12-9-2021 9:30 AM

Exercise as a Treatment for Cognitive Decline in Older Adults: The Role of Growth Factors and Inflammatory Cytokines

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Kinesiology

Abstract

The purpose of this thesis was to investigate the effects that exercise modalities have on neurotrophic and inflammatory blood markers and cognitive outcomes in older adults. A systematic review and meta-analysis were completed. The included studies illustrated that most of the literature evaluated the effect of aerobic exercise interventions on systemic concentrations of the blood marker brain-derived neurotrophic factor (BDNF). The review found that aerobic exercise increases BDNF and resistance training increases insulin-like growth factor 1 (IGF-1). Interventions with sex-specific cohorts presented advantages in males for blood marker and cognitive outcomes compared to females. One of three included interventions decreased C-reactive protein (CRP). This thesis demonstrated the presence of modality-specific outcomes of exercise on blood markers and presents a targeted review of the literature evaluating exercise, cognition, and blood markers.

Keywords

Exercise, Cognition, Older Adults, Neurotrophic Factors, Inflammatory Cytokines

Summary for Lay Audience

Dementia poses a huge burden to older adults, their caregivers, and society. Patients with dementia are faced with increasingly severe and complex impairments to their thinking, otherwise known as cognition, which includes processes such as memory, planning, organization, attention, language, spatial ability, and ability to orient themselves. Additionally, individuals with dementia typically face challenges with mobility, social life, and mental health as their condition progresses.

A possible treatment for dementia is exercise, which has been shown to (at least temporarily) improve or prevent worsening of the symptoms of cognitive decline in older adults. Past research on exercise as a treatment for individuals with cognitive impairments has suggested that exercise triggers a release of specific molecules in the blood and, conversely, reduces harmful molecules. More specifically, exercise triggers the release of molecules, known as growth factors, that increase blood flow and regulate the development, growth, and survival of brain cells. Also, exercise decreases molecules in the blood that are related to heart disease and dementia, known as inflammatory markers.

This manuscript aimed to examine the role of key growth factors and inflammatory markers in the cognitive outcomes seen after an exercise program. A review of this subject was completed and organized to clarify the consensus of all past literature.

The review found that different exercise types (resistance and aerobic) increased different growth factors in the blood. Males showed more positive effects on both blood molecules and mental processes after exercise. Additionally, inflammatory markers were reduced after exercise in some studies. In conclusion, this manuscript suggested that different types of exercise can increase growth factor molecules to improve cognition, and that exercise can protect against age-related declines in memory and growth factor levels in the blood.

Acknowledgments

I would like to begin by acknowledging the land on which this thesis was completed is the traditional territory of the Anishinaabe, Haudenosaunee and the Leni-Lunaape Peoples.

I would like to thank the participants of the SYNERGIC Trial for their time, positivity, and generous contribution to research.

I would next like to thank Dr. Manuel Montero-Odasso, whose invaluable mentorship and ambition granted me the opportunity to complete this thesis. I am grateful for the opportunities that the Gait and Brain Lab has provided, and I am fortunate to have had the opportunity to be a part of it. To my advisory committee, Drs. Richard Camicioli, Lindsay Nagamatsu, and Mark Speechley, I am extremely grateful for the suggestions and expertise you have provided from your respective disciplines.

I would also like to thank the members of the Gait and Brain Lab, past and current, who have supported me during my time in the lab: Dr. Yanina Sarquis-Adamson, Dr. Frederico Faria, Soushyant Kiarasi, Nellie Kamkar, Bhagyashree Sharma, Nick Bray, Stephanie Cullen, Joel Mahon, Abbie Barron, Teran Niemen, Shaylana Nejim, Korbin Blue, Alanna Black and Nattasha Clements.

Also, a big thank-you to my parents, Linda and Don, my brother, Nick, and my friends for their unconditional support through this process.

Lastly, I would like to acknowledge that Dr. Montero-Odasso's SYNERGIC TRIAL is supported by grants from the Canadian Institute of Health and Research (MOP 211220),), the Canadian Consortium on Neurodegeneration in Aging (FRN CNA 137794), and by Department of Medicine Program of Experimental Medicine Research Award (POEM 768915), University of Western Ontario.

Table of Contents

List of Tables

List of Figures

List of Appendices

Chapter 1

1 Literature Review

This thesis aims to evaluate the relationship between longitudinal exercise training and cognition, and whether this relationship is modified by neurotrophic growth factors and inflammation. Chapter 1 will introduce the topics of cognition, exercise, neurotrophic factors, and inflammatory markers. Further, I present the topic of exercise as a non-pharmacological intervention to reduce age-related cognitive decline. Additionally, I describe the impact of growth factors and inflammation on cognition and the role of exercise in this relationship. I conclude by providing study rationale, purpose, and hypotheses of the ensuing chapters**.** Chapter 2 presents a review of randomized controlled trials investigating the impact of particular exercise modalities on neurotrophic factor and inflammatory marker concentrations and cognition.

1.1 Cognition in Aging

Cognition is defined as the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses (Harada et al., 2013). Cognitive decline is a natural result of aging (Harada et al., 2013; Murman, 2015). The physiological processes that drive age-related cognitive decline are multifaceted, interconnected, and largely undetermined (Harman, 2006; López-Otín et al., 2013; Salthouse, 2010). Aging increases the risk of developing cognitive pathologies, which can further compound the deleterious effects of cognitive aging (Riedel et al., 2016). Researchers have delineated associations between several lifestyle factors and resilience to cognitive aging and pathology. Specifically, education, social engagement, physical fitness, and life occupation, among others, have been linked to better prognoses of cognitive aging (Harada et al., 2013). Also, acute and longitudinal health interventions, such as exercise (Northey et al., 2018), cognitive training, or playing a musical instrument (Román-Caballero et al., 2018), have exhibited positive results as preventative treatments for cognitive decline.

An interesting clinical phenomenon, cognitive reserve, explains the disjunction between the expression of cognitive symptoms and the disproportionate severity of cognitive pathology present in post-mortem clinical findings (Ince, 2001; Stern, 2009). More specifically, cognitive reserve is hypothesized to be an individual's ability to cope with injury to the brain or cognitive decline through the individual differences in neural networks and the capacity to reallocate intact networks to surrogate the function of damaged networks. Cognitive reserve is postulated to be primarily driven by education, occupational exposure, leisure activities, and general cognitive activity throughout the lifespan (Stern, 2009; Wilson et al., 2007).

1.1.1 Domains of Cognition

There is limited consensus in research and healthcare on the most effective way to divide cognition into distinct neurocognitive domains. To attain consistent diagnostic categorisation of cognitive impairments, the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), gained consensus from leading experts of psychiatric research and practice. Based on the consensus established in the DSM-5, cognition is divided into six principle domains: Executive Function, Complex Attention, Learning and Memory, Perceptual Motor Functioning, Language, and Social Cognition (Sachdev et al., 2014).

Hunt et al. (2013) defines executive function as an overarching cognitive process, mediated by attention, that coordinates and integrates multiple subordinate cognitive skills to enable goal-directed behaviour. Executive function is categorized into several sub-domains, including planning, decision making, working memory, responding to feedback, inhibition, and flexibility (Sachdev et al., 2014). Additionally, Miyake et al. (2000) explored the existence of three frequently postulated executive sub-components: inhibition, shifting, and updating. These three sub-components can respectively be defined as the ability to suppress dominant, automatic, or prepotent responses when they are inappropriate, as the ability to shift attention between different sub-tasks or different elements of the same tasks, and finally, as the ability to evaluate incoming information and revise the existing contents of working memory by deleting what is no longer relevant and incorporating more recent salient information.

Attention is defined as the behavioral and cognitive process of selectively concentrating on a discrete aspect of information, whether deemed subjective or objective, while ignoring other perceivable information (Anderson, 2004). Complex attention is categorized into several sub-domains including sustained attention, divided attention, selective attention, and processing speed. (Sachdev et al., 2014).

The Encyclopedia of Psychology defines learning as the acquisition of a skill or knowledge, and memory as the expression of previously learned information (Kazdin et al., 2000). Learning and memory are categorized into the sub-domains free recall, cued recall, recognition memory, semantic and autobiographical, long-term memory, and implicit memory (Sachdev et al., 2014).

Perceptual-motor function is the accurate integration of sensory information for the development of motor programming and perceptual orientation (Finney, 2015). This cognitive domain is categorized into visual perception, vasoconstriction reasoning, and perceptual-motor coordination (Sachdev et al., 2014).

Language is defined as the development, acquisition, and maintenance, and use of complex systems of communication (Ramlan, 2018). Language is differentiated into sub-domains that include object naming, word finding, fluency, grammar and syntax, and receptive language (Sachdev et al., 2014)

1.1.2 Epidemiology of Cognitive Dysfunction

The intermediate state between normal aging and dementia is known as mild neurocognitive disorder (Sachdev et al., 2014), or more commonly mild cognitive impairment (MCI). The prevalence of MCI is 10-20% in older adults over 65 years of age (Langa & Levine, 2014). Those diagnosed with MCI have a 20-40% (10-15% per year) risk of progression into dementia (Roberts & Knopman, 2013). The most significant risk factors of cognitive decline and cognitive pathology are age, sex, genetics, and the presence of diabetes or cardiovascular disease (Biessels & Despa, 2018; Riedel et al., 2016).

The prevalence of cognitive decline is predicted to rise substantially in the approaching decades. Researchers predict that by 2050 the population of those 65 years and older will double, while the population of those 85 years and older will triple. Further, it is estimated that 35.6 million people live with dementia worldwide, and this number will double every 20 years (Mavrodaris et al., 2013). Consequently, interest in research has risen dramatically for the treatment or prevention or cognitive decline (Cummings et al., 2018; Morrison-Bogorad et al., 2007).

Research suggests that females are more susceptible to cognitive pathologies compared to males (Barha & Liu-Ambrose, 2018); the incidence of cognitive decline is twice as likely in female older adults (Lin & Doraiswamy, 2015) and females exhibit more rapid brain atrophy than males after onset of cognitive pathology (Hua et al., 2010). Also, the association between peripheral inflammatory markers and cognitive decline is more evident in females than males (Trollor et al., 2012). Further, both natural and surgical menopause are associated with an increased risk of Alzheimer's disease biomarkers and cognitive decline (Hara et al., 2015; Mosconi et al., 2017; Rocca et al., 2007; Scheyer et al., 2018).

1.1.3 Measuring Cognitive Function

Various cognitive assessments have been validated in measuring cognitive performance in different age groups. These assessments can be combined to measure cognitive performance in general, or particular domains of interest. Cognitive assessments commonly used for older adults include: Trail Making Test (Reitan and Wolfson 1985), Digit Span (Wechsler, 1981), Letter Number Sequence (Wechsler, 1981), and Language or Category Fluency (Strauss et al., 2006), and Rey Auditory Verbal Learning Test (Rosenberg et al., 1984). Various cognitive assessment batteries that include multiple assessments have been developed for comprehensive assessments of older adults. Most notable are the Montreal Cognitive Assessment (MoCA), the Mini Mental State Examination (MMSE), both of which are short assessments typically used as screening tools (Tavares-Júnior et al., 2019; Woodford & George, 2007); and the Alzheimer

Disease Assessment Scale (ADAS-Cog) that has been used in clinical trials (Kueper et al., 2018; Montero Odasso et al., 2018; Rosen et al., 1984).

The ADAS-Cog is a valid and reliable battery of cognitive assessments to determine global cognition related to cognitive impairment in older adults (Sheehan, 2012). The ADAS-Cog Plus, a revised version of the ADAS-Cog, incorporates additional measures of executive function and functionality. This scale consists of 10 cognitive tests, with scores ranging from 0 to 90; higher scores represent poorer cognitive performance (Skinner et al., 2012). Compared to previous versions, the ADAS-Cog Plus is more responsive to disease progression and treatment effects in studies of cohorts with MCI (Kueper et al., 2018). The ADAS-Cog has been a significant outcome measure in numerous trials with MCI and AD (Chupel et al., 2017; Fiatarone Singh et al., 2014; Öhman et al., 2014; Suzuki et al., 2013; Toots et al., 2017).

1.2 Physical Exercise

Caspersen, Powell, and Christenson (1985) define exercise as "Physical activity that is planned, structured, repetitive, and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective". The objective of physical exercise is physical fitness, which can be divided into two components, with specific sub-categories: (1) health-related objectives, including cardiorespiratory capacity, muscular endurance, muscular strength, body composition, and flexibility; and (2) skill-related, including agility, balance, coordination, speed, power, and reaction time. If a physical activity does not intentionally fulfil any of these aspects of physical fitness, then it is not considered exercise.

In trials with older adults, the primary consideration of an exercise interventions is usually health-related outcomes of strength, fall reduction, mobility, cardiovascular fitness, physical function, depression, and cognitive outcomes (Cadore et al., 2013; Chen et al., 2020; Shekelle et al., 2003). Common exercise modalities for older adults include aerobic, resistance, stretching, and balance.

1.2.1 Aerobic Exercise

Aerobic exercise involves the use of large muscle groups in dynamic activities that result in sustained increases in heart rate and energy expenditure (Howley, 2001). Aerobic exercise is primarily related to the health-related outcomes of cardiorespiratory capacity, muscle endurance, and body composition due to the moderate-energy, long-duration nature of the exercise (Plowman & Smith, 2008). Aerobic exercise is commonly implemented on ergometer machines (treadmills, stationary bikes, ellipticals, rowing machines, etc.), walking, running, or biking, depending on the fitness level and capability of the subjects.

1.2.2 Resistance Exercise

Resistance exercise is the repeated lifting of weight to overload muscles at an intensity only sustainable for a short duration. The parameters of resistance training include the number of times the resistance is moved in a single set of exercise, the number of sets done, and the rest interval between sets (Howley, 2001). Resistance exercise is primarily related to the health-related outcomes of muscular strength, muscular endurance, and body composition. Also, secondary skill-related enhancements in balance, agility, speed, and power can be attained through resistance exercise (Plowman & Smith, 2008). Common forms of resistance training include the use of free-weights, resistance machines (e.g., leg press, chest press, leg curl, etc.), resistance bands, and body weight exercises (e.g., pull-ups, push-ups, bodyweight squats, etc.).

1.2.3 Balance, Toning, and Stretching Exercise

Balance, toning, and stretching exercises usually exercises that are designed to improve balance, muscle tone, and lengthen muscles, respectively. Balance exercises typically challenge balance systems by limiting senses related to balance, such as sight, proprioception, foot pressure, and vestibular function, and limiting the base of support with or without perturbing the centre of gravity of the participant. Common balance exercises include one-leg stance, standing with eyes closed, standing on a foam pad, or

tandem stance, all usually administered over a set duration (Penzer et al., 2015; Shimada et al., 2003). Toning exercises are exercises that utilize large muscle groups but do not significantly overload the muscles or cause a significant cardiovascular response. Finally, stretching exercises are movements intended to lengthen muscles and improve range of motion for targeted joints (Page, 2012).

Balance, toning, and stretching exercises are commonly used in-combination as active controls for exercise interventions in cognitive trials. This is due to a speculated lack of amelioration on cognitive dysfunction (Kelly et al., 2014; Uffelen et al., 2008). However, some forms of this modality are studied due to their proposed mental and emotional enhancements, such as yoga, tai chi, and Qigong (Abbott & Lavretsky, 2013; Farhang et al., 2019; Mooventhan & Nivethitha, 2017).

1.3 Blood Biomarkers Related to Cognition

Particular blood biomarkers have been identified as having important roles in the regulation of cognitive functioning. Specifically, neurotrophic growth factors (Campos, Rocha, Lattari, Paes, & Nardi 2016; Raab et al., 2004), and inflammatory cytokines (Gu et al., 2017; Teunissen et al., 2003) have been found to exert trophic and atrophic effects on the neural and vascular structures in the brain, respectively (Cotman et al., 2007; Nascimento et al., 2014).

1.3.1 Neurotrophic Factors

Studies have identified particular neurotrophic factors thought to be associated with positive cognitive outcomes after exercise (Ding et al., 2006; Hillman et al., 2008). The primary neurotrophic growth factors implicated in this relationship are brain-derived neurotrophic factor (BDNF), insulin-like growth factor 1 (IGF-1), and vascular endothelial growth factor (VEGF) (Cotman et al., 2007). These molecules play convergent roles in the neuroplastic processes, including gliogenesis, neurogenesis, synaptogenesis, and angiogenesis (El-Sayes et al., 2019).

The protein BDNF is expressed in the central nervous system, gut, and other tissues, and is a member of the neurotrophin family (Bathina & Das, 2015). Functionally, BDNF enhances the growth and differentiation of cells in the brain and is essential to the development of the mammalian brain (Binder & Scharfman, 2004). Specifically, the expression of BDNF contributes to neurogenesis (Benraiss et al., 2001; Pencea et al., 2001), gliogenesis (Cheng et al., 2006), synaptogenesis (Aguado et al., 2003; Alsina et al., 2001; Binder & Scharfman, 2004) and angiogenesis (Kermani & Hempstead, 2007)**.** BDNF is largely expressed in the hippocampus, which is the brain centre for emotion, memory, and learning (Erickson et al., 2011; Lu et al., 2014). Low blood concentrations of BDNF have been associated with neurodegenerative diseases, such as dementia (Weinstein et al., 2014), Alzheimer's disease (Laske et al., 2006; Ng et al., 2019), Huntington's disease (Zuccato & Cattaneo, 2009), and the early stages of Parkinson's disease (Huang et al., 2018).

The signal protein VEGF is released from the endothelial cells in blood vessels, macrophages, and glial cells in response to tissue hypoxia (Roskoski, 2007; Tang et al., 2010) and the presence of blood lactate (Morland et al., 2017) and functions to stimulate angiogenesis and vasculogenesis ubiquitously in the body (Hoeben et al., 2004). VEGF transcription in the brain is thought to elicit neurotropic and neuroprotective functions (Jin et al., 2002; Sun et al., 2003; Tang et al., 2010). The specific functions of VEGF are increasing neuronal survival, decreasing apoptotic proteins and signals, stimulating the release of proteins that improve neuronal health (Sanchez et al., 2010), and increasing general plasticity of mature neurons (Licht et al., 2011). Animal studies have discovered a marked decline in VEGF concentrations in the hippocampus occurring until middle-age that may contribute to age-related cognitive decline (Shetty et al., 2005).

The vascular and neuroprotective functions of VEGF are especially pertinent in the context of vascular dementia (Ding et al., 2004; Sun et al., 2003)**.** After a cerebral vascular event, such as a stroke, VEGF is released to the affected area to promote angiogenic and vasculogenic activity (Krupinski et al., 1994). Patients who have experienced a cerebral vascular event (i.e. stroke) with higher systemic concentrations of

VEGF have significantly better prognoses than those with lower systemic concentrations (Lee et al., 2010). Interestingly, patients afflicted by an acute stroke who had previous transient ischemic attacks (TIA) have better prognoses than those without, thought to be mediated by a higher concentration of VEGF following the damage associated with TIA (Kwon et al., 2015). Thus, the negative impacts of stroke may be mitigated by high concentrations of VEGF in the cerebral vasculature due to its role in angiogenesis and vasculogenesis.

The protein hormone IGF-1 is released by cells of the liver, lungs, kidneys, skeletal muscle, heart, and white adipose tissue in the presence of circulating growth hormone (GH) (Lowe et al., 1988). The primary function of IGF-1 is to stimulate anabolism throughout the mammalian body (Le Roith et al., 2001), including neurogenesis (Llorens-Martín et al., 2009), gliogenesis (Carson et al., 1993), synaptogenesis (Trejo et al., 2007), and angiogenesis (Lopez-Lopez et al., 2004) and is essential for human brain development (Maggio et al., 2012). As humans age, systemic concentrations of GH typically decrease, resulting in a downregulation of IGF-1 (Corpas et al., 1993). Further, research has shown that lower concentrations of IGF-1 are associated with cognitive aging (Corpas et al., 1993; Sonntag et al., 2005); lower cognitive functioning in older adults, with, and without, MCI; and an increased risk of Alzheimer's disease and vascular dementia (Watanabe et al., 2005) .

1.3.2 Inflammation and Inflammatory Cytokines

Inflammation is the body's immune response to harmful stimuli and functions to eliminate necrotic cells and promote healing. Although inflammation is beneficial and necessary for normal bodily functioning (Gronke et al., 2019), chronic low-grade inflammation is particularly detrimental to heart and brain health (Nicklas & Brinkley, 2009). The incidence of inflammatory pathogenesis is dependent on the level of inflammation in an individual's body and their threshold of disease, adjusted by genetic and environmental influences (Franceschi et al., 2006).

The term inflammaging refers to a chronic low-grade inflammatory state resulting from the upregulation of the inflammatory response compelled by multiple factors in old age. These factors are speculated to be driven by the culmination of antigenic stressors over the human lifespan and dysregulated inflammatory processes (Rea et al., 2018). Inflammaging likely represents a mechanism underlying the age-related functional decline across a variety of pathological states (Nicklas & Brinkley, 2009). Research has also demonstrated an association between chronic low-grade inflammation and attenuated hippocampal neurogenesis (Chesnokova et al., 2016; Kohman & Rhodes, 2013), increased risk of stroke with poor functional outcomes and mortality (Ballantyne et al., 2005; Elkind et al., 2006), cognitive impairment (Wichmann et al., 2014), and Alzheimer's disease (Heneka et al., 2015; Krabbe et al., 2004). Multiple studies measuring the effect of inflammation on cognition have employed the inflammatory cytokines interleukin 6 (IL-6) and C-reactive protein (CRP) as valid markers of systemic inflammation and inflammaging (Capuron et al., 2011; Gabay & Kushner, 1999; Ohzato et al., 1992; Tegeler et al., 2016; Yaffe et al., 2003).

The inflammatory protein IL-6 is secreted by macrophages and T-cells in the bloodstream and has both pro- and anti-inflammatory functions (Pedersen & Febbraio, 2008; Scheller et al., 2011). Specifically, IL-6 is released as a pro-inflammatory cytokine in response to injury, cell damage, and cell death. However, in response to muscle contraction, IL-6 is transiently released as an anti-inflammatory myokine (Pedersen & Febbraio, 2008). Though IL-6 has anti-inflammatory pathways, elevated concentrations of IL-6 in the systemic circulation have been associated with lower cognitive performance (Bradburn et al., 2018; Trollor et al., 2012) and brain volume (Gu et al., 2017). This relationship is thought to be mediated through the detrimental effects of chronic low-grade inflammation as well as inflated cytokine responses to ischemia that exacerbate cell damage in the brain (Michaud et al., 2013).

The protein CRP is an acute-phase inflammatory protein that is released from the liver in response to circulating IL-6 (Pepys & Hirschfield, 2003). The measurement of CRP is used as a standard clinical procedure that indicates the systemic level of inflammation in an individual, usually administered on older adults at-risk for cardiovascular events,

infections, or inflammatory disorders (Bray et al., 2016; Pepys & Hirschfield, 2003). High concentrations of CRP are associated with cognitive decline, dementia, and an increased risk of stroke (Kuo et al., 2005; Misiak et al., 2018).

1.4 Exercise as a Treatment for Cognitive Decline in Aging

The use of exercise as a non-pharmaceutical intervention to delay or prevent the trajectory into dementia is a rapidly growing field of interest. Longitudinal exercise programs have shown promise in eliciting significant improvements in cognitive performance with modality-dependent domain-specific effects (Barha, Davis, Falck, Nagamatsu, & Liu-Ambrose, 2017). A meta-analysis, which included individuals over 50 years of age, found that exercise elicited a positive small to moderate effect on improving cognitive performance. This effect was consistent regardless of cognitive status, cognitive domains measured, and the exercise modality utilized (Northey et al., 2018). Other meta-analyses have investigated this relationship in participants with MCI with variable results. In particular, studies primarily found small to moderate improvements in global cognition, memory, and executive function (Biazus-Sehn et al., 2020; Zheng et al., 2016). Conversely, Gates, Singh, Sachdev, & Valenzuela (2013) completed a meta-analysis on the effect of exercise on cognition in individuals with MCI, but did not find significant outcomes. Interestingly, Biazus-Sehn et al. (2020) found that trials utilizing more cognitively engaging forms of exercise (i.e., dance, Tai Chi, Baduanjin) in older adults with MCI had better cognitive outcomes than simple physical exercise regimens. These findings are consistent with the results from a meta-analysis investigating the effect of aerobic dance interventions on cognition. The study found that the dance interventions had a moderate effect on memory, executive function, and global cognition (Zhu et al., 2020). These results may be indicative of a synergistic training effect related to the cognitive as well as physiological demands of exercise.

1.4.1 Physical Exercise and Blood Markers Associated with Cognition

Exercise-induced physiological cascades are known to regulate cognition by exerting trophic effects on neural and vascular structures in the brain (Campos, Rocha, Lattari, Paes, & Nardi 2016; Raab et al., 2004) and preventing brain atrophy associated with inflammation (Gu et al., 2017; Teunissen et al., 2003). Consequently, the relationship between physical exercise and cognition is thought to be mediated by the change in growth factors and inflammatory markers (Cotman et al., 2007; Nascimento et al., 2014)

1.4.1.1 Neurotrophic Growth Factors and Cognition in Response to Exercise

Neurotrophic growth factors mediate the effects of exercise on cognitive performance. Comprehensive reviews have established that BDNF, VEGF, and IGF-1 are the principal mediating neurotrophic growth factors in the exercise-cognition relationship (Cotman et al., 2007; El-Sayes et al., 2019). Figure 1.1 describes the model of neurotrophic growth factor and cognitive outcomes induced by physical exercise. Animal trials have established divergent exercise modality-dependent relationships for neurotrophic growth factors and cognitive outcomes. In particular, it is thought that aerobic exercise increases BDNF concentrations and resistance training upregulates IGF-1 activity, both mediating improvements of cognitive outcomes (Cassilhas et al., 2012). A meta-analysis by Dinoff et al. (2016) investigating the effect of exercise on concentrations of BDNF supported this theory that aerobic and not resistance exercise increased resting systemic BDNF concentrations in humans. Other RCTs have supported these speculated modality-specific pathways to improve cognitive outcomes (Cassilhas et al., 2007; Jiang et al., 2020; Tsai et al., 2019), as well as possible synergistic effects of multimodal exercise interventions (Annibalini et al., 2017). The effect of exercise on VEGF in cognitive trials in humans has been studied considerably less than BDNF and IGF-1. In fact**,** most of the literature on this relationship has been established through animal trials (Cao et al., 2004; Y.-H. Ding et al., 2004; Fabel et al., 2003; Lopez-Lopez et al., 2004; Prior et al., 2004) and results in human trials are variable. A recent systematic review on exercises effects on

VEGF in older adults describes that four of ten studies found significant increases in VEGF concentrations post-intervention. The review was limited by the small number of included studies, and a wide variety of intervention parameters (exercise duration, frequency, intensity, type) and sample characteristics (Vital et al., 2014). Further research evaluating the effect of exercise on VEGF to affect cognition is required to delineate this relationship in humans.

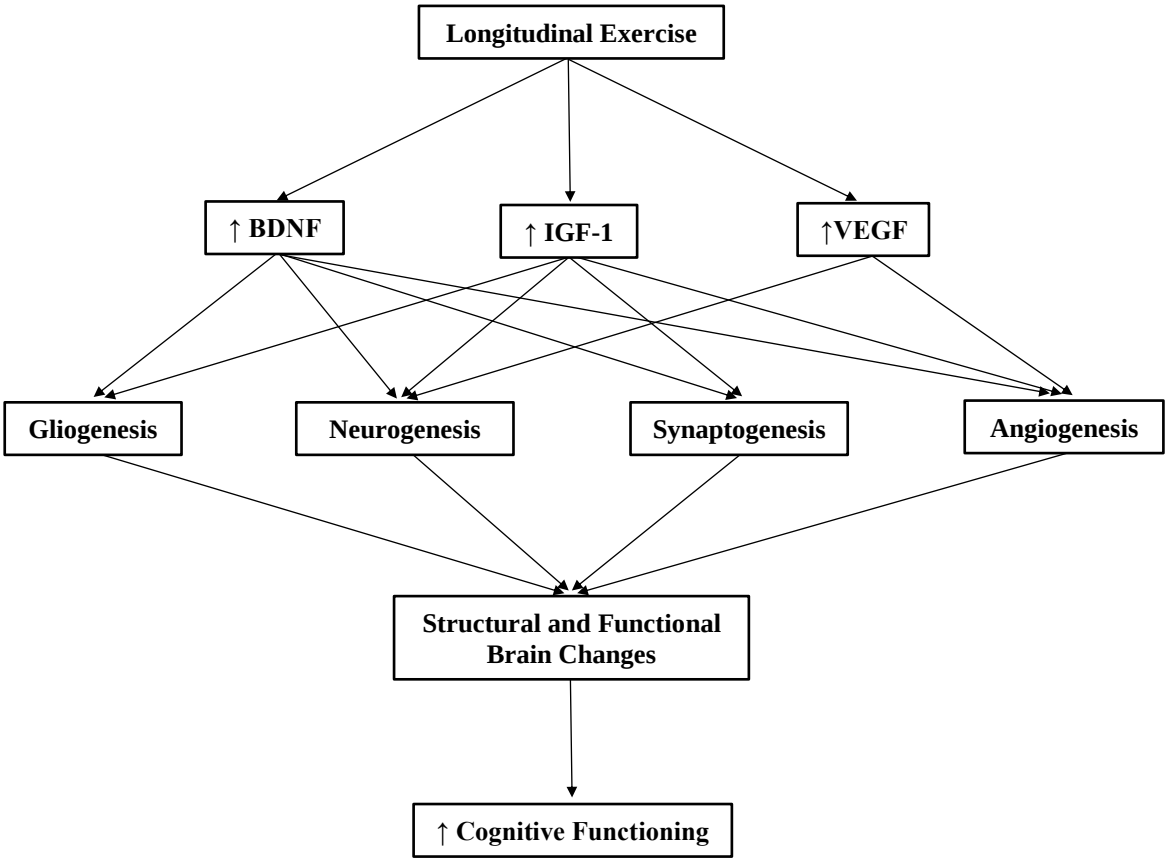

Figure 1.1 Model of neurotrophic growth factor response and action after longitudinal exercise

1.4.2.2 Inflammation and Cognition in Response to Exercise

Longitudinal exercise attenuates inflammation and improves cognition (Gleeson et al., 2011). Figure 1.2 describes the possible mechanisms in which inflammatory cytokines mediate cognitive changes after longitudinal exercise. The mechanism driving the anti-inflammatory response of exercise is largely unknown, but the overall relationship has been well established. Specifically, recent meta-analyses found that exercise was associated with significant decreases in IL-6 concentrations in older adults with cognitive impairments (Stigger et al., 2019) and resistance training was associated with decreases in CRP and IL-6 concentrations for older adults (Sardeli et al., 2018). Further, multiple randomized controlled trials (RCTs) have found evidence that longitudinal exercise reduces inflammation. In particular, concentrations of CRP and IL-6 were reduced by dance training (Borges et al., 2019), combined aerobic and resistance training (Annibalini et al., 2017; Balducci et al., 2010), and high-intensity aerobic training, but not low-intensity aerobic training (Balducci et al., 2010). Other trials found that aerobic and resistance training interventions both decreased CRP, but not IL-6 concentrations (Donges et al., 2010) and did not influence CRP or IL-6 concentrations (Libardi et al., 2012). Cognition, however, was not measured in the aforementioned reviews or RCTs. Exercise interventions that included the measurement of both cognition and inflammation found unanimously that CRP decreased while cognitive performance improved. These RCTs utilized resistance training (Chupel et al., 2017) and aerobic training (Alghadir et al., 2016).

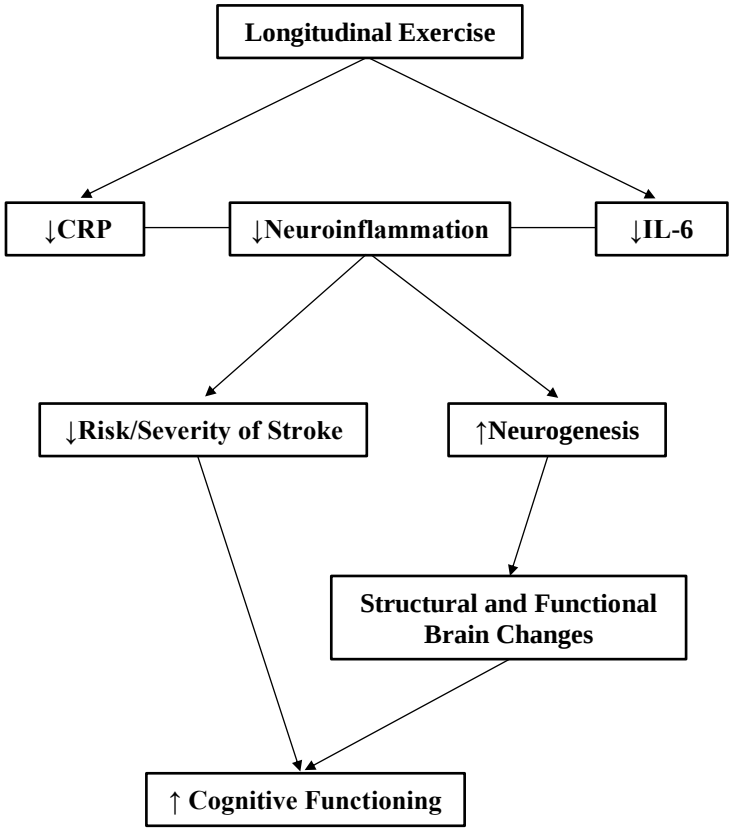

Figure 1.2 Model of inflammatory cytokine response and outcomes after longitudinal exercise.

1.5 Overview of Thesis

1.5.1 Study Rationale

The previous sections summarize the literature surrounding cognition and exercise and explores the how neurotrophic growth factors and inflammation interact with this relationship. Evidence suggests that exercise may have advantages in ameliorating cognitive impairment. However, the varying effects of exercise modalities and subsequent biomarkers involved in this relationship have not been sufficiently explored in research. Exercise modalities may drive divergent changes at the molecular level (i.e., neurotrophic and inflammatory markers), which may describe the changes at the cognitive level in older adults.

1.5.2 Purpose

The purpose of this thesis was to systematically review the effects of exercise modalities on neurotrophic factors, inflammation, and cognition, among older adults and to perform a meta-analysis of the included studies, if feasible.

1.5.3 Hypotheses

It was hypothesized that:

1) The increase in neurotrophic factor and decrease in inflammatory marker concentrations, as a result of exercise, will be associated with cognitive outcomes.

1.1) Exercise will increase growth factor concentrations, which will be associated with an improvement in cognition.

1.2) Exercise will decrease inflammatory markers, which will be associated with an improvement in cognition.

2) Higher baseline concentrations of growth factors and lower baseline concentrations of inflammatory markers will be associated with improvements in cognitive outcomes.

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Chapter 2

2 The Role of Physical Exercise in Modulating Peripheral Inflammatory and Neurotrophic Biomarkers in Older Adults: A Systematic Review and Meta-Analysis

Co-Authorship Statement: **Josh Titus:** Conceptualization, Methodology, Formal Analysis, Investigation, Data Curation, Writing- Original Draft Publication, All Drafts Manuscript; Completed 75-80% of the Total Work; **Nick W Bray:** Conceptualization, Methodology, Validation, Investigation, Data Curation; **Nellie Kamkar:** Methodology, Formal Analysis, Investigation, Writing- Review & Editing, Visualization; **Richard Camicioli:** Conceptualization, Validation, Writing-Review & Editing, Supervision; **Lindsay S. Nagamatsu**: Writing- Review & Editing; **Mark Speechley:** Writing- Review & Editing; **Manuel Montero-Odasso:** Conceptualization, Methodology, Validation, Obtaining Funding, Resources, Writing- Review & Editing, Supervision.

Publication Status: **Published**

Titus, J., Bray, N. W., Kamkar, N., Camicioli, R., Nagamatsu, L. S., Speechley, M., & Montero-Odasso, M. (2021). The role of physical exercise in modulating peripheral inflammatory and neurotrophic biomarkers in older adults: A systematic review and meta-analysis. *Mechanisms of Ageing and Development*, 111431. https://doi.org/10.1016/j.mad.2021.111431

Physical exercise has been shown to prevent age-related cognitive decline, and has even led to significant cognition improvement in older adults (Ahlskog et al., 2011; Bherer and Erickson, 2013; Groot et al., 2016; Hess et al., 2014; Öhman et al., 2014). The underlying mechanisms for these improvements are unknown but emerging evidence shows that physical exercise increases neurotrophic factors (which consist of a family of molecules that support the growth and survival of neurons). Conversely, concentrations of inflammatory cytokines (which impair signal transduction of neurons) are significantly decreased following physical exercise, suggesting that exercise may have a mechanistic

role in promoting cognitive improvement (Cotman et al., 2007). It is hypothesised that these changes stimulate a physiological cascade that promotes angiogenesis, gliogenesis, neurogenesis, and synaptogenesis, while reducing systemic inflammation (Cotman et al., 2007; El-Sayes et al., 2019; Nicklas and Brinkley, 2009).

Several studies have identified neurotrophic and inflammatory markers associated with positive cognitive outcomes after exercise (Ding et al., 2006; Hillman et al., 2008). The primary neurotrophic factors implicated in this relationship are brain-derived neurotrophic factor (BDNF), insulin-like growth factor 1 (IGF-1), and vascular endothelial growth factor (VEGF) (Ahlskog et al., 2011; Cotman et al., 2007; Voss et al., 2013). Alternatively, inflammatory cytokines interleukin 6 (IL-6) and C-reactive protein (CRP) are valid markers of systemic inflammation that impede neuronal signalling (Capuron et al., 2011; Gabay and Kushner, 1999; Ohzato et al., 1992; Tegeler et al., 2016; Yaffe et al., 2003).

Mechanistically, the aforementioned inflammatory cytokines and neurotrophic factors influence cognitive performance via a cascade of neurological processes. For example, BDNF regulates synaptic transmission in neural regions that are integrally related to memory such as the hippocampus (Lu et al., 2014). Across a range of neural networks, BDNF is also critically related to neuroprotection, neuromodulation, and neurogenesis (i.e., gliogenesis and synaptic plasticity; Kowiański et al., 2018). Increases in inflammatory cytokines, on the other hand, are associated with cognitive decline via neuroinflammatory processes. CRP, for example, is strongly associated with the progression of cognitive decline and the pathogenesis of the onset of dementia (Roberts et al., 2009). Thus, efforts to enhance neurotrophic factors and reduce inflammatory cytokines are essential in potentially increasing cognitive performance in individuals at risk for developing dementia.

A recent systematic review and meta-analysis investigated the changes in neurotrophic, inflammatory, and oxidative biomarkers after exercise interventions in older adults with mild cognitive impairment and dementia (Stigger et al., 2019). The reviewers concluded that physical exercise, specifically aerobic exercise, has a positive effect on BDNF

expression, and a decrease in systemic concentrations of IL-6. However, this review was limited by the lack of studies with cognitive performance measures, the limited number of trials that met the inclusion criteria (n = 8), and the exclusion of cognitively healthy participants.

To our knowledge, no prior systematic review has examined the distinct effects of the main physical exercise modalities (aerobic, resistance, and multimodal) on serum biomarkers in cognitive trials that included both cognitively healthy and cognitively impaired older adults. The inclusion of studies targeting cognitive healthy and impaired older adults may improve our understanding of how cognitive status affects blood marker concentrations as well as cognitive outcomes after physical exercise. Further, this review will summarize our existing knowledge of the physiological mechanisms driving the neurotrophic, inflammatory, and cognitive outcomes after exercise. Therefore, the purpose of this systematic review and meta-analysis was to investigate the effects of physical exercise modalities on inflammatory and neurotrophic biomarker concentrations in clinical trials that examined the effects of exercise on cognition in older adults.

2.1 Methods

2.1.1 Study Design & Search Strategy

This systematic review and meta-analysis was registered with PROSPERO – CRD42019110522 (Appendix 1), an international database for prospectively registered systematic reviews that are examining health-related outcomes.

We utilized the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (Moher et al., 2009). A literature search, without date or language restrictions, was conducted via PubMed, SCOPUS, and EMBASE for literature published prior to January of 2019. The search applied appropriate medical subject headings (MeSH) in PubMed and SCOPUS, and subject headings in EMBASE (Tables 2.1, 2.2).

This systematic review was registered with PROSPERO – CRD42019110522 (Appendix 2), an international database for prospectively registered systematic reviews that are examining health-related outcomes. We utilized the preferred reporting items for

systematic reviews and meta-analyses (PRISMA) statement (Moher et al., 2009). A literature search, without date or language restrictions, was conducted via PubMed, SCOPUS, and EMBASE for literature published prior to January of 2019. The search applied appropriate medical subject headings (MeSH) in PubMed and SCOPUS, and subject headings in EMBASE (Tables 2.1, 2.2).

Table 2.1 Search terms.

Main Concepts	PubMed MeSH Term	EMBASE Subject Heading	SCOPUS MeSH Term
Exercise	Exercise OR Physical Exercise OR Physical Activity	Exercise OR Physical Activity OR Physical Exercise	Exercise OR Physical Activity OR Activities
Cognition	Cognition OR Cognitive Dysfunction OR Cognitive Impairment OR Executive Function	Cognition OR Cognitive Dysfunction OR Mild Cognitive Impairment OR Executive Function	Cognition OR Executive Function
Elderly	Aged OR Elderly	Aged OR Elderly	Aged OR Elderly
Blood Biomarkers	Blood Biomarkers	Blood Biomarkers	Blood Biomarkers
Brain Derived Neurotrophic Factor	Brian Derived Neurotrophic Factor OR BDNF	Brian Derived Neurotrophic Factor OR BDNF	Brain-derived Neurotrophic Factor OR BDNF
Insulin-like Growth Factor 1	Insulin-like Growth Factor 1 OR IGF-1	Insulin-like Growth Factor 1 OR IGF-1	Insulin-like Growth Factor-1 OR IGF-1
Vascular Endothelial Growth Factor	Vascular Endothelial Growth Factor OR VEGF	Vascular Endothelial Growth Factor OR VEGF	Vascular Endothelial Growth Factor OR VEGF
Interleukin 6	Interleukin 6 OR IL-6	Interleukin 6 OR IL-6	Interleukin-6 OR IL-6
C-Reactive Protein	C-Reactive Protein OR CRP	C-Reactive Protein OR CRP	C-Reactive Protein OR CRP

Note: BDNF = Brian Derived Neurotrophic Factor; IGF-1 = insulin-like growth factor 1; VEGF = vascular endothelial growth factor; IL-6 = interleukin 6; CRP = C-reactive protein.

Table 2.2 Search strategy for PubMed, EMBASE, and SCOPUS.

Using PubMed Database

1. Exercise/ OR Physical Exercise/ OR Physical Activity/
2. Cognition/ OR Cognitive Dysfunction/ OR Cognitive Impairment/ Or Executive Function/
3. Aged/ OR Elderly/
4. Blood Biomarkers/
5. Brian Derived Neurotrophic Factor/ OR BDNF/
6. Insulin-like Growth Factor 1/ OR IGF-1/
7. Vascular Endothelial Growth Factor/ OR VEGF/
8. Interleukin 6/ OR IL-6/
9. C-Reactive Protein/ OR CRP/
10. Strategy 4 AND 5 OR 6 OR 7 OR 8 OR 9
11. Strategy 1 AND 2 AND 3 AND 10

Using EMBASE Database

1. Exercise/
2. Physical Activity/
3. Physical Exercise/
4. Strategy 1 OR 2 OR 3
5. Cognition/
6. Executive Function/
7. Mild Cognitive Impairment/
8. Strategy 5 OR 6 OR 7
9. Aged/
10. Elderly/
11. Strategy 10 OR 11
12. Blood Biomarkers/
13. Brian Derived Neurotrophic Factor/
14. BDNF/
15. Strategy 14 OR 15
16. Insulin-like Growth Factor 1/
17. IGF-1/
18. Strategy 17 OR 18
19. Vascular Endothelial Growth Factor/
20. VEGF/
21. Strategy 20 OR 21
22. Interleukin 6/
23. IL-6/
24. Strategy 23 OR 24
25. C-Reactive Protein/
26. CRP/
27. Strategy 26 OR 27
28. Strategy 4 AND 9 AND 12 AND 13 AND 16 AND 19 AND 22 AND 25 AND 28

Using SCOPUS Database

1. Exercise/
2. Physical Activity/
3. Activities/
4. Strategy 1 AND 2 AND 3
5. Cognition/
6. Cognitive Dysfunction/
7. Cognitive Impairment/
8. Executive Function/
9. Strategy 5 OR 6 OR 7 OR 8
10. Aged/
11. Elderly/

12. Strategy 10 OR 11
13. Blood Biomarkers/
14. Brian Derived Neurotrophic Factor/
15. BDNF/
16. Strategy 14 OR 15
17. Insulin-like Growth Factor 1/
18. IGF-1/
19. Strategy 17 OR 18
20. Vascular Endothelial Growth Factor/
21. VEGF/
22. Strategy 20 OR 21
23. Interleukin 6/
24. IL-6/
25. Strategy 23 OR 24
26. C-Reactive Protein/
27. CRP/
28. Strategy 26 OR 27
29. Strategy 4 AND 9 AND 12 AND 13 AND 16 AND 19 AND 22 AND 25 AND 28

2.1.2 Screening

After completing the initial search, all duplicates were removed. To be included, articles must have met the following criteria: 1) Published as a randomized controlled trial (RCT) or quasi-randomized controlled trials (QRCT); 2) measured at least one of BDNF, VEGF, IGF-1, CRP, and IL-6, both before and after a longitudinal (>1 session) exercise intervention; 3) measured cognitive performance both before and after a longitudinal (>1 session) exercise intervention; 4) included a sample with a mean age of 60+ years, who were not taking cognitive enhancers, neuroleptics, or anticholinergics, and with an absence of neurological conditions with a residual motor deficit (Parkinson's disease, major stroke, multiple sclerosis), or depression, schizophrenia, severe anxiety, and drug abuse.

The titles and abstracts of the remaining articles were independently screened by two authors (JT and NB). The remaining articles then underwent a full-text review. Disagreements of the selected articles based on the criteria were settled by consensus of the two members, and if consensus could not be reached, the third reviewer (MMO) was consulted to make a decision. The bibliographies of all included articles were hand-searched for other potential articles that were missed during the initial search.

Caspersen et al. (1985) defined exercise as “Physical activity that is planned, structured, repetitive, and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective”. Physical fitness is composed of two categories inclusive of specific sub-categories: 1) Health-related: Cardiorespiratory capacity, muscular endurance, muscular strength, body composition and flexibility; 2) Skill-related: Agility, balance, coordination, speed, power, and reaction time.

2.1.3 Bias Assessment

The Cochrane Collaboration Tool (CCT) was used to appraise the risk of bias (Higgins et al., 2011) because of its recommendation for use in systematic reviews examining RCTs (Zeng et al., 2015). Additionally, the CCT has been used in other similar systematic reviews examining exercise, cognition (Hess et al., 2014), and blood biomarkers (Stigger et al., 2019). The CCT is a bias detection tool based on 7 domains, each of which can be ranked as low, high, unclear or not applicable (Fig. 2). Reviewers agreed to be conservative when deciding between two bias ratings by tending toward higher ratings of bias.

2.1.4 Outcome Measures

The primary outcome measure was the change in concentrations of the specified blood biomarkers (BDNF, VEGF, IGF-1, IL-6, CRP) from pre- to post-exercise intervention. The secondary outcome was the change in cognitive performance scores on neuropsychological assessments. Cognitive performance was split into five domains, when available, as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), criteria (Sachdev et al., 2014) The domains included: Learning and memory (LM), Complex Attention (CA), Executive Function (EF), Language, Perceptual-Motor Function (P-MF), and Global Cognition (GC).

2.1.5 Data Extraction

The following information was extracted from the articles selected for final analysis: authors and publication date, country of origin, study design, sample characteristics

(cohort, sample size, age), intervention details (exercise type, duration/frequency/time), primary outcome (significant change in specified blood biomarker concentrations), and secondary outcomes (cognitive changes in particular domains or global cognition, as applicable) (Table 2.3, Table 2.4, Table 2.5).

Due to the lack of raw data (pre- and post-intervention means, or mean change values) in almost half of the included trials (47 %), measures for the change in both blood biomarker concentrations and cognitive performance outcomes were simplified to either a "↑" representing a statistically significant increase and improvement, respectively, or a "↓" representing a statistically significant decrease and decline, respectively. For the data to be determined as statistically significant, results must be significant relative to both within-group time analyses and between-group comparisons to the control group.

In addition to the qualitative analyses, we planned on examining the strength of the evidence quantitatively by conducting a meta-analysis using Review Manager 5.3©. Additional inclusion criteria for the MA were reporting mean and standard deviation values at follow-up post-intervention in both control and experimental conditions. Included studies were also required to report a sample size.

We set the minimum number of independent studies needed for our meta-analysis at three. The data extracted were continuous and the meta-analysis was conducted using a random effects model, producing standardized mean differences. The studies yielded from our search varied considerably with respect to the populations sampled, with some studies recruiting exclusively male participants (Kohanpour and Peeri, 2017) or exclusively female participants (Damirchi et al., 2018), for example. A random-effects model accounts for data that may include studies sampled from varying populations, for which any potential effects of the intervention may differ. To account for these differences in sampling and the assumption that all studies are not functionally equivalent, we used a random-effects model. To assess heterogeneity (the extent to which differences underlying each study's results are genuine), I2 values were used.

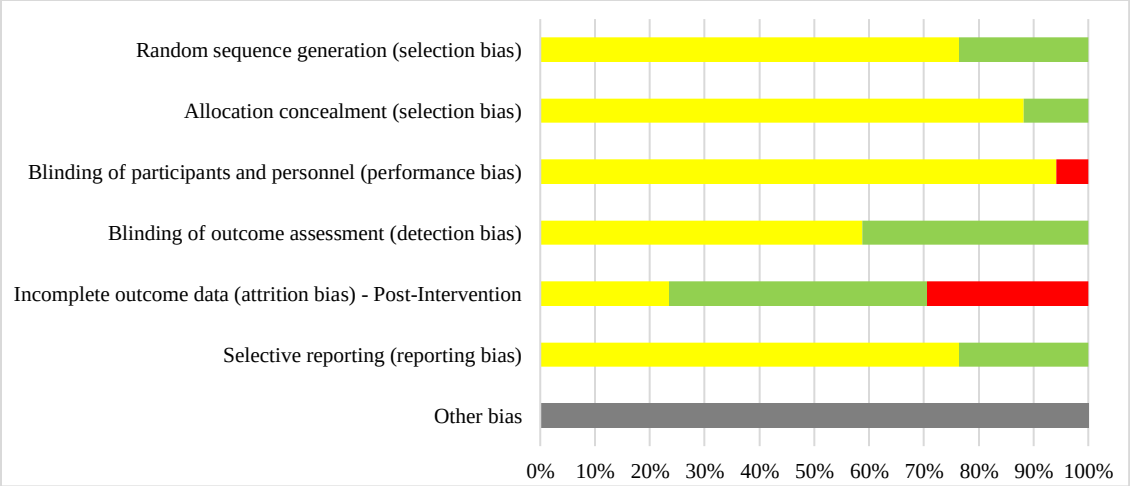

Figure 2.1 Risk of bias graph. Green = low risk; red = high risk; yellow = unclear; and grey = not applicable (NA).

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias) - Post-Intervention	Selective reporting (reporting bias)	Other bias
Alghadir et al., 2016	?	?	?	?	?	?	NA
Baker et al., 2010a	?	?	?	+	-	?	NA
Baker et al., 2010b	?	?	?	+	-	?	NA
Cassilhas et al., 2007	?	?	?	?	+	?	NA
Chupel et al., 2017	?	?	?	?	-	?	NA
Damirchi et al., 2018	?	?	?	?	-	?	NA
Erickson et al., 2011	?	?	?	?	?	?	NA
Fragala et al., 2014	?	?	?	?	+	?	NA
Kohanpour et al., 2017	?	?	?	?	?	?	NA
Leckie et al., 2014	?	?	?	?	?	?	NA
Maass et al., 2016	?	?	?	?	-	?	N/A
Muscari et al., 2009	?	?	?	+	+	?	N/A
Rehfeld et al., 2018	?	?	?	?	+	+	NA
Ruiz et al., 2015	+	?	?	+	+	+	NA
Tarazona-Santabalbina et al., 2016	+	+	?	+	+	+	NA
Tsai et al., 2015	+	?	?	+	+	?	NA
Vaughan et al., 2014	+	+	-	+	+	+	NA

Figure 2.2 Risk of bias summary. Green (+) = low risk; red (-) = high risk; yellow (?) = unclear; and grey = not applicable (NA).

2.2 Results

2.2.1 Search Results and Bias Assessment

Figure 2.1 summarizes all steps in the study selection process. A total of 942 articles were identified by searching PubMed (n = 215), EMBASE (n = 268), and SCOPUS (n = 459). 204 duplicates were removed. The remaining 738 articles were then screened via their title and abstract, resulting in 55 articles for full-text screening. Reviewers removed 39 articles that did not meet the inclusion criteria, and one article was added via the hand search (Tarazona-Santabalbina et al., 2016). In total, 17 articles were found to have met the inclusion criteria.

All included articles were published from 2007 to 2018 (Alghadir et al., 2016; Baker et al., 2010a, b; Cassilhas et al., 2007; Chupel et al., 2017; Damirchi et al., 2018; Erickson et al., 2011; Fragala et al., 2014; Kohanpour and Peeri, 2017; Leckie et al., 2014; Maass et al., 2016; Muscari et al., 2010; Rehfeld et al., 2018; Ruiz et al., 2015; Tarazona-Santabalbina et al., 2016; Tsai et al., 2015; Vaughan et al., 2014). The inter-rater agreement was high (Title and Abstract Kappa = 0.76; Full-Text Kappa = 1.00) during the screening process (Supplemental Material 2).

The majority of items measuring bias were rated “Unclear” for each trial, with the exception of two articles (Ruiz et al., 2015; Vaughan et al., 2014). Random sequence generation, allocation concealment, blinding of participants and personnel, and selective reporting were predominantly ranked “Unclear,” as many studies did not report these methods in detail. Studies frequently reported the blinding of outcome assessments, but many authors did not indicate any specific blinding procedures. The item assessing the extent to which outcome data reported in the studies was incomplete was more frequently ranked as “High” or “Low,” as opposed to “Unclear,”. Because randomized controlled trials were pre-registered in national databases which showed an explicit record of the initial plan of the study and outcome data, we were able to assess risk of bias in each study (Figure 2.2, Figure 2.3).

Table 2.3 Characteristics of studies utilizing aerobic exercise interventions.

Author	*Country*	*Sample Characteristics*			*Intervention Details*		*Blood Marker Measured*	*Cognitive Domain Measured*
		Cohort	*Sample Size (Female)*	*Mean Age in Years (SD)*	*Exercise Type*	*Duration*		
Alghadir et al., 2016	Saudi Arabia	Older Adult, Healthy	100 (35)	I: 66.8 (3.7) C: 67.3 (2.8)	Aerobic Training	24 weeks, 3x/ week, 45-60 mins	CRP: = (decreased in both I and C)	EF: ↑, LM: ↑, CA: ↑, Lang: ↑, P-MF: ↑
Baker et al., 2010a	USA	Older Adult, Prediabetes/ T2DM	28 (18)	I: 66 (6.0) C: 71 (7.5)	Aerobic Training	24 weeks, 4x/ week, 45-60 mins	BDNF: = IGF-1: =	EF: ↑, CA: ↑, LM: =, Lang: =
Baker et al., 2010b	USA	Older Adult, MCI	33 (17)	I: F: 65.3 (9.4) M: 70.9 (6.7) C: F: 74.6 (11.1) M: 70.6 (6.1)	Aerobic Training	24 weeks, 4x/ week, 45-60 mins	BDNF: M/F: = IGF-1: F: =, M: ↑	EF: F: ↑, M: = CA: F: ↑, M: = Lang: F: ↑, M: = LM: M/F: =
Erickson et al., 2011	USA	Older Adults, Healthy	120 (80)	I: 67.6 (5.81) C: 65.5 (5.44)	Aerobic Training	52 weeks, 3x/week, 40 mins	BDNF: =	LM: =
Kohanpour et al., 2017	Iran	Older Adults, MCI, Males	61 (0)	67.85 (3.89) (DNR group age)	Aerobic Training	12 weeks, 3x/ week, 26 mins	BDNF: ↑	GC: ↑
Leckie et al., 2014	USA	Older Adults, Healthy	92 (59)	I: 67.23 (5.39) C: 66.38 (5.83)	Aerobic Training	52 weeks, 3x/week, 40 mins	BDNF: =	EF: =
Maass et al., 2016	Germany	Older Adults, Healthy	40 (22)	I: 68.8 (4.5) C: 67.9 (4.1)	Aerobic Training, Interval Training	12 weeks, 3x/ week, 30 mins	BDNF: = IGF-1: = VEGF: =	LM: =
Muscari et al., 2009	Italy	Older Adults, Healthy	120 (58)	I: 68.8 (2.5) C: 69.6 (2.8)	Aerobic Training	52 weeks, 3x/ week, 60 mins	CRP: ↓	GC: ↑
Rehfeld et al., 2018	Germany	Older Adults, Healthy	38 (20)	I1: 68.16 (4.31) I2: 68.72 (2.68)	Dance Training	24 weeks, 2x/ week, 90 mins	BDNF: I1: ↑	EF: =, CA: ↑, LM: ↑, Lang: =

Note: Articles are listed in alphabetical order. Studies with multiple interventions are numbered i.e. I1, I2, etc. Age (years) is mean ± standard deviation. I = intervention; C = control; Where males and females are measured separately, M = male, F = female; BDNF = brain derived neurotrophic factor; IGF-1 = insulin-like growth factor; VEGF = vascular endothelial growth factor; CRP: c-reactive protein; IL-6: interleukin 6; CA: complex attention; EF = executive function; LM = learning and memory; Lang = language; P-MF = perceptual-motor function; GC = general cognition; DNR = did not report; ↑ = significantly increased; ↓ = significantly decreased; = = unchanged.

Table 2.4 Characteristics of studies utilizing resistance training interventions.

Author	Country	Sample Characteristics			Intervention Details		Blood Marker Measured	Cognitive Domain Measured
		Cohort	Sample Size (Female)	Mean Age in Years (SD)	Exercise Type	Duration		
Cassilhas et al. 2007	Brazil	Older Adult, Healthy, Males	62 (0)	I1: 68.04 (0.67) I2: 69.01 (1.10) C: 67.04 (0.54)	Resistance: I1: (80% 1rm) I2: (50% 1rm)	24 weeks, 3x/week, 60 mins	IGF-1: I1: ↑ I2: ↑	LM: I1: ↑ I2: ↑ CA: I1:↑ I2: ↑
Chupel et al., 2017	Portugal	Institutionalized, Older Adult, MCI, Females	33 (33)	I: 83.50 (5.13) C: 82.12 (6.41)	Resistance	28 weeks, 2-3x/week, mins DNR	CRP: =	GC: ↑
Fragala et al., 2014	USA	Older Adults, Healthy	25 (DNR sex)	70.64 (6.11) (DNR group differences)	Resistance	6 weeks, 2x/week, mins DNR	BDNF: =	P-MF: ↑
Tsai et al., 2015	Taiwan	Older Adults, Healthy, Males	48 (0)	I: 70.79 (3.39) C: 72.00 (4.14)	Resistance	52 weeks, 3x/ week, 60 mins	IGF-1: ↑	CA: ↑

Note: Articles are listed in alphabetical order. Studies with multiple interventions are numbered i.e. I1, I2, etc. Age (years) is mean ± standard deviation. I = intervention; C = control; Where males and females are measured separately, M = male, F = female; BDNF = brain derived neurotrophic factor; IGF-1 = insulin-like growth factor; VEGF = vascular endothelial growth factor; CRP: c-reactive protein; IL-6: interleukin 6; CA: complex attention; EF = executive function; LM = learning and memory; Lang = language; P-MF = perceptual-motor function; GC = general cognition; DNR = did not report; ↑ = significantly increased; ↓ = significantly decreased; = = unchanged.

Table 2.5 Characteristics of studies utilizing multimodal exercise interventions.

Author	*Country*	*Sample Characteristics*			*Intervention Details*		*Blood Marker Measured*	*Cognitive Domain Measured*
		Cohort	*Sample Size (Female)*	*Mean Age in Years (SD)*	*Exercise Type*	*Duration*		
Damirchi et al., 2018	Iran	Older Adults, MCI, Females	20 (20)	I: 68.81 (3.68) C: 69.11 (4.93)	Aerobic, Resistance	8 weeks, 3x/week, 45 mins	BDNF: =	LM: = CA: = EF: =
Ruiz et al., 2015	Spain	Institutionalized, Older Adults, Non-demented	40 (32)	I: 92.1 (2.3) C: 92.3 (2.3)	Aerobic, Resistance	8 weeks, 3x/ week, 45 mins	BDNF: =	GC: =
Tarazona-Santabalbina et al. 2016	Spain	Older Adults, Frail	100 (54)	I: 79.7 (3.6) C: 80.3 (3.7)	Aerobic, Resistance, Stretching, and Proprioception	24 weeks, 5x/ week, 65 mins	BDNF: =	GC: =
Vaughan et al., 2014	Australia	Older Adults, Healthy, Females	48 (48)	I: 69.0 (3.1) C: 68.8 (3.5)	Aerobic, Resistance, Motor Fitness, and Stretching	16 weeks, 2x/ week, 60 mins	BDNF: ↑	EF: ↑ CA: ↑ Lang: ↑
Rehfeld et al., 2018	Germany	Older Adults, Healthy	38 (20)	I2: 68.72 (2.68)	Aerobic, Resistance, and Stretching	24 weeks, 2x/ week, 90 mins	BDNF: I2: =	EF: = CA: ↑ LM: ↑ Lang: =

Note: Articles are listed in alphabetical order. Studies with multiple interventions are numbered i.e. I1, I2, etc. Age (years) is mean ± standard deviation. I = intervention; C = control; Where males and females are measured separately, M = male, F = female; BDNF = brain derived neurotrophic factor; IGF-1 = insulin-like growth factor; VEGF = vascular endothelial growth factor; CRP: c-reactive protein; IL-6: interleukin 6; CA: complex attention; EF = executive function; LM = learning and memory; Lang = language; P-MF = perceptual-motor function; GC = general cognition; DNR = did not report; ↑ = significantly increased; ↓ = significantly decreased; = = unchanged.

Table 2.6 Exercise Parameters.

	FITT-VP					
Study	**Frequency**	**Intensity**	**Time (min /week)**	**Type**	**Volume (min/week)**	**Progression**
Alghadir et al., 2016	I: 3x/week for 24-weeks	I: 60-70% of target HR max (Karvonen method)	I: 45-60	I: Aerobic exercise C: Unclear	I: 135-180	I: Not reported
Baker et al., 2010a	I: 4x/week for 6-months	I: Exercise duration and intensity were gradually increased over the first 6 weeks until exercising at 75% to 85% of HRR, and then remained at that intensity	I: 45-60	I: Aerobic exercise C: Stretching and balance	I: 180-240	I: See Intensity
Baker et al., 2010b	I: 4x/week for 6-months	I: Exercise duration and intensity were gradually increased over the first 6 weeks until exercising at 75% to 85% of HRR, and then remained at that intensity	I: 45-60	I: Aerobic exercise C: Stretching and balance	I: 180-240	I: See Intensity
Erickson et al., 2011	I: 3x/week for 1-year	I: 50-60 % week 1-7; 60-75% of target HR max (Karvonen method) for remainder	I: 10-40	I: Aerobic exercise C: Stretching and toning	I: 30-120	I: 5-min increments from week 1-7 and then remained at 40-minutes for remainder
Kohanpour et al., 2017	I: 3x/week for 12-weeks	I: 75%- 85% of HRR max	I: 8-26	I: Aerobic exercise C: Unclear	I: 24-78	I: 5-min increments from week 1-7 and then remained at 40-minutes for remainder
Leckie et al., 2014	I: 3x/week for 1-year	I: 50-60 % week 1-7; 60-75% of target HR max (Karvonen method) for remainder	I: 10-40	I: Aerobic exercise C: Stretching and toning	I: 30-120	I: 5-min increments from week 1-7 and then 40-minutes for remainder of program
Maass et al., 2016	I: 3x/week for 3-months	I: Target HR (Karvonen et al.), starting at 65%	I: 5-30	I: Aerobic exercise C: Muscle relaxation and stretching	I: 15-90	I: Increasing by 5% in steps for 4 weeks
Muscari et al., 2009	I: 3x/week for 12-months	I: Individually programmed in an incremental manner, up to 70% of max HR	I: 60	I: Aerobic exercise C: Educational material	I: 180	I: See Intensity
Rehfeld et al., 2018	I1 & I2: 2x/week for 6-months	I1 & I2: Measured HR frequency	I1 & I2: 90	I1: Dance I2: "Sport" (Aerobic, Resistance, and Flexibility Training)	I: 180	I1: Continuous learning of new movement patterns and choreographies, I2: Performed same exercises repeatedly
Chupel et al., 2017	I: 2x/week for 8-weeks +3x/week for 12-weeks +2x/week for 8-weeks	I: 6-8 on the OMNI-PES	I: 45	I: Resistance exercise C: Did not follow any type of exercise program	I: 90-135	I: Weeks 1-14 = yellow band; 15-28 = red band

Cassilhas et al. 2007	I1 & I2: 3x/week for 24-weeks	I1: 50 of 1-RM I2: 80% of 1-RM	I: 60	I1 & I2: Resistance exercise C: Warm-up and stretching	I: 180	I1 & I2: 1-RM testing repeated at week 10, 15, 18, and 21
Fragala et al., 2014	I: 2x/week for 6-weeks	I: 5-6 on the OMNI-PES	I: Not reported	I: Resistance exercise C: No intervention	I: Unclear	See Intensity
Tsai et al. 2015	I: 3x/week for 12-months	I: 75–80% 1- RM	I: 60	I: Resistance exercise C: Did not receive a specific intervention or group activity	I: 180	I: As each individual's muscle strength increased, their prescribed training load was also raised to ensure they performed the training at taregt 1-RM
Damirchi et al., 2018	I: 3/week for 8-weeks	I: Aerobic = 55 - 75 % of HRR (Karvonen) Resistance = RPE within 13 to 15 range	I: 41-55	I: Multi-domain (aerobic and resistance exercise) C: no intervention	I: 123-165	I: Aerobic = incrementally reached max HRR by eighth week Resistance = not reported
Ruiz et al., 2015	I: 3x/week for 8-weeks	I: Aerobic = 10-12 on Borg's conventional 6–20 point scale of RPE (confirmed via talk test) Resistance training = 30-70% of estimated 1-RM	I: 40-45	I: Multi-domain (aerobic, resistance, and stretching exercises) C: Gentle stretching	I: 120-135	I: Aerobic = lasted from 5min at the start of the program to 10–15min at the end Resistance = weekly load increase of ~5 % of 1RM
Tarazona-Santabalbina et al. 2016	I: 5x/week for 24-weeks	I: Aerobic training = 40-65% of maximum HR, increasing progressively to 65% Strength training = 25% of 1-RM for months 1-2, 50% for months 3-4, and 75% for months 5-6	I: 65	I: Multi-domain (aerobic, strength, coordination, balance, and flexibility exercises) C: No training	I: 325	I: Aerobic = increased progressively Resistance = See intensity - repetitions and sets were also manipulated
Vaughan et al., 2014	I: 2x/week for 16-weeks	I: Aerobic = 3-4/10 RPE Resistance = 2 sets of 6-8 reps	I: 60	I: Multi-domain (aerobic, strength, and motor fitness) C: Maintained usual activities	I: 120	I: Aerobic = Increasing number of simultaneous limb movements Resistance = Commence with no weight, progress to light weights (1kg)

Note. Details of exercise interventions according to FITT-VP (Frequency, Intensity, Time, Type, Volume, and Progression) parameters. Note that some exercise interventions did not clarify an element of the parameters. Volume is calculated as sessions per week x minutes per session and therefore, a range is required for some studies, which represents the lowest and highest number of minutes required. Volume does not account for rest periods in interventions that included resistance exercise. Additionally, we did not include information on modalities (e.g., machine, free-weight, bands, etc.), or repetition, rest, and set schemes for resistance exercise. HR = heart rate; HRR = heart rate reserve; OMNI-PES = OMNI perceived exertion scale; 1-RM = 1 repetition maximum; RPE = rating of perceived exertion; min = minutes

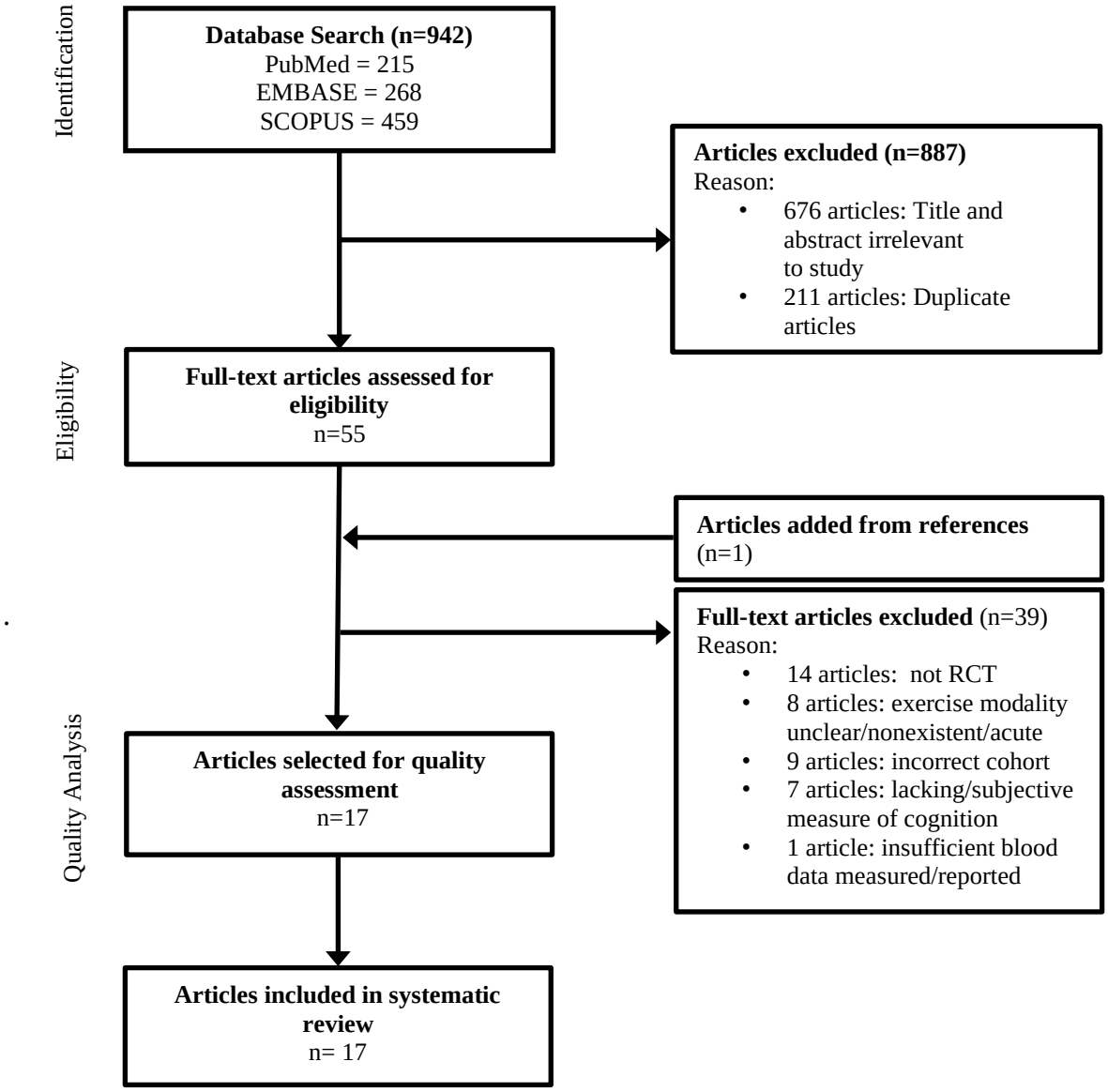

Figure 2.3 Flow diagram of the study selection process.

2.2.2 Study Populations

The sample sizes of included studies ranged from 20 to 120 (n = 1008), 555 of whom were female (55 %). Three trials recruited exclusively male participants (Cassilhas et al., 2007; Kohanpour and Peeri, 2017; Tsai et al., 2015), while two studies exclusively recruited females (Chupel et al., 2017; Damirchi et al., 2018). One trial did not report the sex of their 25 participants (Fragala et al., 2014). Mean (sd) ages of the intervention groups ranged from 66.0 (6.0) to 92.1 (2.3). Study populations were mostly drawn from the general public (Alghadir et al., 2016; Baker et al., 2010a, b; Cassilhas et al., 2007; Damirchi et al., 2018; Erickson et al., 2011; Fragala et al., 2014; Kohanpour and Peeri, 2017; Leckie et al., 2014; Maass et al., 2016; Muscari et al., 2010; Rehfeld et al., 2018; Tarazona-Santabalbina et al., 2016; Tsai et al., 2015; Vaughan et al., 2014), with the exception of two trials of institutionalized older adults (Chupel et al., 2017; Ruiz et al., 2015). The predominant cohorts were cognitively healthy (n = 13) (Alghadir et al., 2016; Baker et al., 2010a; Cassilhas et al., 2007; Chupel et al., 2017; Erickson et al., 2011; Fragala et al., 2014; Leckie et al., 2014; Maass et al., 2016; Muscari et al., 2010; Rehfeld et al., 2018; Tarazona-Santabalbina et al., 2016; Tsai et al., 2015; Vaughan et al., 2014); followed by MCI (n = 3) (Baker et al., 2010a; Damirchi et al., 2018; Kohanpour and Peeri, 2017). One study labelled their criteria as “not severely demented”, but reported mean cognitive scores in the range of MCI at baseline (Ruiz et al., 2015).

2.2.3 Exercise Protocols

The included studies used the following modalities: aerobic training (AT) (Alghadir et al., 2016; Baker et al., 2010a, b; Erickson et al., 2011; Kohanpour and Peeri, 2017; Leckie et al., 2014; Maass et al., 2016; Muscari et al., 2010; Rehfeld et al., 2018); resistance training (RT) (Cassilhas et al., 2007; Chupel et al., 2017; Fragala et al., 2014; Tsai et al., 2015); and multimodal (MMT), which includes AT and RT (Damirchi et al., 2018; Ruiz et al., 2015), with stretching (Rehfeld et al., 2018), proprioception training (Tarazona-Santabalbina et al., 2016) or motor fitness training (Vaughan et al.,

2014). The trial by Rehfeld et al. (2018) employed two distinct exercise interventions (dance and multimodal), both of which were included in this review. Two trials utilized multi-domain interventions including the use of lavender essence (Kohanpour and Peeri, 2017) and cognitive training (Damirchi et al., 2018). However, both trials included exercise-only groups, so the multi-domain interventions were not incorporated in the data extraction.

2.2.4 Aerobic Training (AT)

Nine trials included AT interventions, with sample sizes ranging from 28 to 120 participants, reaching a total of 632 participants, 49 % of whom were female. All trials recruited participants from the general public. One trial recruited exclusively male participants (Kohanpour and Peeri, 2017). Two trials recruited participants with MCI (Baker et al., 2010a; Kohanpour and Peeri, 2017), while the remaining seven trials recruited cognitively intact older adults.

Interventions ranged from 12 to 52 weeks, 2–4 sessions per week, and from 26−90 min. The AT was performed using ergometers (e.g. treadmill, stationary bike, etc.) or walking, running, and dancing. The intensity of AT was controlled by heart rate reserve and ratings of perceived exertion (Table 2.3).

Of the nine studies that investigated AT, seven measured growth factors (Baker et al., 2010a, b; Erickson et al., 2011; Kohanpour and Peeri, 2017; Leckie et al., 2014; Maass et al., 2016; Rehfeld et al., 2018) and two measured inflammatory markers (Alghadir et al., 2016; Muscari et al., 2010). Two of the seven studies measuring BDNF found a significant increase in BDNF concentration (Kohanpour and Peeri, 2017; Rehfeld et al., 2018), and five studies did not find any significant changes (Baker et al., 2010a, b; Erickson et al., 2011; Leckie et al., 2014; Maass et al., 2016). One study measured VEGF and did not find significant changes (Maass et al., 2016). Only one of the three studies measuring IGF-1 showed a significant increase in concentration; however, this was only in the males (Baker et al., 2010b). Of the studies exhibiting a positive relationship between aerobic exercise and growth factors, only one study that

measured BDNF showed improvements in cognitive performance (Kohanpour and Peeri, 2017). However, no formal analysis examined the relationship between the changes in BDNF concentration and cognitive outcomes. The majority of AT trials elicited improvements in at least one cognitive domain (n = 6) (Alghadir et al., 2016; Baker et al., 2010a, b; Kohanpour and Peeri, 2017; Muscari et al., 2010; Rehfeld et al., 2018). Overall, there was no consistent pattern in the review of these articles that linked the duration, frequency, or time spent on the AT to cognitive and growth factor changes.

Both of the studies measuring the effect of AT on inflammatory markers examined CRP. Only one study showed a significant decrease in CRP concentration post-intervention (Muscari et al., 2010). Both studies measuring CRP found cognitive improvements (Alghadir et al., 2016; Muscari et al., 2010).

2.2.5 Resistance Training (RT)

Four trials used RT interventions, and they included a total of 168 participants (ranging from 25−62 participants), 19 % of whom were female. Recruitment was from the general public (Cassilhas et al., 2007; Fragala et al., 2014; Tsai et al., 2015) and an institution (Chupel et al., 2017). Two trials recruited exclusively male participants (Cassilhas et al., 2007; Tsai et al., 2015) and one recruited female participants (Chupel et al., 2017). Two trials recruited participants with MCI (Chupel et al., 2017; Tsai et al., 2015) and two recruited cognitively intact older adults (Cassilhas et al., 2007; Fragala et al., 2014).

The RT interventions ranged from 6 to 52 weeks, 2−3 times per week, and lasted 60 min in the two studies that reported the session durations. The RT interventions utilized resistance bands and machines. Each trial used a range of 1–3 sets per exercise and 8–15 reps per set, depending on the intervention phase. The intensity of exercises was monitored using the 1-repetition maximum test and ratings of perceived exertion (Table 2.4).

Three out of four RT interventions measured neurotrophic factor concentrations (Cassilhas et al., 2007; Fragala et al., 2014; Tsai et al., 2015), while one measured inflammatory markers (Chupel et al., 2017). Of the three studies measuring neurotrophic

factors, two measured IGF-1 (Cassilhas et al., 2007; Tsai et al., 2015), and one measured BDNF (Fragala et al., 2014). Both of the studies measuring IGF-1 demonstrated a significant increase in IGF-1 concentration, as well as a significant increase in cognitive scores (Cassilhas et al., 2007; Tsai et al., 2015). The interventions that measured BDNF (n = 1) and the inflammatory marker CRP (n = 1) did not elicit significant changes (Chupel et al., 2017; Fragala et al., 2014) (Table 2.4).

2.2.6 Multimodal Training (MMT)

Five trials used MMT interventions (Damirchi et al., 2018; Rehfeld et al., 2018; Ruiz et al., 2015; Tarazona-Santabalbina et al., 2016; Vaughan et al., 2014) and ranged from 20 to 100 participants (n = 226), 72 % of whom were female. Recruitment was from the general public (Damirchi et al., 2018; Rehfeld et al., 2018; Tarazona-Santabalbina et al., 2016; Vaughan et al., 2014) and an institution (Ruiz et al., 2015). Two trials recruited exclusively male participants (Cassilhas et al., 2007; Tsai et al., 2015), and one trial recruited only female participants (Chupel et al., 2017). One trial recruited participants with MCI (Damirchi et al., 2018), as opposed to cognitively intact older adults (n = 4).

The MMT interventions ranged from 8 to 24 weeks, were performed 3–5 times per week and lasted 45−90 min. The RT portions of the MMT interventions utilized low-impact, multi-use devices, such as chairs, balls, resistance bands, light dumbbells, and resistance machines. The AT portions of each study used ergometers, walking, or stairs for 10−40 min. Intensity was measured by using heart rate reserve and ratings of perceived exertion. Three of the five studies also used other exercise modalities such as stretching (Rehfeld et al., 2018), stretching and proprioception (Tarazona-Santabalbina et al., 2016), or stretching and motor fitness (Vaughan et al., 2014) (Table 2.5).

Every included MMT intervention measured BDNF concentration (n = 4), but only one demonstrated a significant increase in concentrations post-intervention (Vaughan et al., 2014). However, two MMT interventions showed improvements to cognitive performance in at least one domain (Rehfeld et al., 2018; Vaughan et al., 2014).

2.2.7 Sex Differences

All of the three studies that only included males resulted in a significant increase in neurotrophic factor concentrations and also showed significant increases in cognitive scores (Cassilhas et al., 2007; Kohanpour and Peeri, 2017; Tsai et al., 2015). The one study measuring sex differences in the same sample showed significant increases in neurotrophic factor concentrations in males, however no significant improvements were seen in the cognitive scores. Conversely, the females in this sample exhibited significantly improved cognitive performance, but did not show changes in neurotrophic concentrations (Baker et al., 2010b). Two of the three studies that exclusively recruited females did not show any significant changes to blood marker concentrations (Chupel et al., 2017; Damirchi et al., 2018). Significant improvements in cognitive performance were elicited for two thirds of the female-only trials (Chupel et al., 2017; Vaughan et al., 2014).

2.2.8 Cognitive Performance after Exercise

In total, 11 out of 18 interventions increased performance in at least one cognitive domain. Specifically, complex attention improved in seven and eight of nine interventions in males and females, respectively (Alghadir et al., 2016; Baker et al., 2010a, b; Cassilhas et al., 2007; Rehfeld et al., 2018; Tsai et al., 2015; Vaughan et al., 2014); executive function improved in three and four of six interventions for males and females, respectively; learning and memory improved in four and four of nine interventions for males and females, respectively; language improved in two and three interventions for males and females, respectively (Alghadir et al., 2016; Baker et al., 2010b; Vaughan et al., 2014); perceptual-motor function improved in two and two of two interventions for males and females, respectively (Alghadir et al., 2016; Fragala et al., 2014); and global cognition improved in three and three of five interventions for males and females, respectively (Chupel et al., 2017; Kohanpour and Peeri, 2017; Muscari et al., 2010; Ruiz et al., 2015; Tarazona-Santabalbina et al., 2016).

Seven trials performed correlation analyses of changes in blood marker concentrations and cognitive performance (Alghadir et al., 2016; Damirchi et al., 2018; Erickson et al., 2011; Fragala et al., 2014; Maass et al., 2016; Ruiz et al., 2015; Tsai et al., 2015). CRP had a strong negative correlation with every cognitive domain in one trial (Alghadir et al., 2016). BDNF did not have a significant correlation with cognitive performance (Damirchi et al., 2018; Erickson et al., 2011; Fragala et al., 2014; Ruiz et al., 2015). IGF-1 was had a moderate positive correlation with learning and memory (Maass et al., 2016) and complex attention (Tsai et al., 2015) performance. One trial found that BDNF was a mediator of the exercise-executive function relationship as a function of age (Leckie et al., 2014).

2.2.9 Meta-Analyses Results

Studies examining changes following aerobic training in CRP, IL-6, and VEGF did not meet the minimum criteria of at least three independent studies. However, eight independent studies examined BNDF concentrations in individuals assigned to control or active experimental conditions, and were therefore included in the meta-analysis (Damirchi et al., 2018; Erickson, 2010; Fragala et al., 2014; Kohanpour and Peeri, 2017; Leckie et al., 2014; Maass et al., 2016; Tarazona-Santabalbina et al., 2016; Vaughan et al., 2014).

2.2.10 Weighted Results

As evidenced in Figure 2.4, of the eight studies, only one (Kohanpour and Peeri, 2017) yields results that favour the hypothesis that the experimental group has higher BDNF concentrations post intervention (relative to the control group). This is evidenced by the fact that the 95 % confidence interval wings extend entirely within the right hand side of Fig. 4. It is critical to note that while the results of this study are uniquely heterogeneous relative to the other seven studies—the sample size of Kohanpour and Peeri (2017) is very small (N = 10 in each group)—thus it had a low overall weight in the model. Conversely, the studies with the highest sample sizes (Erickson, 2010; Tarazona-

Santabalbina et al., 2016)—and therefore overall weights—demonstrate no particular trend in either direction.

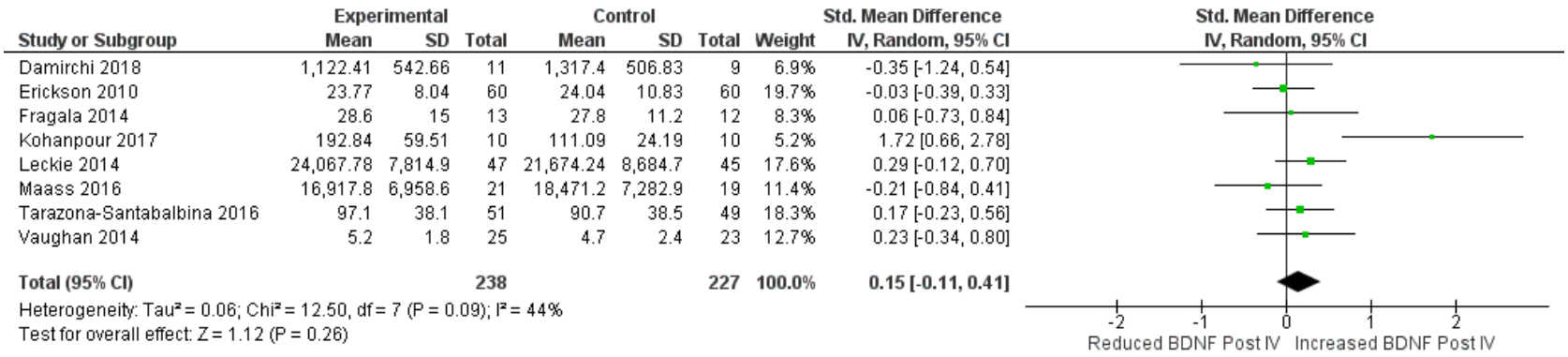

Figure 2.4 Forest Plot of Meta-Analysis. BDNF = Brain Derived Neurotropic Factor; IV = Intervention.

2.2.11 Overall Effect

Across the eight studies, there is a moderate degree of heterogeneity ($I2 = 44$ %), thus the findings should be interpreted with caution. The overall results are slightly in favour of the hypothesis that aerobic exercise yields higher BDNF concentrations, as compared to control exercises. But importantly, as depicted in Fig. 4, there is some overlap across the center line of no effect. This indicates that the overall effect is not completely indicative of increased BDNF post intervention and this is confirmed statistically, as the test of the overall effect is not significant, $Z = 1.12$, $p = .26$.

2.3 Discussion

This systematic review and meta-analysis investigated the effects of physical exercise on inflammatory and neurotrophic biomarker concentrations in clinical trials that aimed to improve cognition as a primary outcome. We found that exercise interventions, independent of the modality, were associated with changes in neurotropic and inflammatory blood marker concentrations in 8 of the 18 trials. IGF-1 was the most responsive to exercise, independent of modality. Aerobic training primarily increased or did not change BDNF concentration while resistance training increased IGF-1 concentration. MMT interventions elicited changes to BDNF in one of four trials. Males demonstrated greater blood marker changes in response to exercise. Finally, 11 of 17 trials resulted in an improvement in at least one domain of cognition and 5 (46 %) of those trials also demonstrated positive changes in biomarker concentrations. IGF-1 showed moderate positive correlations with LM and CA, while CRP was negatively correlated with all cognitive domains in one trial. There were no significant correlations between BDNF and cognitive outcomes.

Since the time of running this search (January 2019), two large scale studies have been published (as of December 2020) that show similar trends. Specifically, a study in which 146 participants were randomized to receive either aerobic training, cognitive training,

mindfulness training, or an active control found that the aerobic training group did not show significant changes in BDNF following the intervention (Ledreux et al., 2019). Similarly, another recently published study with 112 nursing home residents in Spain discerned that multimodal training did not significantly change BDNF concentrations in the intervention condition (Arrieta et al., 2020). These findings are consistent with the findings of our systematic review indicating that BDNF concentrations either increase *or* remain unchanged following aerobic or MMT interventions.

Lastly, although our systematic review excluded RCTs in which the intervention consisted of only one acute, single bout intervention session, a recent study found a significant increase in BDNF concentrations following an acute bout of high-intensity exercise (Devenney et al., 2019). This, too, is consistent with our findings that AT either increases or does not change BDNF concentrations.

2.3.1 Effects of Exercise Modalities on Blood Markers and Cognition

AT was the most commonly studied intervention strategy (n = 9), followed by MMT (n = 5), and RT (n = 4). The AT interventions were associated with positive changes in BDNF and improved cognitive performance in six of the nine trials. Two RT interventions increased IGF-1 concentrations, but all four RT interventions improved cognitive performance. Interestingly, only one of five MMT intervention led to significant increases in BDNF concentration and two trials improved cognitive performance.

Consistent with the results of this review, previous research has suggested that AT increases BDNF concentrations, while RT primarily functions to increase IGF-1 concentrations (Cassilhas et al., 2012). As all MMT programs in this review utilize both RT and AT, we can expect that a more interactive cascade can be driving the observed cognitive improvements. Thus, more comprehensive measurements of neurotrophic and inflammatory markers are necessary to delineate the potentially divergent mechanisms that mediate MMT-induced cognitive improvements.

Recent systematic reviews and meta-analyses measuring the effect of exercise on biomarkers in older adults with MCI or dementia reported that exercise significantly increased BDNF concentrations and significantly decreased IL-6 and tumor necrosis factor-α (TNF-α) concentrations (Stigger et al., 2019). These results may relate to the relatively low baseline concentration of neurotrophic factors (Xie et al., 2019) or high concentrations of inflammatory cytokines in individuals with MCI or dementia (Öztürk et al., 2007), compared to healthy older adults. This may indicate that participants who have cognitive impairments have more room to ameliorate concentrations of neurotrophic and inflammatory markers after longitudinal exercise, while cognitively intact participants may be limited by a ceiling effect. However, data from the studies that recruited participants with MCI (n = 4) did not suggest that exercise was more effective at increasing or decreasing growth factor and inflammatory cytokine concentrations, respectively, for participants with cognitive impairments (Baker et al., 2010b; Fragala et al., 2014; Tsai et al., 2015). Previous reviews of exercise effects on neurotrophic and inflammatory concentrations were limited by the number of trials and heterogeneity, especially when considering the complexity and interactive nature of the variables (Stigger et al., 2019). Notably, the Stigger et al. (2019) review did not include studies with healthy control participants—but ours did. Additionally, like the Stigger et al. (2019) review, we also conducted a meta-analysis on the data extracted.

Overall, the results of the meta-analysis suggest a minimal trend towards increases in one growth marker (BDNF) following aerobic exercise. This finding, however, is not statistically significant. Heterogeneity across studies paired with small sample sizes and the lack of studies meeting our inclusion criteria that examine biological markers aside from BDNF strongly suggest that this field is wanting of more robust research.

One hypothesis explaining the heterogeneity in biomarker concentrations post intervention across studies may be the variability in exercise parameters (see Table 2.6). Generally, there was considerable variability across all exercise parameters (frequency, intensity, time, type, volume, and progression). For example, total volume of exposure across studies ranged from 15−325 min per week; thus, in some studies, volume of exercise intervention exposure was less than the recommended 150 min per week of

aerobic activity for older adults (https://csepguidelines.ca/adults-65/) to 240 min per week. The variability observed across studies in exercise training exposure does not appear to explain the differences across studies in blood marker concentrations post intervention. For example, the Kohanpour and Peeri (2017) study showed a robust increase in BDNF concentrations following intervention; however, exposure to the exercise intervention occurred over only 12 weeks. In contrast, Erickson et al. (2011) and Leckie et al. (2014) conducted their exercise intervention sessions over an entire year. But despite this prolonged exposure, increases in BDNF concentrations post intervention were smaller relative to those observed in other studies (i.e., Kohanpour and Peeri, 2017). Taken together, what these data indicate is that differences across studies in intervention exposure (exercise frequency) do not appear to shed light on the variability observed across studies in biomarker changes post intervention.

2.3.2 Discussion of Sex Differences

There were notable sex differences in changes to biomarker concentrations in trials that exclusively recruited one sex, as well as the single trial that analyzed sex-differences in their sample. In particular, every male-only cohort (n = 3) exhibited increases in neurotrophic factor or decreases in inflammatory markers that accompanied significant improvements in cognition (Cassilhas et al., 2007; Kohanpour and Peeri, 2017; Tsai et al., 2015), but there was no correlation between changes in blood marker and cognitive function when analyzed (Tsai et al., 2015). Also, the single trial that measured sex differences within their sample found significant improvements to neurotrophic factor concentrations in the male, but not the female participants (Baker et al., 2010b). Interestingly, none of the female-only cohorts (n = 3) showed changes to blood marker concentrations (Chupel et al., 2017; Damirchi et al., 2018; Vaughan et al., 2014).

The sex-specific biomarker responses might be related to the different exercise modalities performed. In particular, two of three female-only cohorts participated in MMT; the only modality that did not elicit any changes to blood marker concentrations. Also, no female samples exclusively participated in AT. Alternatively, two of three male-only cohorts participated in RT, which was the modality exhibiting the greatest proportion of positive

changes to blood marker concentrations and cognitive scores. Interestingly, trials utilizing RT were mostly composed of male participants, suggesting that sex might moderate the positive neurotrophic outcomes of RT. Thus, the sex differences might be confounded by the lack of equal representation of sexes across exercise modalities, or potential sex-related moderation. Alternatively, there are sex-specific differences within the aging process (Barha and Liu-Ambrose, 2018; Gordon et al., 2017), which may be related to the sex-specific responses to intervention strategies. This has been addressed by recent studies investigating how pre-frail older females respond to free-weight resistance training interventions to reduce frailty and improve functional capabilities with promising results (Bray et al., 2019a, 2019b). Therefore, increased attention to the sex-specific responses to exercise is imperative to improve understanding of this complex relationship.

There is a growing body of literature examining sex-specific responses to exercise interventions implemented in older adults at risk for dementia (Barha and Liu-Ambrose, 2018). For example, results from a recent systematic review and meta-analysis indicate that exercise intervention studies in which samples are predominantly female show more robust benefits on executive function than those with fewer female participants (Barha et al., 2017). These data suggest that the cognitive domains involved in executive functioning in women may be more sensitive to the neurological cascade resultant of exercise interventions. Additionally, there is evidence suggesting that there may be an interaction between the type of exercise intervention and sex on cognitive outcomes. Aerobic exercise, for example, appears to be more effective in producing cognitive benefits to women than to men (Colcombe and Kramer, 2003). Taken together, the literature suggests that sex is a critical factor to consider in studies examining neutrally mediated cognitive outcomes of exercise interventions in aging populations.

2.3.3 Cognitive Performance Outcomes

In total, 11 out of 18 interventions augmented at least one domain of cognition. More specifically, exercise preferentially improved complex attention in seven and eight out of nine interventions in males and females, respectively, and improved perceptual-motor

function in two of two interventions. These findings strengthen the relationship between exercise and cognition, especially in perceptual-motor function, which was the least measured cognitive domain in this review. Other domains showed only moderate modulation by exercise. Out of the exercise modalities, RT interventions were the most effective in augmenting cognitive performance. Further, RT elicited cognitive benefits in complex attention, learning and memory, perceptual-motor function, and global cognition. Recent research investigating the effect of RT on cognition in older adults also demonstrates this relationship. In particular, a systematic review by Li et al. (2018) examined the cognitive effects of RT on older adults. Similar to our review, their results indicated that longitudinal RT interventions significantly improved executive function and global cognition performance.

From the seven trials that analyzed correlations between the changes in blood marker concentrations and cognitive outcomes, IGF-1 seems to have the strongest correlation with cognitive performance, showing moderate positive correlations to complex attention (Tsai et al., 2015) and learning and memory (Maass et al., 2016). The relationship between IGF-1 and cognition is inconsistent. For example, some work has shown that IGF-1 is positively correlated with cognition (Okereke et al., 2006) but others suggested that it is negatively correlated with cognition (Stein et al., 2018). Further, it has been suggested that moderate, as opposed to a high or low, concentrations of systemic IGF-1 is correlated with positive cognitive outcomes (Tumati et al., 2016). Thus, further research is needed to evaluate the correlation between IGF-1 and cognitive outcomes after exercise.

Surprisingly, in the four trials that performed correlation analyses, no correlations were found between the changes in BDNF and cognitive outcomes. However, consistent with previous literature (Vaynman et al., 2004), BDNF was shown to be a mediator of the exercise-cognition relationship in one trial (Leckie et al., 2014). To establish more a concrete understanding of how growth factors correlate with cognition, more comprehensive neuropsychological assessments, growth factor measurements, and appropriate statistical analyses should be utilized.

2.3.4 Future Studies

This systematic review exposed gaps in the literature. Future research should focus on the effect of exercise on multiple neurotrophic and inflammatory markers simultaneously, while measuring cognitive performance. An ongoing RCT is examining the effect of MMT on BDNF, IGF-1, VEGF, IL-6, CRP and cognitive performance in older adults consisting of 200 participants with MCI and may help to decipher the role of these neurotrophic and inflammatory markers (Montero-Odasso et al., 2018). Further, research should be developed to specific exercise modalities. In addition, the role of sex-related factors, such as hormone concentrations and their interactions with neurotrophic and inflammatory blood markers, is a potential avenue for further research in this topic. Additional reasons for the contrasting findings may be related to the diversity of participants in each study. That is, future studies examining varying ethnic backgrounds or comorbidities in the populations under study may offer fruitful insights in explaining the mixed findings. However, in the present study, the majority of selected studies were similar with respect to demographic characteristics such as ethnic background and comorbidities. Finally, difference across studies can also be related to the target population and when the intervention was provided across the spectrum of the decline. Future research focusing on the timing in which interventions are implemented in individuals at risk for developing dementia may provide interesting findings.

2.3.5 Limitations

Our review has limitations. Firstly, it is possible that our search strategy missed relevant material in our selected databases. Additionally, the included studies were heterogeneous in terms of exercise modalities and parameters, preferred blood markers, sample sizes, cognitive domains measured, and analyses employed. Also, given the limitations of the published studies, we reported results as “increase” or “decrease,” which limited the examination of the relative effect size of each intervention. Further, only extracting results of significance from the trials means that large samples sizes are required, but not obtained, in all individual studies to prevent Type II errors. Also, the number of studies in

our review was limited by a lack of available literature that measured both the changes to concentrations of blood markers of interest and cognitive performance.

Regarding our meta-analyses, the eight included studies were limited by small sample sizes, with sample sizes ranging from N = 10 per condition to N = 60 per condition, with an average sample size of 29 individuals per arm across studies. In addition, studies were highly heterogeneous, requiring a high degree of caution in interpreting the results. The absence of trials that included the mean change values for inflammatory blood markers limited our ability to perform any additional meta-analyses. And finally, trials preferentially measured single blood markers (typically BDNF or IGF-1) in the majority of cognitive trials and lacked measurements of inflammatory markers.

2.4 Conclusion

Exercise has an effect on the serum concentrations of neurotrophic and inflammatory marker in cognitive trials. Specifically, AT primarily increased or did not change the concentrations of BDNF, while RT increased or did not change the concentrations of IGF-1. A small number of trials demonstrated changes in biomarkers may be sex specific, as males exhibited greater increases in neurotrophic biomarker concentrations after exercise interventions than females. This systematic review was limited by heterogeneity of exercise modalities and parameters, as well as the variability in the measurements of blood markers and cognition. Despite the limitations, this is the first review to examine and compare the effect of the type of exercise on neurotrophic and inflammatory markers on cognition in older adults. Based on the gaps detected, we suggest that further research on the effect of exercise on cognition should simultaneously measures neurotrophic and inflammatory markers, to gain a more comprehensive understanding of this relationship.

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Appendix A Prospero Registration.

You have 1 records

My other records

These are records that have either been published or rejected and are not currently being worked on.

ID	Title	Status	Last edited
CRD42019110522	The role of physical exercises modulating peripheral inflammatory and neurotrophic biomarkers in cognitive trials: a systematic review of experimental studies in older adults	Registered	23/10/2019

Appendix B Kappa Statistics Calculations.

		Reviewer 2			Total
		Include	**Exclude**	**Unsure**	
Reviewer 1	**Include**	a	b	c	I_1
	Exclude	d	e	f	E_1
	Unsure	g	h	i	U_1
Total		I_2	E_2	U_2	K

$P_O = a + e + i / K.$

$P_E = I_1 \times I_2 + E_1 \times E_2 + U_1 \times U_2 / K^2$

Kappa = $P_O - P_E / 1 - P_E.$

Title and Abstract:

		Reviewer NB			Total
		Include	**Exclude**	**Unsure**	
Reviewer JT	**Include**	28	2	6	36
	Exclude	1	683	7	691
	Unsure	4	2	5	11
Total		33	687	18	738

Kappa = 0.76

Full-Text:

		Reviewer NB			Total
		Include	**Exclude**	**Unsure**	
Reviewer JT	**Include**	17	0	0	17
	Exclude	0	39	0	39
	Unsure	0	0	0	0
Total		17	39	0	56

Kappa = 1.00.

Curriculum Vitae

Name	Joshua Titus
Post-Secondary Education and Degrees	Western University London, Ontario, Canada 2012-2016 B.A. (Honours) Kinesiology Western University London, Ontario, Canada 2017-2021 M.Sc. Kinesiology (Integrated Biosciences) University of Toronto Toronto, Ontario, Canada 2020-2022 M.Sc.OT Occupational Therapy
Honours and Awards	Joseph A. Scott Studentship in Mobility and Aging 2018
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Publications

***Titus, J.**, Bray, N. W., Kamkar, N., Camicioli, R., Nagamatsu, L. S., Speechley, M., & Montero-Odasso, M. (2021). The role of physical exercise in modulating peripheral inflammatory and neurotrophic biomarkers in older adults: A systematic review and meta-analysis. *Mechanisms of Ageing and Development*, 111431. https://doi.org/10.1016/j.mad.2021.111431

Montero-Odasso, M., Sarquis-Adamson, Y., Kamkar, N., Pieruccini-Faria, F., Bray, N. W., Cullen, S., Mahon, J., ***Titus**, **J.**, et al. (2020). Dual-task gait speed assessments with an electronic walkway and a stopwatch in older adults. A reliability study. *Experimental Gerontology*, *142*, 111102. https://doi.org/10.1016/j.exger.2020.111102