2020). New inflammatory and oxidative stress-

based biomarker changes in response to a half-marathon in recreational athletes. *The Journal of Sports Medicine and Physical Fitness*, *60*(10), 1390–1395. https://doi.org/10.23736/S0022-4707.20.10738-2

Veteleanu, A., Pape, S., Davies, K., Kodosaki, E., Hye, A., Zelek, W. M., Strydom, A., & Morgan, B. P. (2023). Complement dysregulation and Alzheimer's disease in Down syndrome. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *19*(4), 1383–1392. https://doi.org/10.1002/alz.12799

Walter, S., Letiembre, M., Liu, Y., Heine, H., Penke, B., Hao, W., Bode, B., Manietta, N., Walter, J., Schulz-Schuffer, W., & Fassbender, K. (2007). Role of the toll-like receptor 4 in neuroinflammation in Alzheimer's disease. *Cellular Physiology and Biochemistry: International Journal of Experimental Cellular Physiology, Biochemistry, and Pharmacology*, *20*(6), 947–956. https://doi.org/10.1159/000110455

Wang, J., Markesbery, W. R., & Lovell, M. A. (2006). Increased oxidative damage in nuclear and mitochondrial DNA in mild cognitive impairment. *Journal of Neurochemistry*, *96*(3), 825–832. https://doi.org/10.1111/j.1471-4159.2005.03615.x

Wang, L.-Y., Pei, J., Zhan, Y.-J., & Cai, Y.-W. (2020). Overview of Meta-Analyses of Five Non-pharmacological Interventions for Alzheimer's Disease. *Frontiers in Aging Neuroscience*, *12*. https://www.frontiersin.org/articles/10.3389/fnagi.2020.594432

Wannamethee, S. G., Lowe, G. D. O., Whincup, P. H., Rumley, A., Walker, M., & Lennon, L. (2002). Physical activity and hemostatic and inflammatory variables in elderly men. *Circulation*, *105*(15), 1785–1790. https://doi.org/10.1161/hc1502.107117

Weber, G. E., Koenig, K., Khrestian, M., Shao, Y., Tuason, E. D., Gramm, M., Lal, D., Leverenz, J. B., & Bekris, L. M. (2020). Altered Relationship between Soluble TREM2 and Inflammatory Markers in Young Adults with Down Syndrome: A Preliminary Report. *Journal of Immunology (Baltimore, Md. : 1950)*, *204*(5), 1111–1118. https://doi.org/10.4049/jimmunol.1901166

Whitt-Glover, M. C., O'Neill, K. L., & Stettler, N. (2006). Physical activity patterns in children with and without Down syndrome. *Pediatric Rehabilitation*, *9*(2), 158–164. https://doi.org/10.1080/13638490500353202

Wing, R. R., & Jeffery, R. W. (1999). Benefits of recruiting participants with friends and increasing social support for weight loss and maintenance. *Journal of Consulting and Clinical Psychology*, *67*(1), 132–138. https://doi.org/10.1037//0022-006x.67.1.132

Winter, B., Breitenstein, C., Mooren, F. C., Voelker, K., Fobker, M., Lechtermann, A., Krueger, K., Fromme, A., Korsukewitz, C., Floel, A., & Knecht, S. (2007). High impact running improves learning. *Neurobiology of Learning and Memory*, *87*(4), 597–609. https://doi.org/10.1016/j.nlm.2006.11.003

Wiseman, F. K., Al-Janabi, T., Hardy, J., Karmiloff-Smith, A., Nizetic, D., Tybulewicz, V. L. J., Fisher, E. M. C., & Strydom, A. (2015). A genetic cause of Alzheimer

disease: Mechanistic insights from Down syndrome. *Nature Reviews. Neuroscience*, *16*(9), 564–574. https://doi.org/10.1038/nrn3983

Wrann, C. D., White, J. P., Salogiannnis, J., Laznik-Bogoslavski, D., Wu, J., Ma, D., Lin, J. D., Greenberg, M. E., & Spiegelman, B. M. (2013). Exercise induces hippocampal BDNF through a PGC-1α/FNDC5 pathway. *Cell Metabolism*, *18*(5), 649–659. https://doi.org/10.1016/j.cmet.2013.09.008

Wright, G. L., Maroulakou, I. G., Eldridge, J., Liby, T. L., Sridharan, V., Tsichlis, P. N., & Muise-Helmericks, R. C. (2008). VEGF stimulation of mitochondrial biogenesis: Requirement of AKT3 kinase. *The FASEB Journal*, *22*(9), 3264–3275. https://doi.org/10.1096/fj.08-106468

Yahia, S., El-Farahaty, R. M., El-Hawary, A. K., El-Hussiny, M. A., Abdel-Maseih, H., El-Dahtory, F., & El-Gilany, A.-H. (2012). Leptin, insulin and thyroid hormones in a cohort of Egyptian obese Down syndrome children: A comparative study. *BMC Endocrine Disorders*, *12*, 22. https://doi.org/10.1186/1472-6823-12-22

Yirmiya, R., & Goshen, I. (2011). Immune modulation of learning, memory, neural plasticity and neurogenesis. *Brain, Behavior, and Immunity*, *25*(2), 181–213. https://doi.org/10.1016/j.bbi.2010.10.015

Yoshida, Y., Umeno, A., & Shichiri, M. (2013). Lipid peroxidation biomarkers for evaluating oxidative stress and assessing antioxidant capacity in vivo. *Journal of Clinical Biochemistry and Nutrition*, *52*(1), 9–16. https://doi.org/10.3164/jcbn.12-112

Zaki, M. E., El-Bassyouni, H. T., Tosson, A. M. S., Youness, E., & Hussein, J. (2017). Coenzyme Q10 and pro-inflammatory markers in children with Down syndrome: Clinical and biochemical aspects. *Jornal De Pediatria*, *93*(1), 100–104. https://doi.org/10.1016/j.jped.2016.04.012

Zambrano, J. C., Marquina, R., Sulbarán, N., Rodríguez-Malaver, A. J., & Reyes, R. A. (2009). Aerobic exercise reduced oxidative stress in saliva of persons with Down syndrome. *Research in Sports Medicine (Print)*, *17*(3), 195–203. https://doi.org/10.1080/15438620903120843

Zamponi, E., Zamponi, N., Coskun, P., Quassollo, G., Lorenzo, A., Cannas, S. A., Pigino, G., Chialvo, D. R., Gardiner, K., Busciglio, J., & Helguera, P. (2018). Nrf2 stabilization prevents critical oxidative damage in Down syndrome cells. *Aging Cell*, *17*(5), e12812. https://doi.org/10.1111/acel.12812

Zana, M., Janka, Z., & Kálmán, J. (2007). Oxidative stress: A bridge between Down's syndrome and Alzheimer's disease. *Neurobiology of Aging*, *28*(5), 648–676. https://doi.org/10.1016/j.neurobiolaging.2006.03.008

Zarrouk, A., Debbabi, M., Bezine, M., Karym, E. M., Badreddine, A., Rouaud, O., Moreau, T., Cherkaoui-Malki, M., El Ayeb, M., Nasser, B., Hammami, M., & Lizard, G. (2018). Lipid Biomarkers in Alzheimer's Disease. *Current Alzheimer Research*, *15*(4), 303–312. https://doi.org/10.2174/1567205014666170505101426

Zhao, R. (2024). Exercise mimetics: A novel strategy to combat neuroinflammation and Alzheimer's disease. *Journal of Neuroinflammation*, *21*(1), 40. https://doi.org/10.1186/s12974-024-03031-9

Zigman, W. B., & Lott, I. T. (2007). Alzheimer's disease in Down syndrome: Neurobiology and risk. *Mental Retardation and Developmental Disabilities Research Reviews*, *13*(3), 237–246. https://doi.org/10.1002/mrdd.20163

Zucchella, C., Sinforiani, E., Tamburin, S., Federico, A., Mantovani, E., Bernini, S., Casale, R., & Bartolo, M. (2018). The Multidisciplinary Approach to Alzheimer's Disease and Dementia. A Narrative Review of Non-Pharmacological Treatment. *Frontiers in Neurology, 9.* https://www.frontiersin.org/articles/10.3389/fneur.2018.01058

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