Comparative Efficacy of Exercise Intensity on Cognitive Function for Older Adults with Cognitive Impairment: A Systematic Review with Meta-Analysis

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Table of Contents

ABSTRACT **5**

INTRODUCTION **6**

Dementia 7

Diagnosis and Clinical Symptomology of Dementia *9*

Mild Cognitive Impairment *10*

Societal Impact *12*

Alzheimer's Disease 15

Post-Mortem Neuropathology *15*

In-Vivo Biomarkers *17*

Prevention and Intervention 20

Current Drug Interventions *21*

Preventative Prospects *23*

Best Practice *25*

Physical Exercise 26

The Protective Effect for an Unhealthy Brain *27*

Cardiovascular Fitness Hypothesis *29*

Oxygen Saturation and Angiogenesis Hypothesis *31*

Upregulation of Neurotropins Hypothesis *32*

Social Impacts *33*

Psychological Impacts *35*

Exercise Intensity 36

High-Intensity Exercise *37*

Low- to Moderate-Intensity Exercise *38*

This Meta-Analysis 40

METHOD **40**

Protocol and Registration 40

Information Source and Search Strategy 41

Eligibility Criteria 42

Data Extraction 45

Risk of Bias Assessment 47

Data Analysis 47

RESULTS **48**

Included Studies 49

Analysis Plan 53

Risk of Bias 54

Main Results 56

Intervention vs Control Groups *56*

Intensity Comparison *57*

Moderator Analyses *62*

Heterogeneity *66*

Subgroup Analyses 68

Cognitive Impairment *68*

Age of Participant *72*

Length of Intervention *73*

Study Quality *76*

Additional Analyses 78

Frequency of Exercise and Exercise Intensity *79*

Adherence and Exercise Intensity *81*

Exercise Type and Exercise Intensity *81*

Small-Study Bias 83

Trim-and-Fill Method *83*

Funnel Plot *84*

Egger's Test *84*

P-Curve Analysis *88*

DISCUSSION **90**

Included Studies 91

Exercise Interventions 92

Neurobiological Explanations *93*

Psychological and Social Explanations *95*

Multifaceted Approach *96*

Exercise Intensity 97

Contextualising within Prior Research *99*

Translation into the Real World *102*

Moderators and Additional Analyses 103

Frequency and Duration of Exercise *103*
Adherence to Exercise Intervention *106*
Type of Exercise *107*
Implications *108*
Heterogeneity 109
Subgroup Analyses 110
Clinical Diagnosis *111*
Age of Participant *112*
Length of the Exercise Intervention *113*
Quality of the Study *115*
Small-study bias 117
Implications *119*
GRADE Assessment 120
Quality Rating *120*
Overall Confidence *121*
Methodological Considerations 121
Risk of Bias *122*
Future Research 123
Conclusion 124
REFERENCES 126
APPENDICES 149
Appendix A: Pre-Registration for PROSPERO 149
Appendix B: Dataset for Meta-Analysis 154
Appendix C: Code Used for Meta-Analysis in RStudio 156

Abstract

The incidence of mild cognitive impairment (MCI) and dementia is on the rise due to an ageing population, and there is currently a lack of pharmacological prospects in mitigating this risk. As a result of this, physical activity has been identified as a potential preventative and intervention measure for delaying or preventing cognitive impairment. This meta-analysis aims to explore the effect of high-intensity exercise and low- to moderate-intensity exercise on cognition for older adults with a diagnosis of either MCI or dementia. A number of different online databases were searched, and 18 studies were identified as meeting all of the inclusion criteria for this meta-analysis. Results indicated that exercise significantly improves cognitive ability for older adults with cognitive impairment. High-intensity exercise did not have a significant effect on cognition, and higher frequency of high-intensity exercise led to poorer cognitive performance. Low- to moderate-intensity exercise did have a significant effect on cognition, and longer durations at this level of intensity leads to better cognitive outcomes. The results of the subgroup analyses indicates that the effect of exercise differs depending on the length of the intervention with short-term interventions eliciting significant cognitive benefits but long-term interventions not having an effect. A diagnosis of MCI also leads to exercise having a larger effect than a diagnosis of dementia. This meta-analysis provides information that can help to inform best practice and further our understanding of what intensity of exercise elicits greater cognitive benefits for this population.

Introduction

As younger age mortality declines, the number of older people living with neurocognitive disorders increases. As of 2015 there were around 47 million people living with dementia, and this number is projected to triple by the year 2050 under the expectation that no cure or way of slowing the disease is identified (Livingston et al., 2017). In Aotearoa New Zealand specifically, the estimated number of people living with dementia is 69,713 which is 1.3% of the total population (Ma'u et al., 2021). The majority of these individuals are aged 65+ and make up 8% of the 65+ population (Ma'u et al., 2021). This number is expected to more than double by the year 2050, comprising 2.7% of the total population and 10.8% of the population aged 65+ (Ma'u et al., 2021). Currently, most of the knowledge we have about neuropathology behind dementia has been acquired through post-mortem research (Braak & Tredici, 2014; Thal et al., 2002), mainly because there is a lack of effective imaging techniques that allow for accurate in-vivo identification of the stages of dementia (Buchhave et al., 2012; Jack et al., 2013). This is part of the reason why dementia is diagnosed so late in the neuropathological stages, as we are unable to detect this disease until there are noticeable cognitive changes that are inhibiting the individual from performing everyday tasks (American Psychiatric Association, 2013). Pharmacological solutions to slow cognitive decline have been tried but are yet unproven. A previously promising looking drug, aducanumab (Sevigny et al., 2016), has since been discovered to be less effective than first thought (Schneider, 2020). More recently, there have been some preliminary results that point to potentially effective drug treatments (Sandusky-Beltran & Sigurdsson, 2020). There is also some indication that a combination of these new drugs with old drugs, or drugs that target symptomology, will be successful (Lahiri, 2019). However, this research is still in its early stages and there is no sign of a potential cure or effective drug

that can help to combat the neuropathological progression of dementia in the immediate future. Therefore, research is moving towards a focus on the clinical symptomology of dementia and looking for accessible and easily implemented interventions to slow or reverse the cognitive impairment that is seen with dementia. The factors being considered are modifications within everyday life that everyone can put into action, and one such factor that has received a lot of attention is physical exercise (Livingston et al., 2017). There is a mounting body of research that speaks to the significant effect that physical exercise can have on cognition (Foster et al., 2011; Kirk-Sanchez & McGough, 2014; Ploughman, 2008), and now the question is what aspects of physical exercise are more beneficial for those with cognitive impairment. In particular, the intensity of these interventions is a contested point (Y.-K. Chang & Etnier, 2009; Kovacevic et al., 2020). Currently, there is limited research pointing to whether high-intensity or low- to moderate-intensity should be recommended to older adults experiencing cognitive decline. Understanding the impact that exercise can have on delaying cognitive decline requires a good understanding of the science behind dementia-related neurodegenerative disease.

Dementia

Dementia is characterized by a decline in cognitive functioning that significantly affects daily living or social functioning, and significant brain atrophy in areas of executive function, such as the hippocampus (Kirk-Sanchez & McGough, 2014). Significant decline in executive functioning tasks such as attention-switching, inhibitory control, response times, information processing and memory are indicative of this (Kirk-Sanchez & McGough, 2014). The most common form of dementia is Alzheimer's disease, which makes up approximately 60-80% of dementias worldwide (Alzheimer's Association, 2020). Other forms of dementia include vascular dementia, dementia with Lewy bodies, and a group of diseases that

contribute to frontotemporal dementia. The progression to dementia usually includes a transition through the pre-clinical stage of mild cognitive impairment (MCI). A diagnosis of MCI exhibits a significant level of decline from the individual's baseline; however, the individual can mostly still function normally in everyday life (R. C. Petersen, 2016).

The difficulty with neurodegenerative diseases, such as dementia, is that we are lacking techniques to diagnose it early in its progression and with certainty. Whilst we know that there are certain biomarkers in the brain that are present in Alzheimer's disease, the most common form of dementia (Alzheimer's Association, 2020), these biomarkers are also present in other non-dementia neurodegenerative diseases (Braak & Tredici, 2014). Even if specific biomarkers could be pinpointed that contribute to dementia alone, there are further complications with identifying these biomarkers in vivo. Whilst some imaging techniques such as PET scans or examination of cerebrospinal fluid can help us to gain some information around the levels of biomarkers present in an individual's brain (Knopman et al., 2019), they are unable to gain sufficient information in the early stages of the disease. Commonly, these techniques are only able to detect significant levels of biomarkers once an individual is exhibiting the clinical symptoms of dementia (Jack et al., 2013; Jack Jr. et al., 2018). Due to this, the earliest indicators that we currently have that an individual has dementia are the cognitive symptoms that appear in the late stages of the disease. Whilst these clinical symptoms are helpful, without confirmation through biomarkers or brain atrophy – which current imaging techniques are unable to ascertain with certainty – only a provisional diagnosis of Alzheimer's can be made until a post-mortem confirmation of the disease (Braak & Tredici, 2014).

Diagnosis and Clinical Symptomology of Dementia

There is currently an upstream movement to diagnose neurocognitive disorders such as dementia earlier. Emerging literature is improving early diagnostic indicators and there is growing recognition that neuropathological determinations can be made well before the onset of clinical symptoms. Due to this, the first step in diagnosing dementia is to differentiate between normal neurocognitive function and mild cognitive disorder (MCI; Blazer, 2013). As cognition declines, an etiological category such as Alzheimer's disease (AD) or frontotemporal neurocognitive disorder will be assigned (Blazer, 2013). As there is some degree of cognitive slowing associated with normal ageing, the first challenge a clinician has when diagnosing dementia is to identify what cognitive changes are clinically significant. Typically, dementia is diagnosed when the cognitive impairment seen in the individual is severe enough to compromise their social and/or occupational functioning (American Psychiatric Association, 2013). The framework within the American Psychiatric Association's Diagnostic and Statistical Manual (DSM-5) outlines this difference, with a diagnosis of Major Neurocognitive Disorder, which relates to dementia, requiring substantial impairment in one or more cognitive domains that interferes with independence in everyday activities (American Psychiatric Association, 2013).

Behavioural and psychological symptoms of dementia (BPSD), or neuropsychiatric symptoms (NPS) as they are more commonly known, are almost universally present in dementia patients with roughly 90% of those with Alzheimer's being affected by them (Radue et al., 2019). They are associated with high levels of distress and adverse outcomes for both the individual and the caregiver (Aalten et al., 2005). BPSD's generally include disturbed emotions, thought, mood, apathy, appetite and sleep changes, agitation, psychosis, motor disruptions, and dementia is often found to be comorbid with anxiety and

depression (Aalten et al., 2005; Cerejeira et al., 2012; Radue et al., 2019). These symptoms are heterogeneous and predominately unpredictable. Whilst some pathological sub-types of dementia have symptoms that have become more recognised, there is still wide variation in presentation at the sub-type and the individual level (Cerejeira et al., 2012). There is also significant overlap between symptoms and a lack of proper criteria or definitions for their diagnosis (Aalten et al., 2005; Cerejeira et al., 2012). Due to this, only some sub-types of dementia have NPS included within the criteria for a diagnosis according the DSM-5, such as visual hallucinations in dementia with Lewy bodies (Radue et al., 2019). It can be difficult to ascertain what symptoms are present within the individual, and broadly at what stage of the disease they materialise. Sex or age at baseline does not appear to be a predictor of NPS, however there is a strong relationship between severity of dementia and NPS, with a peak in prevalence in moderate stages and a drop off of NPS in the more severe forms of dementia (Aalten et al., 2005; Radue et al., 2019). It has further been demonstrated that, irrespective of behavioural problems that may appear, dementia patients have a very high risk of developing psychiatric problems later in the course of the disease (Aalten et al., 2005).

Mild Cognitive Impairment

Mild cognitive impairment (MCI) is an intermediate state between normal cognition and dementia, characterised by a cognitive decline that is greater than expected for the individual when considering their educational level and age, but it is still not great enough to have an impact on daily functioning or inhibit independence in everyday activities (Gauthier et al., 2006; Hugo & Ganguli, 2014; R. Petersen & Negash, 2008). Longitudinal studies have shown a prevalence of 3%-19% in the general elderly population, with many factors affecting cognitive performance such as vascular risk factors, education, genetic background,

psychiatric statues, hormonal changes and use of anticholinergic drugs (Gauthier et al., 2006). MCI increases the risk of dementia by five- to ten-fold. (R. C. Petersen et al., 1999).

The rationale behind including a MCI within the stages of diagnosing neurocognitive disorders lies primarily in the need for treating individuals that seek medical and psychiatric evaluation for problems that are clearly disturbing them but may not meet the threshold for a major neurocognitive disorder (Blazer, 2013). Whilst some individuals diagnosed with MCI remain stable or return to cognitively normal over time, longitudinal population studies have found that the risk of developing dementia is between 11-33% over two years (Gauthier et al., 2006), with some studies finding an even higher progression rate of 41% after one year and 64% after two years (Geslani et al., 2005). Due to this, it is considered to be a risk state for dementia and the identification of it could be valuable for secondary prevention measures (R. Petersen & Negash, 2008).

Diagnostic criteria for MCI has wavered between whether there should be a splitting approach, with assorted categories of the disorder, or to consider it as one diagnosis. Currently, there is a difference found between amnestic and non-amnestic MCI as there is potential for these subtypes to have differing prognoses for progression to dementia, the type of dementia they may progress to, and their effect on lifespan (Gauthier et al., 2006). The operational definition for amnestic MCI has minor differences in entry level for memory impairment, specifically for the test on delayed recall and cut-off scores (R. C. Petersen et al., 1999). There are additional subtypes within this, where the clinician determines amnestic or non-amnestic MCI followed by whether it is single or multiple domain. A diagnosis of amnestic MCI-single domain is characterised by the impairment only affecting one memory domain, whereas amnestic MCI-multiple domain assumed impairments in the memory domain plus at least one other cognitive domain (R. Petersen & Negash, 2008). Non-

amnestic MCI-single domain is diagnosed when there is impairment in one domain that is not memory, and non-amnestic MCI-multiple domain pertains to impairments in multiple non-memory domains (R. Petersen & Negash, 2008). The predicted outcome of these MCI subtypes can be determined using the presumed etiology, which is typically done based on the patient history and laboratory testing (R. Petersen & Negash, 2008). Typically, amnestic MCI, regardless of the domain subtype, will progress to AD, whereas non-amnestic MCI has a higher likelihood of progressing to non-AD dementia, such as Lewy bodies or frontotemporal dementia (R. Petersen & Negash, 2008).

The ability to predict which individuals with MCI will progress to dementia is a major area of research and interest within the field. With the increasing elderly population, recognising the risks or indicators of progression is imperative for identifying not only the potential preventative measures but also the optimal time for implementing them. The emergence of amnestic MCI in particular has increased awareness that memory complaints within the elderly population should be assessed in a more systematic way, especially when these memory complaints are accompanied by more subtle cognitive performance difficulties (Gauthier et al., 2006).

Societal Impact

There is a common statement "When you meet a person with dementia, you have only met one person with dementia", which highlights that whilst there are some universal elements of dementia there is wide versatility in how people living with dementia experience it. This can depend on the disease risk, environment, preferences, life and social circumstances and the level of support or resources the individual has access to (Aranda et al., 2021). This variability in experiences has potentially made treatment efficacy, dissemination, and implementation difficult to determine.

Major neurocognitive disorders, such as dementia, have monumental consequences for not only the individual, but for the family, the healthcare system, and the economy. In the United States in 2010, Alzheimer's disease was the sixth leading cause of death (Murphy et al., 2013). Additionally, it is the leading cause of skilled nursing facility admissions, hospital admissions, and home health care (Hugo & Ganguli, 2014). The costs of healthcare and the informal costs seen with unpaid caregiving from family members or friends for individuals with dementia are high. In the United Stated in 2020, the combined caregiving and medical costs for people with Alzheimer's disease was estimated to exceed $500 billion, and they are only expected to grow with the ageing population, the projected costs for 2050 rising to $1.6 trillion (Aranda et al., 2021). In Aotearoa, the burden of dementia in 2020 was $6.2 billion, which is an increase of 24% since 2016 due to an increase in dementia prevalence and the cost in caring for an individual with dementia per year (Ma'u et al., 2021). Of these costs, $274 million of it can be attributed to healthcare costs, such as hospital admissions, and $1.39 billion can be attributed to social care costs, which includes aged residential care or community support services (Ma'u et al., 2021). These costs are likely to be unsustainable for the healthcare system if the numbers of people with dementia rise the way they are expected to. Insurance typically does not cover full-time care, therefore even among those who receive paid care 50% or more of the total care hours are performed by unpaid family members (Aranda et al., 2021). Caring for a person with dementia is associated with poorer mental health, with a higher prevalence of depression (Schulz & Martire, 2004). There is also some indication of effects on physical health with lower immune system functioning, and higher blood pressure, inflammation and cortisol levels (Allen et al., 2017; Fonareva & Oken, 2014; D. L. Roth et al., 2019).

These impacts are substantial, but they are also disproportionate. Racial and ethnic minorities, as well as persons with lower socioeconomic statuses, rural populations, and gender and sexual minorities, experience greater challenges receiving and gaining access to healthcare, with these disparities only growing more extreme with an increasingly more diverse and stratified older adult population (Aranda et al., 2021). Consequently, there is a higher likelihood that families from these populations will be caring for a relative with dementia with less external assistance (Aranda et al., 2021). There are mixed findings regarding whether caregivers from minority groups experience poorer health outcomes, with Chen et al. (2020) stating that White, Black and Hispanic spousal caregivers are equally likely to have negative health effects. However, caregivers from minority communities are more likely to have poorer health when commencing the caregiving role (Chen et al., 2020). Another consideration is the onset of dementia. In Aotearoa there is a greater proportion of young onset dementia (dementia being diagnosed before age 65) in Pacific (18.0%), Māori (19.0%) and Asian (16.8%) populations compared to Europeans (8.0%; Ma'u et al., 2021). This results in a greater impact on financial income for families within these communities. Māori, Pacific and Asian people are disproportionately impacted due to a higher prevalence of dementia, and less utilisation of social care which leads to a higher cost of unpaid care performed by families and whānau (Ma'u et al., 2021). Therefore, while the total economic cost per person is similar across ethnicities in Aotearoa, ethnic minorities actually bear a greater economic disadvantage and increased familial care than NZ Europeans.

Dementia increases the burden on individuals, families, communities, healthcare systems, government and society at large an unsustainable amount. These effects are disproportionate, significant and ultimately lead to poorer health outcomes not only for the person with dementia but for the family members and workers caring for them. If the

prevalence of dementia continues to increase the impact on society will not be able to be supported in the future.

Alzheimer's Disease

Alzheimer's disease (AD) is the most common neurodegenerative disease and is characterized by a progressive loss of synapses and neurons, an accumulation of amyloid plaques and neurofibrillary tangles, and prominent cognitive deficits. It is diagnosed later in life, with most receiving the diagnosis around 80 years of age, but early onset forms of the disease can be diagnosed as early as 50 years of age (Braak & Tredici, 2014). The burden of AD is recognised as one of the most pressing, and there is an urgent need for healthcare to find solutions for this disease. Due to this, understanding how this disease functions is necessary for understanding how to inhibit the cognitive degeneration seen with dementia. It has been described as a progressive and insidious neurodegenerative disorder of the human central nervous system, and is characterised by a subtle decline In memory functions when the individual is still in a clear state of consciousness (Braak & Tredici, 2014). Currently, only a provisional diagnosis of AD can be made until a post-mortem confirmation of the disease can be carried out (Braak & Tredici, 2014). Due to this, a large amount of research has been dedicated to identifying biomarkers in-vivo.

Post-Mortem Neuropathology

The post-mortem confirmation of AD is aided by the analysis of aggregates of abnormal proteins within the brain that are hallmarks of the disease, such as amyloid-beta (Aβ) and misfolded tau. Once the pathological process of AD has begun it is not known to spontaneously regress, and clinical symptoms associated with AD do not emerge until the later stages of this pathological process (Braak & Tredici, 2014). Due to this, post-mortem neuropathology is essential for understanding what stages of the disease occur and when,

allowing researchers to identify the pre-symptomatic phase and at what point interventions could be implemented to delay the onset of clinical symptoms.

As Aβ is unique to AD it is often considered to be preeminent. It is formed through the abnormal metabolic processing of the amyloid precursor protein, where under certain pathological conditions within vulnerable nerve cells the process can become unbalanced and cause excess Aβ to be released into the individual's system (Braak & Tredici, 2014). The distribution of Aβ throughout the brain follows five distinct phases, which were coined by Braak and Tredici (2015) by analysing post-mortem neuropathology in 2366 individuals. These phases follow a distinct, hierarchical sequence, with deposition spreading in an anterograde direction into regions that receive neuronal input from brain regions that have already been affected, beginning in the neocortex and spreading to the cerebellum and brainstem (Thal et al., 2002). Progression of Aβ begins between the ages of 60 – 80 and continues as the individual ages, with very few individuals reaching the final two stages (Braak & Tredici, 2014; Thal et al., 2002).

Tau tangles, otherwise known as misfolded tau, are another hallmark of AD neuropathology and can be identified within the brain at earlier stages than Aβ. The non-aggregated version of tau is present within healthy nerve cells and will promote the self-assembly and stabilisation of axonal microtubules, but abnormal tau will form when it is left unprotected and aggregates into an abnormal fibrous assembly (Braak & Tredici, 2014). Aggregated tau is also present in other neurological diseases, such as corticobasal degeneration or progressive supranuclear palsy, however it more commonly appears in AD and is present in different brain regions for alternative diseases when compared to AD (Braak & Tredici, 2014). Like Aβ, tau also follows distinct stages of progression throughout the brain. Tau is characterised by five initial stages where immature tau can be identified

using AT8 immunohistochemistry in the brainstem, and then six stages where mature phosphorylated tau can be identified using the Gallyas-Braak silver staining method progressing throughout the regions of the brain in the opposite direction to Aβ, ending in the neocortex (Braak & Tredici, 2014). It is important to note that tau can begin progressing through the brain from as early as age 10, even though clinical symptoms of dementia do not typically begin until around 80 years of age (Braak & Tredici, 2014). This leaves a significant presymptomatic period of time that could be used for slowing or stopping the eventual cognitive decline that comes with dementia.

In-Vivo Biomarkers

The current barrier within the field of AD is that there are several distinctive meanings of the disease, and each meaning goes in tandem with a different model that will hero a different aspect of AD. Initially, diagnoses were purely based on neurologic examination, where AD was regarded as a clinicopathologic entity where a minimum of two cognitive domains were impaired and there needed to be significant impairment seen in the individual's daily life (Knopman et al., 2019). The definition of AD that came after this was that it was a neuropathologic constellation with multiple pathologies present, therefore the combination of some level of neuritic plaques and pathology needed to be present to make a diagnosis (Knopman et al., 2019). However, with the introduction of Aβ PET imaging, the shift was made to where the literature currently rests, defining AD by its biomarkers. The definition now is that AD is a combination of Aβ and tau neuropathology, with greater pathology leading to clinical symptoms (Knopman et al., 2019). There is still some controversy as there is a likelihood that AD is due to a combination of different causal factors, not just biomarkers, but this has created a great shift away from the phenotype

description towards a better understanding of neuropathology features that can be seen in-vivo.

The Current In-Vivo Model. This model currently states that there is amyloidopathy followed by tauopathy, following a cascade model where Aβ exacerbates the production of tau, and that any tau present before the presence of Aβ is due to aging or other non-AD related diseases (Jack et al., 2013). Evidence for this is seen in the general dynamic modelling approach by Jack et al. (2013). This model focuses on the most established biomarkers of AD and divides them into measures of Aβ and measures of neurodegeneration, showing that increased concentrations of total tau and phosphorylated tau, alongside atrophy on the MRI, are measures of neurodegeneration. Aβ deposition is measured using PET imaging and cerebrospinal fluid (CSF; Jack et al., 2013). It has been found that CSF Aβ is the most abnormal at any time during the disease, and that it is fully abnormal around 5-10 years before the clinical diagnosis is made (Buchhave et al., 2012). CSF tau becomes progressively more abnormal overtime (Braak & Tredici, 2014; Buchhave et al., 2012; Jack et al., 2013). Considering post-mortem evidence of tau preceding the production of Aβ, this model has been adapted to look at tau and Aβ as independent processes, with subcortical tauopathy being the first AD pathophysiological process to arise, but acceleration of this tauopathy does not occur until Aβ biomarkers are seen as abnormal (Jack et al., 2013). This model has been created due to the need for a way to identify AD before the loss of brain matter is too large to make a difference. This model can also be used to better label individuals at risk for MCI and subsequent progression to dementia.

The AT(N) Model. The shift away from clinically driven dementia diagnoses to an underlying neuropathological basis has additionally increased research on a new biologically-informed framework labelled the AT(N) model (Jack Jr. et al., 2018). This model

recognises three general groups: Aβ plaques, phosphorylated and cortical tau, and neurodegeneration or neural injury. There are differing categories and biomarker profiles for individuals based on their levels of each of these biomarkers, with syndromal categorical cognitive staging and numeric clinical staging that will link the cognitive stage with the pathological stage (Jack Jr. et al., 2018). This leads to three diagnoses: cognitively unimpaired, MCI and dementia, with dementia then being divided into mild, moderate and severe. This model treats cognitive impairment, not as the definition of the disease, but rather as a symptom of it. This should enhance efforts to understand the biology of AD, and it allows for an in-vivo framework of what stage of cognitive decline an individual resides at.

These models can provide insight into what neuropathological processes are happening at what stages of AD, and could become imperative for identifying times at which interventions can occur and what parts of the brain or areas of functioning they could be targeting. Currently, the issue lies in the inability for modern neuroimaging to detect early stages of tau and Aβ. Until such time where these biomarkers can be detected before clinical symptoms arise, this information is unable to inform us on how to best combat progression of AD.

However, the understanding that we had of Alzheimer's etiology has undergone some changes in recent years after new research has identified another potential dementia-related disease that could have been misdiagnosed as Alzheimer's disease in the past. A study conducted by Nelson et al. (2019) indicated that transactive response DNA binding protein of 43kDa (TDP-43) proteinopathy in limbic brain structures mimics the same substantial cognitive impairment that is seen within Alzheimer's disease. There is currently no consensus-based nomenclature for this finding even though evidence from a number of different sources point to the public health impact of this, but it has given rise to the new

terminology limbic-predominant age-related TDP-43 encephalopathy (LATE; Nelson et al., 2019). LATE is commonly found in individuals over the age of 80 and may account for 20-50% of all dementia-related cognitive impairment seen within this age range (Nelson et al., 2019). It progresses significantly slower than AD, but similarly to AD it is detectable at post-mortem. Post-mortem neuropathology for LATE focuses on the misfolding of TDP-43 in limbic regions, and often occurs in tandem with AD or mimics the effects of AD (Nelson et al., 2019). As this is a relatively new addition to the dementia field, more research is needed so that we can better understand the etiology behind LATE and how much of the dementia population it may be affecting. It would also be important to know what areas of cognition may be differently affected by LATE so that interventions can be modified accordingly.

Prevention and Intervention

Research into how to best intervene or prevent progression to dementia has been the primary focus of dementia research. The search for a cure to the neurodegeneration and atrophy associated with dementia has encouraged a large amount of research into pharmaceutical options that target Aβ or tau. The original theory was that Aβ is more preeminent for AD, as it is unique to the disease, however drug treatments focused on reducing Aβ plaques have overall been unsuccessful (Schneider, 2020). Now, the research is beginning to consider combatting tau through targeted drug treatments, or combining drug treatments for both Aβ and tau into a cocktail that attacks all biomarkers associated with AD. This research is still in its preliminary stages, and whilst some seem promising for slowing the progression of the disease, there is little evidence of a curative option or that there will be available treatments in the near future. It is also important to take into account that drug treatments are not widely accessible, with some classes of society finding it more difficult to gain access to healthcare or potential treatment options (Aranda et al., 2021; Chen et al.,

2020). Non-pharmacological and accessible treatments have therefore begun to gain ground in potential interventions for dementia, where research is focusing on easily modifiable everyday factors that can improve cognitive functioning and lower risk of progression to dementia.

Current Drug Interventions

Due to the differing opinions within the neuroscience community on the pre-eminence of Aβ or tau, the aspect of the disease in which to focus pharmacological treatments has been a contested point. Currently, the cascade hypothesis of Aβ is at the forefront of discussions, with money, journal publications, focus and treatment experiments focusing on slowing the spread of Aβ (Sevigny et al., 2016). This theory postulates that synaptic dysfunction and neurodegeneration is primarily caused by Aβ-related toxicity, and this is what characterizes the progression of AD (Sevigny et al., 2016).

It has been posited that the lack of success that biological therapies have had so far in combatting dementia is due to the inability of the antibodies to target the right area of the brain, or that drug studies have employed the wrong patient population (Sevigny et al., 2016). With the popularisation of the cascade theory, the drug aducanumab was developed to implement an antibody-based immunotherapeutic approach. Aducanumab is a Aβ directed monoclonal antibody that will selectively react with deposits of Aβ, with preclinical studies showing it was capable of crossing the blood-brain barrier within mice and effectively reduce deposits (Sevigny et al., 2016). A double-blind, placebo-controlled study conducted by Sevigny et al. (2016) found that this drug was effective within humans, with a decrease in Aβ deposits in individuals with AD in a time- and dose-dependent manner. This study also indicated there were changes in cognitive decline, with a stabilization in Clinical Dementia Rating – Sum of Boxes (CDR-SD) and Mini Mental State Examination (MMSE)

scores. This led to hope within the community that it may be possible for drug interventions to slow the decline of dementia, however there was significant commentary around the legitimacy of the study. The positive results found within the study were likely due to greater worsening in the placebo group rather than exposure to a greater dose of aducanumab, and the producers of the drug, Biogen, were found to have p-hacked their results to skew towards a more significant difference between groups (Schneider, 2020).

It is more likely that the lack of progression that has been seen in finding a viable drug treatment is due to the fixation that the cascade hypothesis places on Aβ. It is contestable whether AD can be treated as a single-molecule disease when tau in particular plays such a vital role, and there are other ways that the neurodegeneration from dementia can be targeted (Sandusky-Beltran & Sigurdsson, 2020; Schneider, 2020). After the primary researchers involved in finding a drug treatment recognised this issue, there was a change in focus to tau-targeted therapies or multidrug cocktails that target both Aβ and tau. This change in focus has led to nine antibodies and two tau vaccines in clinical trials with several more in their late-stage pre-clinical development (Sandusky-Beltran & Sigurdsson, 2020). The successful completion of Phase 1 tau trials has shown some promising results, as well as potentially providing earlier intervention due to a shift in implementation from late-stage disease to early AD or MCI (Sandusky-Beltran & Sigurdsson, 2020). AD has additionally proved to not be susceptible to a single-target therapy (Lahiri, 2019). Treatments may be more effective if anti-Aβ and anti-tau drugs were used in combination with symptomatic drugs, and these drug cocktails could be modified and refined as our knowledge of dementia, and AD in particular, increases (Lahiri, 2019; McDade et al., 2021).

Preventative Prospects

Even though researchers have invested a lot of time and money into intervention methods, particularly drug treatments, biological therapies show no immediate promise. The focus on biomarkers, and the aforementioned difficulties in identifying these biomarkers early, also alienates a large portion of time where preventative measures could be employed to slow or stop cognitive decline. With the added pressure of a growing elderly population, increasing emphasis has been placed on finding these preventative measures that can be implemented at any time in a person's life.

It is important to note the concepts of brain reserve and cognitive reserve when discussing this topic. Brain reserve refers to the phenomena that there are many brains that have been autopsied and shown to have Alzheimer-type pathology, but the individual did not exhibit any clinical symptoms during their life (Katzman et al., 1988). This opens up some interesting commentary around what other factors may be at play that prevent significant pathology from materialising into clinical symptoms. Those who did not show clinical symptomology but had evidence of Alzheimer-type pathology were seen to have larger brain mass and better preserved large neurons, as well as a lack of cerebrovascular disease (Ganguli, 2009; Snowdon et al., 1997). Cognitive reserve, however, refers to the effect that brain reserve can have alongside other factors that increase cognitive capacity, such as education, mental stimulation or intelligence (Stern, 2002). Whilst these two concepts may not delay the onset of pathology, what they may do is delay or prevent the onset of significant cognitive decline that is seen with dementia and MCI (Ganguli, 2009). Due to this, intervention prospects that influence brain or cognitive reserve are considered to be beneficial in delaying or halting the cognitive decline that is seen within neurodegenerative diseases such as dementia and MCI. It also shows that the neuropathology that underlies

Alzheimer's disease and other neurodegenerative disorders can occur without impacting clinical symptoms and the individuals capacity to function well in everyday life. This further extends the need to focus on interventions that enhance things like brain and cognitive reserve instead of focusing on interventions that target neuropathology.

A meta-analysis looking into preventative measures developed a 12 risk factor life-course model for dementia prevention, which suggests that 40% of worldwide dementia cases could be delayed or prevented (Livingston et al., 2020). The 12 modifiable risk factors are lower education level, hearing loss, traumatic brain injury, hypertension, excess consumption of alcohol, obesity, smoking, depression, social isolation, physical inactivity, air pollution and diabetes (Livingston et al., 2020). These risk factors were found to have varying effects depending on the point in the lifespan they appear. Factors such as obesity and hypertension have a significant impact in midlife, contributing to 3% of worldwide dementia cases, but factors such as social isolation or depression have a significant impact in later life leading to 8% of worldwide dementias (Livingston et al., 2020). How the modification these risk factors can help slow or prevent progression to dementia also differs. Those that have the most impact earlier in life, such as education level, will work to positively influence cognitive reserve and protect against the effects of neurodegeneration (Livingston et al., 2017). In contrast, factors that have a significant influence in mid- to late-life will help to reduce neuropathological damage as well as promote brain and cognitive reserve (Arida & Teixeira-Machado, 2021; Livingston et al., 2017).

The interplay between these 12 risk factors is also important to consider. Making a change with one of these areas can subsequently cause changes in other areas. For example, engaging in physical activity can not only aid the physical inactivity risk, but also help with hypertension, social isolation, obesity, depression and diabetes (Barnes et al., 2003;

Fratiglioni et al., 2004; Jenkins et al., 2002). Taking into account this interplay and interaction between risk factors, the best prevention outcomes tend to come from multifactorial preventions that will simultaneously target these 12 risk factors. The Finnish Geriatric Intervention Study (FINGER) employed this method, implementing a 2-year multidomain study to prevent cognitive decline and dementia (Ngandu et al., 2015). With a focus on nutrition, exercise, cognitive training and vascular/metabolic management there was small group-level improvement in overall cognitive performance (Ngandu et al., 2015). Even though the effects were small, it did point towards a significant impact on population incidence rates, as well as beneficial effects seen within the secondary cognitive domains of processing speed, executive functioning and memory (Ngandu et al., 2015). FINGER has been challenged by the wider scientific community for having self-selection bias and that the reduction in disease risk was too high to be indicative of what would be seen at the population level (Kivimäki et al., 2015; Lampit & Valenzuela, 2015). Due to this, the results are to be interpreted with greater caution, but it is still considered to be a methodically robust trial that provides a reference frame that is representative of the elderly population. It is more appropriately interpreted in a public health context, where large population effects will occur because of small individual changes.

Best Practice

Whilst drug treatments may still prove to be effective or valuable in treating dementia, there are a number of issues that make it difficult for drug treatments to ever have absolute success. Whilst biomarkers such as Aβ and tau can indicate there is a risk of progression to AD, there are some people who have these biomarkers alongside normal cognition and they never progress to clinically diagnosed dementia (Katzman et al., 1988). These issues also appear when diagnosing other neurodegenerative disorders, such as Lewy

body dementia, LATE or frontotemporal dementia (Braak & Tredici, 2014). The neuropathology for these diseases is complex. Neuropathological studies have also indicated there is a high prevalence of co-existent TDP-43, AD and cerebrovascular pathologic cases alongside Lewy pathology (Nelson et al., 2019; Toledo et al., 2012). Although having an accurate diagnosis is important for the patient and their family, and neuropathology contributes to this, there is no evidence to support pre-symptomatic diagnosis in everyday practice (Livingston et al., 2020). This further makes it difficult for drug treatments to be provided early.

These uncertainties mean that current best practice is to implement non-pharmacological interventions. Focusing on the 12 modifiable risk factors introduced by Livingston et al. (2020) allows for an individualised and cost-effective approach. Keeping cognitively, physically and socially active in mid- to late-life can help to influence triggering and reserve of neuropathological and clinical developments. Currently, there is little evidence around what factors within those 12 risk factors provide the best protection against cognitive impairment, but preliminary data indicates that sustained physical exercise in mid- to late-life might be one of the larger contributors to slowing or preventing cognitive decline (Livingston et al., 2020).

Physical Exercise

Physical inactivity is one of the 12 modifiable risk factors identified by Livingstone et al. (2020). The complex interaction between dementia risk and physical inactivity is evident across all stages of the lifespan, and the patterns change as you move through generation, sex, social class, age and more. Small positive effects are seen when an individual exercises in midlife and a long-term study found that 2.5 or more hours of exercise per week lowered dementia risk over 10 years (Sabia et al., 2017). However, an individual level meta-analysis

found that there was no difference in dementia risk measured 10-15 years before dementia incidence, which indicates that for physical activity to be an effective preventative measure it may need to be sustained and employed nearer to the time of risk to see any significant effects at the individual level (Kivimäki et al., 2019). This is potentially due to exercise decreasing diabetes, obesity and cardiovascular risk. Physical inactivity during later life has been seen to contribute to 2% of worldwide dementia cases, further emphasising the importance on exercise for elderly individuals (Livingston et al., 2020).

It is already known that exercise is essential in maintaining a healthy body, but it also has benefits for the cellular and vascular systems that sustain a healthy brain, as well as promotes cognitive reserve (Arida & Teixeira-Machado, 2021). This influence can in part be attributed to exercise protecting against the effects of stressful events, prevent or minimise neurological diseases, and induce positive psychological and physiological improvements (Arida & Teixeira-Machado, 2021). Exercise interventions employed to effect cognition can either be chronic or acute, with acute exercise being defined by a single session of exercise and chronic exercise consisting of a workout routine or accumulation of sessions that involved multiple sessions of exercise over a period of time.

The Protective Effect for an Unhealthy Brain

Exercise may protect against neurodegenerative diseases by preserving hippocampal volume (Erickson et al., 2009, 2011) or neural plasticity (Cotman & Berchtold, 2002), or by lowering cardiovascular risk (Aarsland et al., 2010). There is also evidence of higher total brain volume and grey matter for those that are physically active (Rovio et al., 2010).

Chronic exercise can maintain the integrity of the blood-brain-barrier (BBB), and work to protect the neurovascular unit (Vecchio et al., 2018). The BBB is a membrane at the interface between the circulatory system and the brain parenchyma and it works to

selectively limit the passage of molecules between the extracellular fluid in the brain and circulating blood (Vecchio et al., 2018). This may be done by modulating the expression of TJ-proteins, which are critical to forming the protective layer of the BBB. By upregulating these TJ-associated proteins the BBB is strengthened, consequently providing the brain more protection from circulating diseases or toxicity (Vecchio et al., 2018). Engagement in regular physical activity can maintain the BBB and support the neurovascular unit in this way.

Mice studies have shown that exercise can additionally promote glymphatic clearance in older individuals. This system delivers glucose and signalling molecules to the cerebrospinal fluid, and it has an important role in the clearance of waste products and compounds in the interstitial fluid, such as Aβ and tau (Vecchio et al., 2018). Therefore, dysfunction in this system has significant implications in AD and other neurodegenerative disorders the involve these proteins. Aerobic exercise, specifically six weeks of voluntary running, was shown to accelerate the efficiency of glymphatic clearance, suggesting that increased physical activity can have neuroprotective benefits (He et al., 2017). Mouse models have also indicated that regular, long-term aerobic activity can facilitate the clearance and degradation of hippocampal and cortical Aβ deposits (Adlard et al., 2005; Maliszewska-Cyna et al., 2016). Although this research has not been replicated in human studies, it suggests that physical exercise can be used as a strategy against AD.

There are a number of theories for how exercise can induce brain plasticity and allow for changes in cognition. Plasticity can be broadly defined as the ability of the nervous system to adapt to changes in the external environment, as well as its integrity in order to maintain or recover and optimize its functions (Farhani et al., 2022; Foster et al., 2011; Zhao et al., 2020). This includes the potential for synaptic connections to be changed, the elongation of axons, remodeling to allow for the establishment of new synapses and operations, and the growth

of collateral ramifications, all of which could be adaptive or maladaptive to the situation that triggered the change (Farhani et al., 2022; Foster et al., 2011). Exercise has been suggested to induce brain plasticity to improve network performance and overall neurological function, and potentially help neural networks spared, or less affected by a disease, to compensate for deteriorated circuits (Foster et al., 2011). This suggests that exercise may stop, slow down or even reverse the deterioration seen in those with cognitive impairments. Currently, there are three hypotheses explaining how exercise may affect executive control and induce brain plasticity: exercise causes a reduction in cardiovascular risk factors and increases cardiovascular fitness (Barnes et al., 2003; Etnier et al., 2006; Tomoto et al., 2021); exercise increases oxygen saturation and angiogenesis in brain regions associated with task performance (Foster et al., 2011; Kovacevic et al., 2020; Lautenschlager et al., 2008; Moriarty et al., 2019); and exercise upregulates neurotropins that support neuronal survival and differentiation in the developing brain, and dendritic branching and synaptic machinery in the adult brain (Kirk-Sanchez & McGough, 2014; Moriarty et al., 2019; Ploughman, 2008; Vaynman et al., 2004).

Cardiovascular Fitness Hypothesis

The cardiovascular fitness hypothesis suggests that aerobic fitness is a physiological mediator that can explain the various mental health benefits of physical activity. Gains in cerebrovascular fitness are thought to be associated with underlying changes in physiological mechanisms such as cerebral blood flow, brain-derived neurotropic factor, and cerebral structure – all of which have been shown to be independently associated with cognitive performance (Etnier et al., 2006).

There are several potential mechanisms by which cardiovascular fitness could affect cognitive function (Barnes et al., 2003): it could reduce the risk of medical conditions that

are associated with poor cognitive function, such as cardiovascular disease, hypertension, cerebrovascular disease and diabetes; it could be positively associated with cerebral blood flow, and reductions in cerebral blood flow has been linked to poor cognitive function in normal and impaired older adults; and it may stimulate nerve cell growth and provide a buffer to protect against neurodegeneration (Barnes et al., 2003). One such example of this is the suggestion that exercise-induced alterations in cerebral vasomotor reactivity (CVMR) is the reason for enhanced cognitive function with exercise. Cerebrovascular dysfunction is one of the potential underlying mechanisms of AD, with altered CVMR seen in patients with AD or MCI and found to be associated with cognitive impairment (Tomoto et al., 2021). A study conducted by Tomoto et al. (2021) found that one year of moderate to high-intensity exercise training increased hypocapnic CVMR and decreased hypercapnic CVMR, as well as improved cardiovascular fitness overall. These changes were correlated with improved memory and executive function. It has been speculated that the exercise-induced reduction in hypercapnic CVMR may reflect reduced cerebral vasoconstriction or cerebrovascular tone which may lead to improvement in cognitive performance and brain perfusion (Tomoto et al., 2021).

Due to this, it is possible that cardiovascular fitness can mediate the relationship between exercise and cognitive performance, however it is not a particularly sensitive measure of the physiological changes that occur in response to chronic physical activity. It may be that a more consistent relationship could be seen in studies that assess mechanisms with closer ties to cognitive performance, or it may be that cardiovascular fitness is the first event in a cascading series of events that will affect cognitive performance (Etnier et al., 2006). Subsequently, changes in cardiovascular fitness may be needed for the changes in cognitive performance to occur, but a measure of cardiovascular fitness by itself may not be

indicative of the cognitive benefits obtained through participating in exercise (Etnier et al., 2006).

Oxygen Saturation and Angiogenesis Hypothesis

It is possible that exercise increases flow of oxygenated blood to not only motor areas of the brain, but also areas involved in executive functioning, subsequently enhancing cognitive function. During exercise there is an increase in cerebral blood flow and oxygenation, which possibly promotes the distribution of nutrients throughout the brain and increases resources being sent to brain regions needed for executive function, such as the dorsal lateral prefrontal cortex (DLPFC) which is responsible for cognitive control and goal-directed behavior (Moriarty et al., 2019). This increase in oxygenation to the DLPFC has been linked with increased concentration or mental focus (Lautenschlager et al., 2008; Moriarty et al., 2019).

Research groups have reported elevated left DLPFC and medial PFC oxygenation during cognitive testing after moderate-intensity aerobic exercise, and a short duration of high-intensity exercise has been shown to promote cortical activation in the left DLPFC (Moriarty et al., 2019). Physical activity is associated with increased blood perfusion of the brain regions that modulate attention (Lautenschlager et al., 2008), and improvements in cardiorespiratory fitness is correlated with improvements in memory indicated that adaptions in the utilization of oxygen during exercise may have the ability to influence brain function in ageing (Kovacevic et al., 2020). Aging is associated with impaired spatial memory and a reduced resting cerebral blood flow, therefore increased blood flow to the hippocampus in particular is associated with greater memory performance in older adults (Foster et al., 2011). It is possible that the increase in cerebral blood flow associated with exercise increases the oxygenation and resources in brain regions responsible for executive

function, promoting brain health, cognitive functioning, and subsequently promoting cognitive benefits for those with cognitive impairments.

Upregulation of Neurotropins Hypothesis

Another possible explanation of exercise-induced rapid enhancement in cognitive performance is through the upregulation of neurotropins such as brain-derived neurotropic factor (BDNF), which is a neural growth factor that has been associated with memory enhancing benefits (Moriarty et al., 2019). BDNF is also known to play a prominent role in the survival, growth, and maintenance of neurons during development, and the ability to modulate synaptic-plasticity in the adult brain (Vaynman et al., 2004). BDNF has also been associated with regulating synaptogenesis in arborizing axon terminals, axonal and dendritic branching and remodeling, functional maturation of excitatory and inhibitory synapses and the efficacy of synaptic transmission (Vaynman et al., 2004). A study by Foster et al. (2011) found that exercise increases BDNF levels in the hippocampus in both young and aged brains. Aerobic exercise in particular has a growing body of evidence that it increases BDNF levels in older adults, as well as improving the plasticity of brain networks, spatial memory and increasing the size of the hippocampus (Foster et al., 2011).

It was seen that the greatest effects of exercise on BDNF occur in highly transformable areas that are responsive to environmental stimuli (Foster et al., 2011). Given the importance of BDNF in learning and memory, as well as synaptic plasticity, it has been proposed that the exercise-induced increases in BDNF may underlie the ability of exercise to enhance cognitive function. This theory also allows for cognitive benefits from exercise to be long-term and show enhanced cognitive performance over an extended period of time. Promotion of growth and survival of neurons in those with cognitive impairment could slow

the progression from MCI to dementia or the decline in function seen within AD and other dementia-related diseases.

Social Impacts

The aforementioned information speaks to the neurobiological benefit that exercise can have on cognition, but perhaps there are additional social impacts that need to be considered. An active and socially integrated lifestyle seems to protect against dementia in later life, and three lifestyle components (mental, physical and social) seem to have common pathways and act at the same time (Fratiglioni et al., 2004). There is also great potential for physical exercise to influence psychosocial aspects that benefit cognition.

There is some evidence that maintaining a socially integrated lifestyle can have to protect both mental health and cognition in later life. Two psychosocial aspects that are considered to be key for this, particularly in middle to older age, are social connectedness and social engagement (Fratiglioni et al., 2004). Social connectedness refers to the social ties or networks that one has (Fratiglioni et al., 2004). This appears in the notion of social capital for older people that was proposed by Gray (2009), which refers to the cluster of social contacts that provides people with support. Social support is considered to be an outcome of this social capital, and these networks can be considered an individual or a collective resource (Gray, 2009). The complexity of this aspect is considered difficult to capture, with previous literature identifying several dimensions, such as size, frequency, reciprocity or proximity, as imperative to consider when researching social networks (Bowling, 1994; Victor et al., 2000; Zunzunegui et al., 2003). On the other hand, social engagement is defined as being involved and/or being engaged in both informal and formal social activities (Litwin, 2010). This is most commonly researched through the lens of type and frequency (Kelly et al., 2017; H.-X. Wang et al., 2002; Zunzunegui et al., 2003) There is a clear interrelationship

between these two concepts, considering it logically follows that stronger social connectedness will lead to greater social engagement and vice versa.

These are elements that have been shown to influence cognition in several ways. Higher levels of both social connectedness and social engagement are independently associated with higher cognition scores (Paiva et al., 2023). There is strong evidence that shows maintaining meaningful social relationships can play a protective role against cognitive decline (Fratiglioni et al., 2004; Schwartz & Litwin, 2019), as well as it acting to build cognitive reserve (Kelly et al., 2017; Paiva et al., 2023). A loss of these social ties can remove this protective effect and lead to a decline in cognition (Fratiglioni et al., 2004; Kelly et al., 2017). It is also possible that older adults who suffer from cognitive decline are more likely to remove these social ties instead of the other way around with cognitive decline removing social ties (Schwartz & Litwin, 2019). This shows that both processes may be involved (Kelly et al., 2017; Schwartz & Litwin, 2019). Participation in social activities may also promote self-efficacy and a competent self-concept that has been linked to a variety of positive health outcomes (H.-X. Wang et al., 2002). This is particularly true for middle-aged and older adults, where a self-concept of usefulness or competence is a protective factor for several health outcomes alongside cognition (Paiva et al., 2023).

This creates a connection with physical activity, as the type of activity that one engages in can open up an opportunity for strengthening this social engagement and connectedness. Physical inactivity is an independent risk factor for dementia, but it also has a beneficial effect on social isolation, another independent risk factor for dementia (Livingston et al., 2017). Social interaction and engagement is typically fostered when older adults participate in exercise programs, and it may buffer at-risk populations from declining health (Jenkins et al., 2002). It has also been shown in a population of older adults over 50

years of age that an increase in physical activity engagement leads to a decrease in loneliness, and social connectedness can further strengthen this association (Gyasi et al., 2021). Exercise also has the added benefit of improving physical health, such as cardiovascular health or hypertension, therefore it has an opportunity to impact cognition and dementia risk in a number of different ways. This is yet another example of how physical exercise can have cognitive benefits for older adults with cognitive impairment.

Psychological Impacts

In addition to these social benefits, there are psychological benefits to exercise. As mentioned earlier, depression is one of the risk factors for dementia, leading to 4% of worldwide dementia cases (Livingston et al., 2017). This relationship is complex, but evidence suggests that a history of depression nearly doubles the risk of developing dementia (Jorm, 2001) and a neuropathological study has shown that there is increased hippocampal Aβ plaque and tau tangle formations in dementia patients that have had a lifetime history of depression (Rapp et al., 2006). This suggests a significant interaction between depression and Alzheimer's neuropathology, and it is possibly to due hypercortisolemia linked to depression (Ganguli, 2009). The hypercortisolemia theory suggests that depressive illness, especially if it has not been treated effectively or continues for an extended periods of time, may result in sustained levels of serum cortisol, leading to hippocampal damage and reducing the ability of the hippocampus to resist or compensate for the degenerative damage seen with Alzheimer's disease (Checkley, 1996; Ganguli, 2009). This same theory can be applied to stress, as stress also raises cortisol levels (Checkley, 1996).

Exercise can lead to improvements in mood and the ability to cope with stress, as well as improve many psychiatric problems such as depression, stress disorders and anxiety

(Plante et al., 2007). Whilst part of this may be due to the social interaction that comes with exercising, there is also evidence that exercise can independently improve depressive symptoms, even for those with chronic illnesses or treatment-resistant major depressive disorder (Herring et al., 2012; Mota-Pereira et al., 2011; Stathopoulou et al., 2006). Physical exercise has been found to reduce the symptoms of depressive as effectively as cognitive-behavioural therapy (CBT) or pharmacological interventions (Blumenthal et al., 2020; Carek et al., 2011; Gill et al., 2010). Exercise has also been shown to have a stress-buffering effect, thought to derive from a reduced sensitivity to stress through both autonomic and hypothalamic pathways (Popovic et al., 2022; Tsatsoulis & Fountoulakis, 2006).

This previous research shows that exercise can indirectly effect cognition and the risk of progression to dementia through psychological pathways. A reduction in depression and stress can subsequently lead to an improvement in cognitive health, and it may be one of the reasons why exercise has been shown to have a significant impact on cognition for older adults with cognitive impairment.

Exercise Intensity

The intensity of the exercise refers to either the amount of oxygen consumed or the energy expended per minute whilst performing the activity (Medicine, 2014). The American College of Sports Medicine (2014) recommends that the heart rate reserve (%HRR) is the most accurate way of establishing a target heart rate, as %HRR has been shown to accurately reflect the same percentages of oxygen uptake reserve (VO_2R) whilst also considering the resting heart rate of the individual. High-intensity exercise has been defined as 60-89 %HRR and moderate-intensity is defined as 40-59 %HRR, and low-intensity is defined as 20-39 %HRR (Medicine, 2014). The question about what level of intensity leads to improved cognitive benefits for those with cognitive impairment is yet to be answered. Low, moderate

and high-intensity exercise have all reportedly improved performance in various cognitive constructs (Moriarty et al., 2019), however there are mixed results on what intensity elicits better results.

High-Intensity Exercise

It is possible that there is a dose-dependent relationship between exercise intensity and cognitive performance depending on the particular demands of the cognitive task (Y.-K. Chang & Etnier, 2009). This has been suggested due to the finding that there is a significant linear relationship between exercise intensity and the cognitive area of processing speed, but there is a significant quadratic relationship between intensity and higher-order cognitive measures (Y.-K. Chang & Etnier, 2009). This is consistent with results from other studies that have found the relationship between exercise intensity and cognitive performance is moderated by the type of cognitive task that is being measured (Arent & Landers, 2003; Humphreys & Revelle, 1984). However, these results have been from acute exercise interventions, therefore it is unclear if this same pattern would be found in chronic exercise interventions.

Other studies have found results that indicate higher intensity exercise has better cognitive benefits. High-interference memory is a subtype of memory function that has been found to be particularly vulnerable to age-related changes, with a decline in this area compromising decision-making and social interactions (Kovacevic et al., 2020). It was found that higher-intensity exercise improved memory in sedentary older adults over a 12-week intervention, with improvements in cardiorespiratory fitness correlating with this improvement in memory suggesting that the utilization of oxygen during high-intensity exercise may influence brain functioning (Kovacevic et al., 2020). This was seen particularly in high-interference memory, and a significant correlation between cardiorespiratory fitness

and improvements in memory were demonstrated, indicating that adaptations in the utilization of oxygen whilst exercising may influence brain function in ageing (Kovacevic et al., 2020). There was no significant improvement in memory for those who followed moderate-intensity training during the 12-week intervention. High-intensity exercise was also seen to promote cognition for those with MCI in a study conducted by Broadhouse et al. (2020). Additionally, it was found that over a six month intervention period, subfields of the brain that are vulnerable to AD degeneration were protected for at least 12-months post-intervention (K. M. Broadhouse et al., 2020). This literature suggests that high-intensity exercise has a significant effect on cognition for those that are cognitively impaired, however due to the mixed findings it is difficult to determine whether high-intensity or moderate-intensity exercise has greater cognitive benefits as an intervention.

More frequent high-intensity exercise has been found to be associated with better active coping in coping with challenging situations, and it is also associated with greater personal growth and self-perceived autonomy (Nakagawa et al., 2016). This suggests that high-intensity exercise may show increased mental health benefits that can subsequently effect cognition. High-intensity exercise was additionally seen to show fewer symptoms of anxiety (Nakagawa et al., 2016). Aerobic exercise can enhance memory in older adults, with high-intensity exercise leading to greater memory performance when compared with moderate-intensity exercise or sedentary individuals.

Low- to Moderate-Intensity Exercise

Other studies have found contrasting information, with some suggesting that low- to moderate-intensity exercise is more beneficial for cognition. Brain processes that involve executive functions and memory are seen to react differently to increasing exercise intensity and it is likely this is due to differing sensitivities to physiological stress (Kovacevic et al.,

2020). Moderate-intensity exercise may have a more positive effect on executive functioning areas of the brain. Activation of the prefrontal cortex has been seen to follow an inverted U-shape curve where moderate-intensity exercise will increase glutamatergic transmission and improve executive functioning whereas high-intensity exercise will interfere with this process (Hains & Arnsten, 2008; Yuen et al., 2009).

One of the prominent theories behind why low- to moderate-intensity exercise may be more beneficial for cognition is the transient hypofrontality theory. This theory posits that when exercise at a higher intensity is performed, the neural activation and oxygenation is predominantly focused in motor areas of the brain in order to maintain the intense physical movement that is being undertaken (Jung et al., 2022). This may result in a temporary deactivation of structures that are involved in higher-order processing and executive functioning areas – areas that deteriorate in diseases such as dementia and MCI (Jung et al., 2022). If this theory is combined with the oxygen saturation and angiogenesis hypothesis, high-intensity exercise is not able to reap any of the cognitive benefits of more oxygenated blood flow and nutrients to executive functioning areas of the brain that need strengthening in order to combat the cognitive impairment seen in neurocognitive disorders (Foster et al., 2011; Kovacevic et al., 2020; Moriarty et al., 2019). This has been demonstrated in a study by Wang et al. (2013), where high-intensity exercise resulted in decrements in cognitive performance measures that relied on executive functioning. This study was conducted on acute exercise interventions; however, it is likely that this would occur whenever an individual engages in high-intensity exercise therefore it is possible the same effect would be seen in chronic interventions. In fact, the effect may be more pronounced when considering a longer time period due to executive functioning areas receiving less oxygenated blood and nutrients as the exercise frequency increases. Low- to

moderate-intensity exercise likely does not induce transient hypofrontality, therefore both executive functioning areas and motor areas are provided with increased oxygenation and nutrients and there may be long-term cognitive benefits from this (Jung et al., 2022).

This Meta-Analysis

The current literature has identified that exercise is beneficial for maintaining cognition, and it can have a preventative as well as an intervention effect, slowing the cognitive decline for those with dementia or MCI. However, there is mixed information about what intensity of exercise elicits better cognitive benefits. Clinical trials have been unable to ascertain which intensity of exercise is more effective for slowing cognitive decline, with only a small number comparing moderate-intensity to high-intensity and these studies showing contrasting results. There is evidence for different intensities having an effect on different cognitive processes, such as high-intensity improving memory function (Kovacevic et al., 2020) and moderate-intensity exercise improving executive functioning (Hains & Arnsten, 2008; Yuen et al., 2009). However, there is little indication as to what intensity is better for global cognitive functioning. This meta-analysis will focus on comparing the effects high-intensity versus low- to moderate-intensity exercise can have on global cognition for individuals with dementia or MCI.

Method

Protocol and Registration

This article adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Moher et al., 2015). The protocol was registered in accordance with PRISMA with the international prospective register of systematic reviews

(Appendix A; PROSPERO CRD42023433569). Registration of the protocol was completed on 1st August 2023.

Information Source and Search Strategy

The systematic literature search for work published before August 2023 was performed on the following electronic databases: PsycINFO (all fields), Web of Science (all fields), Science Direct (keywords, title, author) ProQuest (all fields), PubMed (all fields), SPORTDiscus (all fields), CENTRAL (all fields) and Scopus (title, abstract, keywords). Additionally, MedRxiv and bioRxiv were searched to identify potential gray literature. Search terms are shown in Table 1. Authors that were identified as prominent within the literature, or that had published a protocol or pre-registration for a study that fit the criteria, were contacted for any unpublished data they may possess, and reference lists of key articles were reviewed to make sure no relevant literature was missed.

An example of how this search strategy could be used on PubMed is: ((((((((((((((((high intensity exercise) OR (interval exercise)) OR (moderate intensity exercise)) OR (resistance training)) OR (aerobic exercise)) OR (yoga)) OR (sports)) OR (multicomponent exercise)) AND (dementia)) OR (Alzheimer's disease)) OR (mild cognitive disorder)) OR (mild cognitive dysfunction)) OR (mild cognitive decline)) OR (mild neurocognitive disorder)) AND (chronic effects)) OR (long-term effects)) AND (cognitive function*)) OR (executive function*) OR (memory) OR (cognition).

Table 1.

Literature search terms. To be indexed, studies had to mention at least one term from each column (i.e., exercise type AND participants AND exercise effect AND outcome).

Exercise Type	Participants	Exercise Effect	Outcome
High intensity training	Dementia	Chronic effect	Cognitive function*
Interval exercise	Alzheimer's disease	Long-term effect	Executive function*
Moderate intensity exercise	Mild cognitive impairment		Memory
Resistance training	Mild cognitive disorder		Cognition
Aerobic training	Mild cognitive dysfunction		
Yoga	Mild cognitive decline		
Sports	Mild neurocognitive disorder		
Multicomponent exercise			

Eligibility Criteria

An independent reviewer screened the abstracts and full-text articles of the selected works. PICOS was used to screen relevant studies (Richardson et al., 1995). PICOS is short for participants (P), intervention (I), comparisons (C), outcomes (O), and study design (S) (Richardson et al., 1995). The present systematic review focused on studies featuring human participants that had been formally diagnosed as having dementia-related cognitive impairment, such as mild cognitive impairment (MCI) or Alzheimer's disease, and are considered older adults e.g., older than 50 years of age. The primary intervention of the study must be either a high-intensity exercise or a low- to moderate-intensity exercise

intervention that has been defined using a validated measure of intensity to meet the inclusion criteria. Some examples of a validated measure of intensity include: the heart rate reserve (%HRR) method defined by the American College of Sports Medicine (ACSM) where high-intensity is 60-89 %HRR, moderate intensity is 40-59 %HRR and low intensity is 20-39%HRR; or the Borg Rating of Perceived Exertion (RPE) where high-intensity is scored between 15-17 on the 6-20 scale, moderate intensity is scored between 12-14, and low intensity is scored between 6-11 (Borg, 1982). Due to the literature findings more long-term or beneficial effects from chronic exercise interventions, the intervention used within the study must be chronic to be included in the meta-analysis. Chronic exercise is defined as repeated bouts of exercise during a short or long-term period of time. However, there is not a length of time that is universally used within this definition, with previous research ranging from interventions needing to be longer than two weeks to needing to be longer than eight weeks (Fedewa et al., 2018; Qiu et al., 2015; Xue et al., 2019). Considering previous research and the definition, this meta-analysis will include studies where the exercise intervention lasted more than eight weeks and exclude any studies that have shorter interventions. Studies will be excluded if the intervention includes any non-exercise intervention as the primary intervention, or if intensity was not specified or measured in a validated way. Studies were included in the review if they applied a control group that has not participated in the exercise intervention (passive control), participated in a non-exercise intervention such as cognitive training (active control), or consisted of healthy older adults (cohort control). Studies that directly compared high-intensity to low- to moderate-intensity exercise in older adults with dementia-related cognitive impairment were also included. Studies were excluded if there were no control or comparison group. To meet the inclusion criteria the primary outcome of the study was cognitive function that had been assessed using validated

neuropsychological or cognitive tests, such as the Mini Mental State Examination (MMSE; Folstein et al., 2014) or the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog; Skinner et al., 2012). Studies were included in the review if they followed a randomised controlled trials or an intervention study design, and if they included effect sizes or the information necessary to calculate effect sizes. Studies that were prospective or retrospective cohort studies, case reports, conference abstracts or that were not available in English were excluded.

All studies that appear during the literature search were uploaded to Rayyan (Ouzzani et al., 2016), a platform that can aid with screening articles for inclusion or exclusion for meta-analyses. This platform allows for screening by title and abstract, as well as containing the link to the full article for easy access when reaching that stage of the screening process. It also has its own screening process that can identify and exclude duplicate studies, although this process was also corroborated by the researcher. The platform also allows the researcher to sort excluded articles by reason for exclusion, allowing for the platform to keep track of important pieces of information in an easy-to-use way. A total of 10,628 articles were found in the literature search. Duplicates were identified first and were excluded from the review. After removing the duplicates there were 9,625 articles remaining. The articles were initially screened by title to exclude studies that clearly stated they had been conducted on individuals with non-dementia cognitive impairment, such as Parkinson's or cancer patients, or articles that did not involve participants with dementia-related cognitive impairment at all. After this there were 497 articles remaining. The abstracts of these 497 articles were read to determine eligibility, and 365 articles were excluded based on the abstract. Of the 132 articles remaining, the full text was not available for 26 articles leaving 104 full text articles to be evaluated for eligibility. A total of 11 authors

were contacted as their study met the inclusion criteria for the meta-analysis, but were missing an effect size, enough data to calculate an effect size, or a specified intensity for their exercise intervention. Only one author replied and provided the data needed to be included in the meta-analysis. After this final screening process, there were 18 articles remaining that were included in this meta-analysis (see Figure 1 for a detailed flow chart). The most common reasons for exclusion were that the primary outcome was not cognition (*n* = 25), the wrong population was used (*n* = 17), and that not solely an exercise intervention was used (*n* = 11).

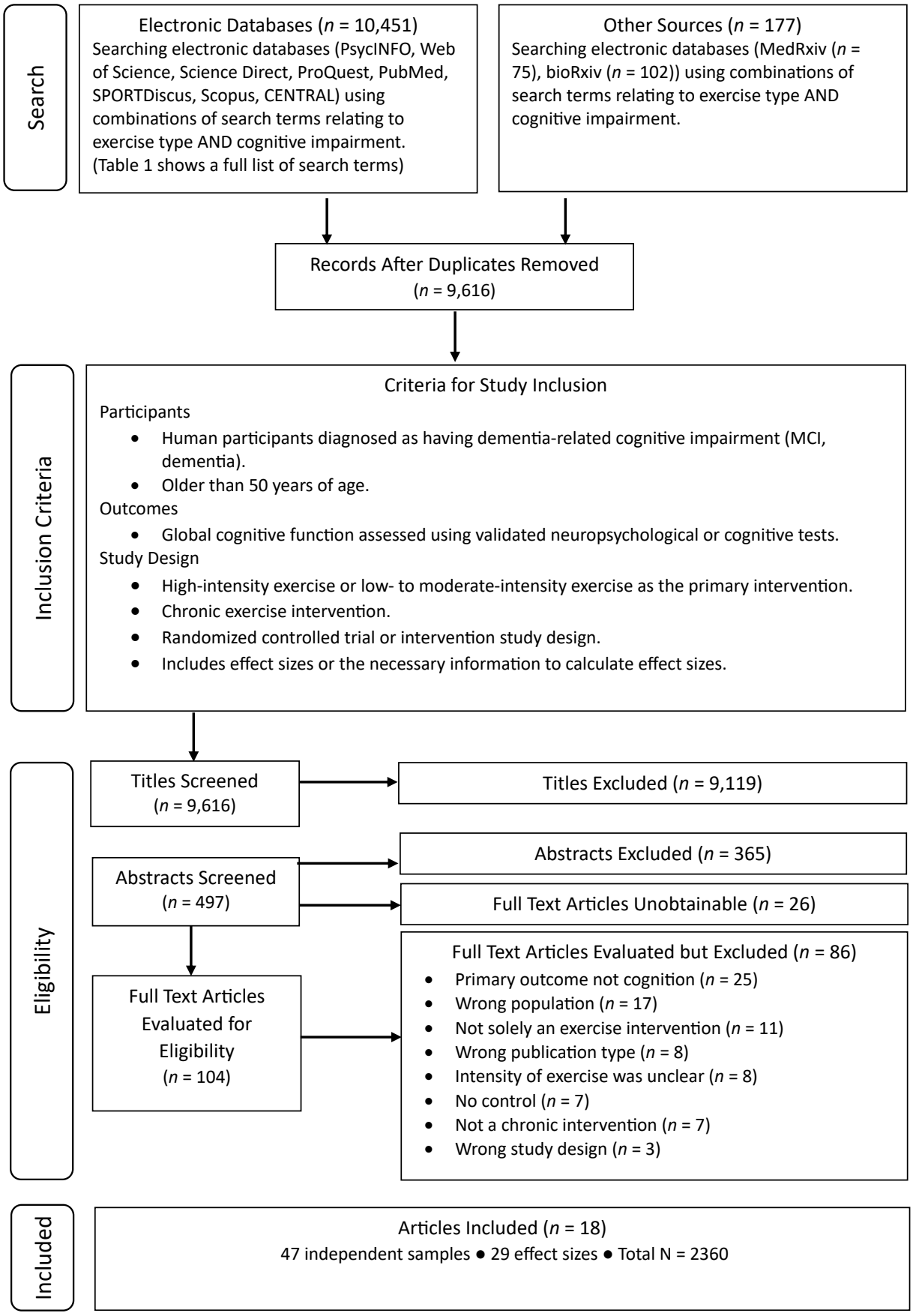
Data Extraction

The same process for screening the articles was followed for the data extraction with one researcher extracting data. Study information about the authors, the place the study was conducted, and the year of publication was extracted. Demographic information was also collected, specifically the average age of the participants, the sex of the participants, the cognitive impairment diagnosis that the participants had received and the total number of participants that were randomised and analysed within the study. Intervention characteristics were extracted, such as the intensity of the exercise intervention and the length of the intervention, as well as information about what measure of global cognition was used to measure cognitive change. Furthermore, information on effect sizes, means and standard deviations for pre- and post-intervention cognitive measures, and change scores were also extracted to allow for thorough calculation of the effect sizes.

Information on key moderator variables was also extracted if part of the study, including information on the duration of each exercise session, frequency of exercise, type of exercise, and adherence to the exercise program. In the event that an article lacked key data or further clarification was needed, the corresponding author was contacted.

Figure 1.

Flow chart of identification of studies from databases and registrars.



Risk of Bias Assessment

This risk of bias was assessed in each of the 18 studies using the Cochrane Collaboration's Risk of Bias tool (RoB.2; Sterne et al., 2019). Each study was rated in five categories, including the "randomization process", "deviations from the intended interventions", "missing outcome data", "measurement of the outcome", and "selection of the reported result" (Sterne et al., 2019). An overall risk of bias score was determined based on each paper's individual scores in each of the five categories and was rated as either "high", "some concerns", or "low". Each study was independently rated, and reliability was calculated. Study quality was considered as a moderating variable.

As this study involves exercise interventions, it is not possible to blind participants to treatment allocation. Due to this, the blinding of participants and personnel will be deemed a high risk of bias in all studies and will not be factored into the overall risk bias assessment. It is also recognized that there is a possibility for small-study bias. Small-study bias will be examined by inspecting a funnel plot of obtained standard errors and effect sizes for each of the studies, and the trim-and-fill analysis will be used to determine the number of missing effect sizes (Duval & Tweedie, 2000). An Egger's test will also be used to determine small-study bias. A p-curve will also be created (Simonsohn et al., 2014) to determine if the resulting p-value distribution for the studies that have been included is what would be expected for a true effect.

Data Analysis

A random effects meta-analytic model was used for the data synthesis. Heterogeneity is calculated via I^2 statistics, and moderating variables were assessed accordingly. The measure of effect size is Cohen's *d*, based on means and standard deviations extracted for each cognitive test. Change scores have been considered and

converted to effect sizes as some studies employed them in their data rather than means and standard deviations. An R script template that employs the “metafor” package for meta-analysis (Moreau & Gamble, 2022) is used. This template was modified appropriately. Subsequent analyses (subgroup analysis and mixed effects meta-analysis modelling) were conducted following the initial random-effects meta-analysis and heterogeneity determination if necessary. The same R script was modified accordingly and employed for this.

Grading of Recommendations, Assessment, Development and Evaluations (GRADE) was used as a framework for determining the quality of the meta-analysis. An overall GRADE quality rating will be applied to the meta-analysis by taking the lowest quality of evidence from all of the outcomes that are critical to the decision making, and the evidence will be rated on a certainty scale (very low, low, moderate or high certainty). Certainty will be rated down for risk of bias, imprecision, indirectness, small-study bias and inconsistency, and will be rated up for a large magnitude of effect, a dose-response gradient and when all residual confounding would decrease the magnitude of effect. GRADE is consistent with the Cochrane Risk of Bias tool which was used to determine the risk of bias in each individual study within the review.

Results

In this section, the results of the meta-analysis are presented, which synthesizes findings from 18 studies examining the effect of exercise intensity on cognitive functioning for older adults with cognitive impairment. The meta-analysis aims to determine whether high-intensity exercise interventions or low- to moderate-intensity exercise interventions

produce greater cognitive benefits. This helps to inform best practice for exercise recommendations for those who suffer from dementia or MCI.

Included Studies

Before delving into the specific results, we provide an overview of the studies included in the meta-analysis. A total of 18 relevant studies were identified through a comprehensive literature search of databases PsycINFO, Web of Science, Science Direct, ProQuest, PubMed, SPORTDiscus, Scopus and CENTRAL, and additional sources MedRxiv and bioRxiv. The studies encompass a diverse range of exercise interventions and intensities whilst maintaining a population of older adults with cognitive impairment and a validated measure of global cognition as the outcome, reflecting the breadth of research in this area. Due to some studies looking at both high-intensity and low- to moderate-intensity exercise, there are 29 total effect sizes across 18 studies. This is due to some studies looking at both high-intensity and low- to moderate-intensity or employing different intervention methods for different samples within their study. Descriptive findings of the selected studies are displayed in Table 2.

Pre-intervention and post-intervention cognitive scores were extracted from the data to be used within the analysis. The post-intervention scores were taken from the tests done immediately after the intervention ended, not from follow-up tests. The moderator variable type of exercise was able to be further specified after gaining information from the studies. Type of exercise was organised into five separate groups: mind-body exercise (for example tai chi), walking, aerobic (for example running or strength training), cycling and sport (such as team-based exercise e.g., basketball).

Table 2

Descriptive Findings of the Studies Included

Author, year, country	Sample characteristics				Study intervention				Outcome Measure	Risk of Bias (RoB.2)
	N	Female sex (%)	Average age (yrs)	Diagnosis	Intervention type	Length (wks)	Intensity of intervention	Adherence to intervention		
Arcoverde et al., 2013, Brazil	20	55	78.8	Dementia	Walking	16	High	93.7	MMSE & CAMCOG-CAMDEX	Some concerns
Chang et al., 2021, China	136	N/A	76.3	MCI	Aerobic	18	High	87.6	MoCA	Some concerns
Huang et al., 2019, China	80	67.5	81.9	Dementia	Tai-chi (mind-body)	40	Low to mod	N/A	MMSE & MoCA	Low
Lam et al., 2014, Hong Kong	389	76.3	77.8	MCI	Aerobic	52	Low to mod	76	ADAS-Cog & MMSE	High
Lamb et al., 2018, England	494	60.7	77.5	Dementia	Aerobic	48	Low to mod	N/A	ADAS-Cog	Low

Langoni et al., 2018, Brazil	60	76.9	72.6	MCI	Aerobic	26	Low to mod	89.5	MMSE	Some concerns
Li et al., 2022, United States	70	57	74.6	MCI	Tai ji quan (mind-body)	16	Low to mod	94	MoCA	Some concerns
Morris et al., 2017, United States	76	51.3	72.9	MCI & dementia	Aerobic	26	High	89	Composite battery	High
Ohman et al., 2016, Finland	210	39	78.1	Dementia	Aerobic	52	High	N/A	MMSE	Some concerns
Uffelen et al., 2008, Netherlands	179	44.1	75	MCI	Walking	52	Low to mod	63	MMSE	High
Varela et al., 2011, Spain	68	56.3	78.3	MCI	Cycling	12	Low to mod & high	70	MMSE	Some concerns
Venturelli, Scarsini & Schena, 2011, Italy	25	85.7	84	Dementia	Walking	26	Low to mod	93.4	MMSE	Some concerns

Wang et al., 2020, China	66	71.2	81.1	MCI	Jiamusi happy dance (mind-body)	12	Low to mod	80.3	MMSE & MoCA	Some concerns
Wei and Ji, 2014, China	60	33.4	66	MCI	Handball	26	Low to mod	N/A	MMSE	High
Yu et al., 2021, United States	96	45	77.4	Dementia	Cycling	26	High	N/A	ADAS-Cog	Low
Yu, Salisbury & Mathiason, 2021, United States	78	41	77.4	Dementia	Cycling	26	High	85.6	ADAS-Cog	Some concerns
Yu et al., 2022, Hong Kong	50	89.2	63.5	MCI	Walking	12	Low to mod & high	93.1	HK-MoCA	Low
Yu et al., 2022, Hong Kong	37	67.4	73.5	MCI	Aerobic & tai chi (mind-body)	26	Low to mod	79.1	HK-MoCA	Low

Note. N = total number of participants. NI = no information. MMSE = Mini Mental State Examination. ADAS-Cog = The Alzheimer's Disease Assessment Scale – Cognitive Scale. MoCA = Montreal Cognitive Assessment. HK-MoCA = Hong-Kong version of MoCA. Composite batteries = executive functioning and memory composite batteries.

The various validated cognition measures that were used throughout the studies included the Mini Mental State Examination (MMSE; Folstein et al., 2014), the Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog; Kueper et al., 2018), the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) as well as the Hong-Kong version of this measurement (HK-MoCA; Yeung et al., 2014), the Cambridge Cognition Examination – Cambridge Examination for Mental Disorders of the Elderly (CAMCO-CAMDEX; M. Roth, 1988) and a composite battery of executive functioning and memory that was validated and found to be reliable (Morris et al., 2017). All of these measures have been found to be validated and reliable and are consistently used by researchers as measures of cognition. For all of these measures lower scores indicated better cognitive functioning, therefore a reduction in cognition scores post-intervention is associated with an improvement in cognitive functioning.

Analysis Plan

The analysis plan involved a random effects meta-analytic model. All analyses were performed using R Statistical Software (v4.3.1; Urbanek et al., 2023) and RStudio (v.2023.09.01+494; RStudio Team, 2022). A template script that employs the 'metafor', 'tidyverse' and 'ggplot2' packages was used and modified appropriately to fit the data. The measure of effect size used was Cohen's d. Exercise intensity was treated as a moderator within the data, as well as the frequency of exercise, minutes per week spent exercising, adherence to the intervention and the type of exercise implemented. An assessment of heterogeneity was made using the I^2 statistic and sensitivity analyses were performed, as well as subgroup analyses for age, diagnosis, length of intervention and study quality. A small-study bias assessment was done in RStudio to generate a funnel plot, run an Egger's test and a p-curve. These methods were selected to ensure rigor and comprehensiveness in

synthesizing the available evidence on the effect of exercise intensity on cognitive functioning for individuals with impairment, such as MCI or dementia. It is important to note that an improvement in cognitive functioning is characterised by a decline in score on a validated measure of global cognition, therefore negative associations are analogous with an improvement in cognition. This additionally means that negative effect sizes are associated with a reduction in the measure of cognition and, therefore, an improvement in cognitive functioning. The dataset that has been used to conduct this meta-analysis is available in Appendix B.

Risk of Bias

The assessment of risk of bias (RoB) is paramount in ensuring the reliability and validity of synthesized evidence. The Risk of Bias 2 (RoB.2) tool, endorsed by Cochrane, represents a comprehensive framework for evaluating potential biases across individual studies included in meta-analytic investigations. Of the 18 studies included in this meta-analysis, 5 studies were low risk (Huang et al., 2019; Lamb et al., 2018; A. P. Yu et al., 2022; D. J. Yu et al., 2022; F. Yu, Vock, et al., 2021), 9 studies showed some concern (Arcoverde et al., 2014; J. Chang et al., 2021; Langoni et al., 2019; Li et al., 2022; Ohman et al., 2016; Varela et al., 2012; Venturelli et al., 2011; S. Wang et al., 2020; F. Yu, Salisbury, et al., 2021) and 4 studies showed high risk (Lam et al., 2014; Morris et al., 2017; Uffelen et al., 2008; Wei & Ji, 2014). More information on the RoB.2 assessment is available in Figure 2 and Figure 3 which outline what categories most commonly exhibited higher risk for the included studies. As it is difficult to blind interventions that are focused on exercise that is considered a similar risk across all of the included studies and has not been considered when conducting the RoB.2 assessment.

Figure 2

Risk of Bias as Percentage (Intention to Treat)

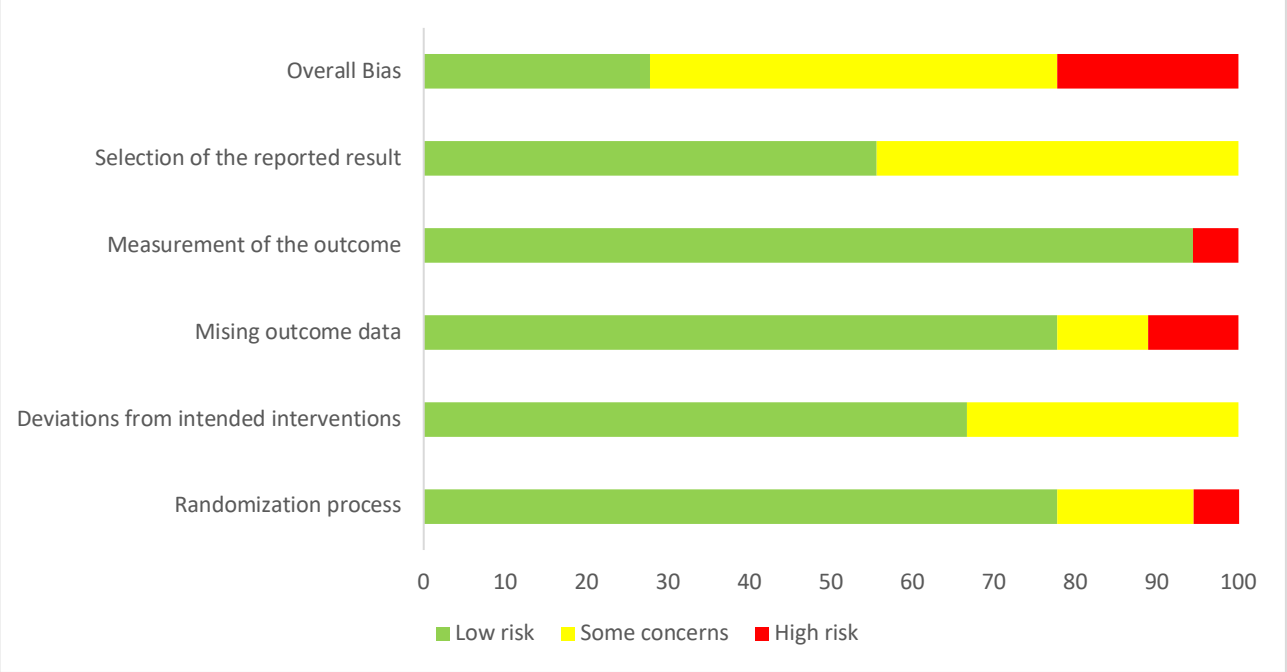


Figure 3

Risk of Bias

Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
1	10	High-Intensity	Control	MMSE & CAMCOG-CAMD	1	+	+	+	+	!	!
2	9	High-Intensity	Control	MoCA	1	!	+	!	+	!	!
3	2	Moderate-Intensity	Control	MMSE & MoCA	1	+	+	+	+	+	+
4	12	Moderate-Intensity	Control	ADAS-Cog & MMSE	1	+	!	-	+	!	-
5	5	Moderate-Intensity	Control	ADAS-Cog	1	+	+	+	+	+	+
6	1	Moderate-Intensity	Control	MMSE	1	+	!	+	+	!	!
7	13	Moderate-Intensity	Control	MoCA	1	+	!	+	+	+	!
8	14	High-Intensity	Control	Composite battery	1	+	!	+	-	+	-
9	18	High-Intensity	Control	MMSE	1	+	+	+	+	!	!
10	15	Moderate-Intensity	Control	MMSE	1	+	+	-	+	+	-
11	3	Mod & High-Intensity	Control	MMSE	1	!	+	!	+	!	!
12	16	Moderate-Intensity	Control	MMSE	1	+	+	+	+	!	!
13	6	Moderate-Intensity	Control	MMSE & MoCA	1	!	+	+	+	+	!
14	7	Moderate-Intensity	Control	MMSE	1	-	!	+	+	!	-
15	11	High-Intensity	Control	ADAS-Cog	1	+	+	+	+	+	+
16	4	Mod & High-Intensity	Control	MoCA	1	+	+	+	+	+	+
17	8	Moderate-Intensity	Control	MoCA	1	+	+	+	+	+	+
18	17	High-Intensity	Control	ADAS-Cog	1	+	!	+	+	+	!

+ Low risk
! Some concerns
- High risk

D1 Randomisation process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

Main Results

We present the main findings of the meta-analysis regarding the effect that exercise can have on cognition, and specifically the effect that differing intensities of exercise have on cognition. This includes the overall effect of the intervention groups, who received an exercise intervention, compared to the control groups, which could have received a non-exercise intervention or no intervention at all. There will additionally be a comparison of high-intensity exercise and low- to moderate-intensity exercise to determine which intensity elicits greater effects on cognition. Moderators will be considered, including the frequency of the exercise intervention, adherence to the intervention, and the type of exercise that was introduced such as aerobic or mind-body exercise. Heterogeneity will also be considered.

Intervention vs Control Groups

A multivariate meta-analysis model was conducted with a total of 29 effect sizes from 18 studies using the restricted maximum likelihood estimation (REML) method on RStudio. This model was conducted to determine whether there was a significant difference in the change scores for cognitive performance between the control and the intervention groups. A test for heterogeneity was performed, yielding $Q(28) = 0.00$, $p = 1.00$, indicating no significant heterogeneity across the studies. The estimate of the effect size was -2.64 (SE = 0.11), which was statistically significant ($p < .001$), indicating a significant difference between the intervention and the control groups. This implies that the intervention group showed significantly more change in cognition scores during the course of the intervention period than the control group did. The 95% confidence interval ranged from -2.85 to -2.43. The estimate of -2.642 indicates that, on average, the intervention group performed 2.64

standard deviations better compared to the control group on cognitive performance at the end of the intervention period.

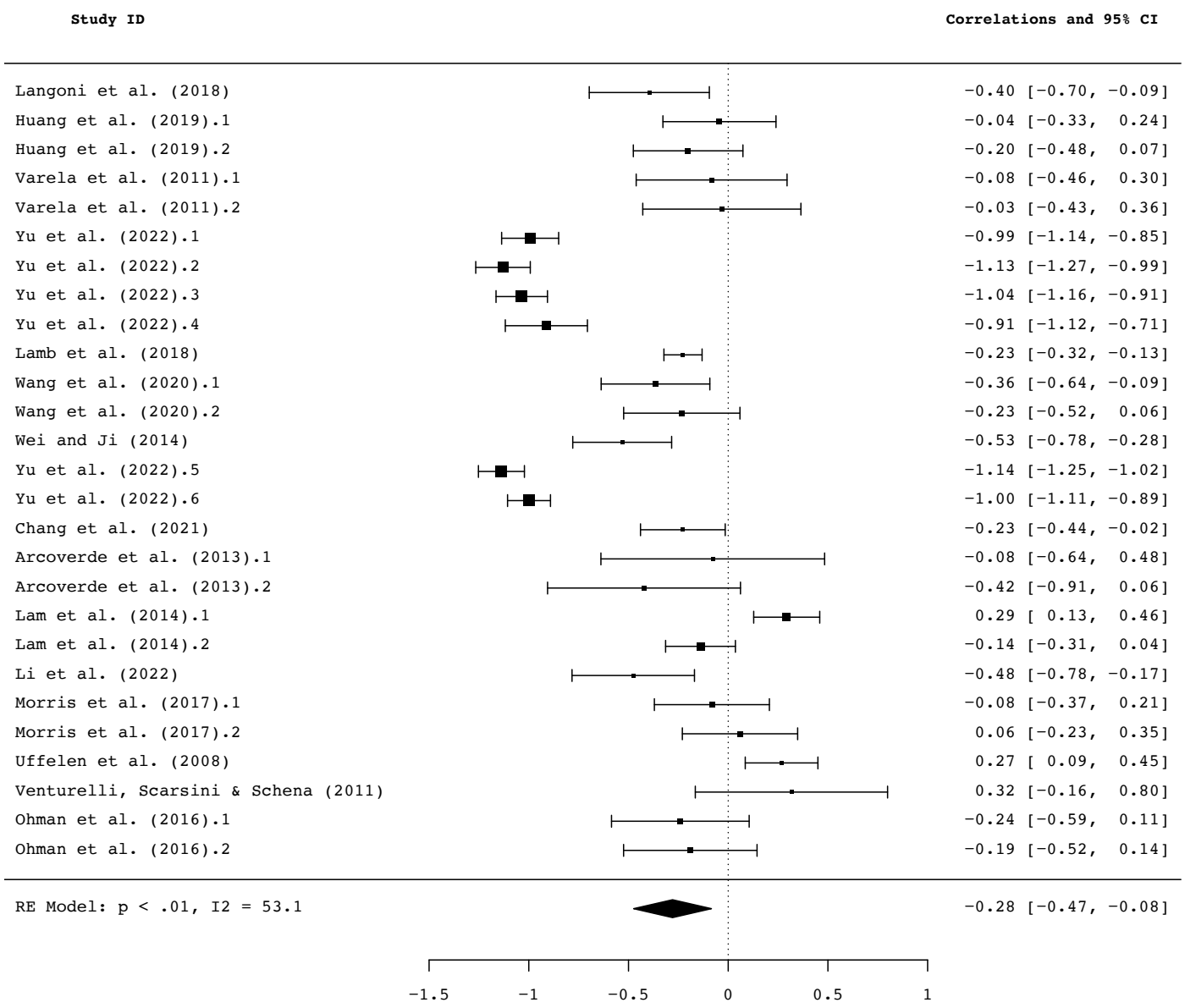
Intensity Comparison

When focusing on the intervention groups within the meta-analysis, as it has been established, they elicit significantly better outcomes than the control group. A secondary model was run on just the intervention groups to determine the direction of the change in cognition after receiving an exercise intervention. A multivariate meta-analytic model using the REML method indicated that there was additionally a significant difference in post-intervention cognitive performance than pre-intervention cognitive performance. The estimate of the effect size was -0.28 (SE = 0.10), indicating a statistically significant effect ($p < .01$). The 95% confidence interval ranged from -0.47 to -0.08, providing the range within which we are 95% confident that the true effect lies. This effect size indicates that, on average, cognitive measure scores for older adults with cognitive impairment was 0.28 standard deviations lower post-intervention than they were pre-intervention, indicating an improvement in cognitive functioning after undergoing the exercise intervention. A test for heterogeneity indicated that there was significant variability in the effects observed between pre- and post-intervention cognitive performance, $Q(24) = 676.95$, $P < .001$. This can be seen in the forest plot shown in Figure 4.

To compare high-intensity exercise interventions to low- to moderate-intensity exercise interventions, a multivariate meta-analysis model with 27 effect sizes using the REML methods and a test of moderators was run to determine if the intensity of the intervention significantly effects the effect sizes. The results showed no significant effect of intensity, $QM(1) = 0.78$, $p = 0.378$. The estimates for the intercept and intensity as a moderator are also provided.

Figure 4

Forest Plot: Exhibiting the Effect Sizes and Confidence Intervals of Studies Included in the Meta-Analysis Comparing Post-Intervention Scores to Pre-Intervention Scores



Note. Size of the square indicates sample size. Error bars indicate confidence interval. Diamond indicates overall effect estimate with the width indicating variability of this estimate.

In this case, the intercept of -0.24 indicates estimated effect when the moderator is zero (or when the variable is not present), and the estimate for intensity of -0.06 suggests the estimated additional effect when the moderator increases by one unit. The intercept

demonstrated statistical significance; estimate = -0.24, $p < .05$. This indicates that there is a significant effect when exercise intensity is absent, signifying a consistent effect across studies even without considering any additional factors. This implies that there is a real effect present in the data that cannot be attributed solely to random variability. The intensity moderator not being significant (estimate = -0.06, $p = 0.378$) implies that intensity does not have a significant impact on the outcome. A test for residual heterogeneity was also performed, indicating significant variability across studies, $QE(25) = 676.35$, $p < .0001$. Overall, these results suggest that while there is significant residual heterogeneity among the studies, the intensity level of the exercise intervention does not have a significant effect on cognitive performance in older adults with cognitive impairment. However, it is also important to look more closely at high-intensity and low- to moderate-intensity exercise to better see how these intensities may affect cognition.

Subgroup analyses for high-intensity and low- to moderate-intensity exercise were also performed to better understand the nuances of these different models and the effect differing intensities may have on cognition. The high-intensity model, composed of 10 effect sizes from 6 studies, aimed to assess the effect of high-intensity exercise interventions on cognitive functioning specifically. The multivariate meta-analysis model estimated the within-study variance to be 0.13, indicating moderate variability in effect sizes across the included studies. The test for heterogeneity yielded a significant result, $Q(9) = 117.67$, $p < .001$, suggesting substantial heterogeneity among the effect sizes observed in the study.

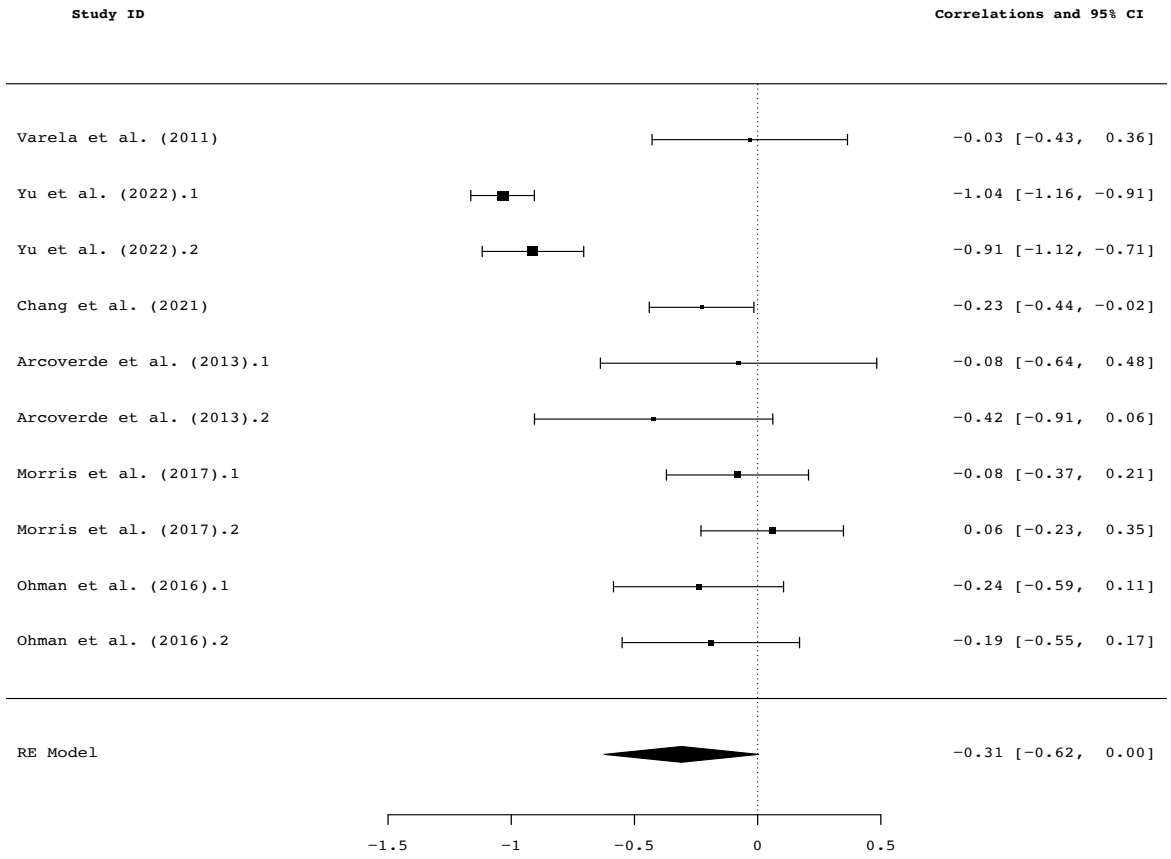
However, when examining the model results, the effect estimate for high-intensity exercise was found to be -0.31 (SE = 0.16), indicating a negative association between high-intensity exercise and cognitive functioning. Although the effect estimate trended towards significance ($p = 0.053$), the 95% confidence interval [-0.62, 0.00] included zero, indicating a

lack of statistical significance. This suggests that while there may be an effect of high-intensity exercise on cognition, it was not robustly supported by the available evidence in this subgroup analysis. This is represented within Figure 5.

The low- to moderate-intensity model, comprised of 17 effect sizes from 12 studies, explored the impact of low- to moderate-intensity exercise interventions on cognitive functioning. The estimated within-study variance was slightly higher at 0.19, indicating a similar level of variability in the effect sizes among the included studies compared to the high-intensity model. The test for heterogeneity also yielded a significant result, $Q(16) = 558.68$, $p < .001$, indicating notable variability in effect sizes. In contrast to the high-intensity

Figure 5

Forest Plot of Only High-Intensity Exercise Intervention Studies



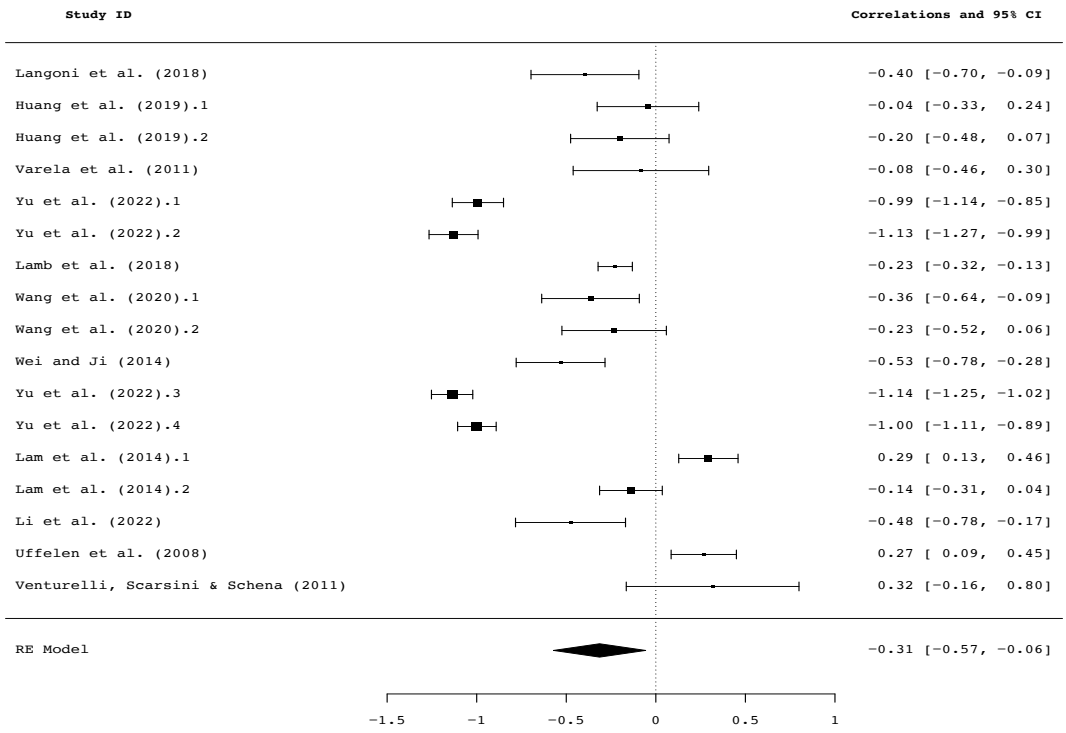
Note. Size of the square indicates sample size. Error bars indicate confidence interval. Diamond indicates overall effect estimate with the width indicating variability of this estimate.

model, the model results for low- to moderate-intensity exercise revealed a statistically significant effect estimate of -0.31 (SE = 0.13, p <.05). The 95% confidence interval [-0.57, -0.06] did not include zero, indicating a robust negative association between low- to moderate-intensity exercise and cognitive functioning for older adults with cognitive impairment. This is represented within Figure 6.

Comparing the two models, both high-intensity and low- to moderate-intensity exercise interventions demonstrated significant heterogeneity in effect sizes across studies. Despite the high-intensity model (es = -0.31) and the low- to moderate-intensity model (es = -0.31) demonstrating the same effect size, this was only significant for the low- to moderate-intensity intervention. This suggests that whilst both intensities may impact cognition, the effect may be more reliably observed with low- to moderate-intensity regimens.

Figure 6

Forest Plot of Only Low- to Moderate-Intensity Exercise Intervention Studies



Note. Size of the square indicates sample size. Error bars indicate confidence interval. Diamond indicates overall effect estimate with the width indicating variability of this estimate.

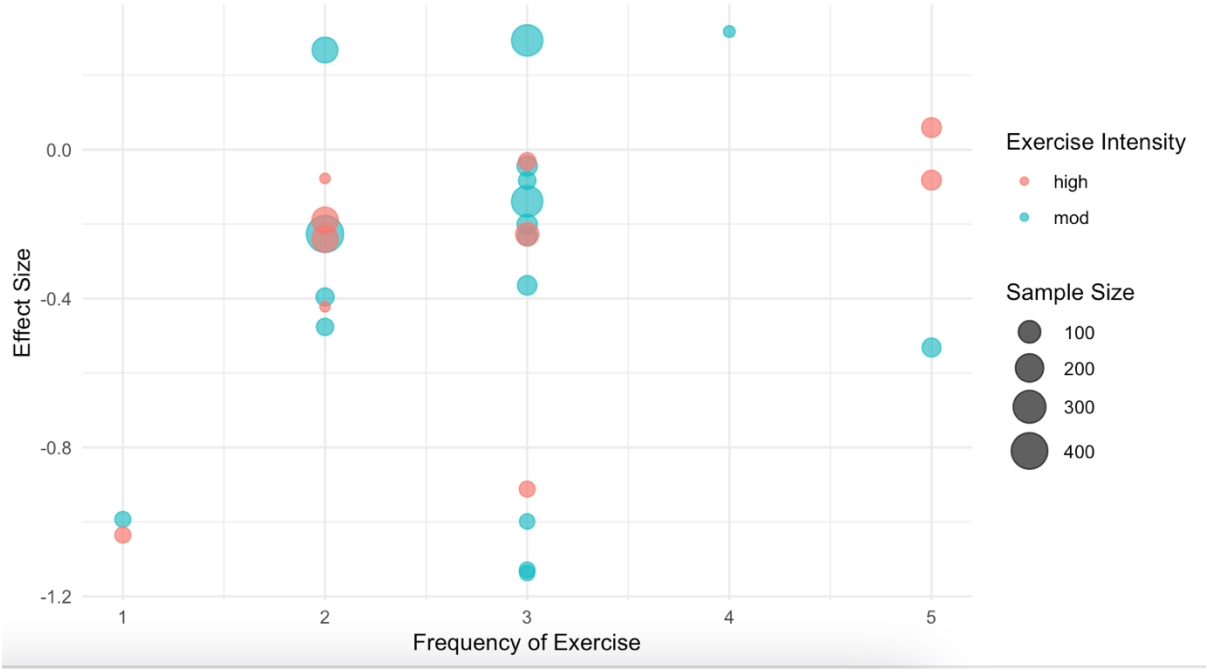
Moderator Analyses

Moderator analyses were additionally run for four different moderator variables: the frequency of exercise (how many times a week did the individual exercise), minutes of exercise (the number of minutes spent exercising per week), the adherence to the intervention program (the percentage of participants that completed the entire exercise intervention within their study), and type of exercise (e.g., aerobic, mind-body, etc.). These analyses were run to determine whether there are other factors that need to be considered when looking at the effect of exercise on cognitive functioning, and it can help to inform on best practice and recommendations for exercise interventions in the future.

Frequency of Exercise. We examined the influence of the moderator variable, the frequency of exercise, on the effect sizes. The test for residual heterogeneity indicated significant variability in effect sizes across studies after accounting for the moderator, QE(25) = 657.66, p <.0001. The results revealed no significant effect of exercise frequency, QM(1) = 0.11, p = 0.740. This suggests that variations in the frequency of exercise during the week does not significantly influence the effect sizes. The model estimates for the intercept and the exercise frequency were also calculated. Neither the intercept (estimate = -0.25, p = 0.085) nor the moderator variable (estimate = -0.01, p = 0.740) demonstrated statistical significance. These results suggest that whilst there is significant residual heterogeneity across studies, the frequency of exercise does not appear to significantly impact the cognitive performance of older adults with cognitive impairment. This effect is demonstrated in Figure 7.

Figure 7

Bubble Plots of the Effect that Frequency of Exercise has on the Effect Size for Post-Intervention versus Pre-Intervention Cognition Scores



Minutes of Exercise. The influence of the minutes of exercise per week on effect sizes was also examined. After accounting for potential moderators, a significant amount of residual heterogeneity was observed across studies, QE(25) = 564.89, P < .0001. The results of the moderator analysis indicated that the minutes of exercise per week did not significantly affect the effect sizes, QM(1) = 1.64, p = 0.200, suggesting that the variables in the minutes per week spent exercising did not lead to significant differences in cognitive performance for older adults with cognitive impairment. Model estimates for the intercept and minutes of exercise were also calculated, and neither the intercept (estimate = -0.13, p = 0.364) nor the moderator (estimate = -0.001, p = 0.200) demonstrated statistical significance. This is demonstrated in Figure 8.

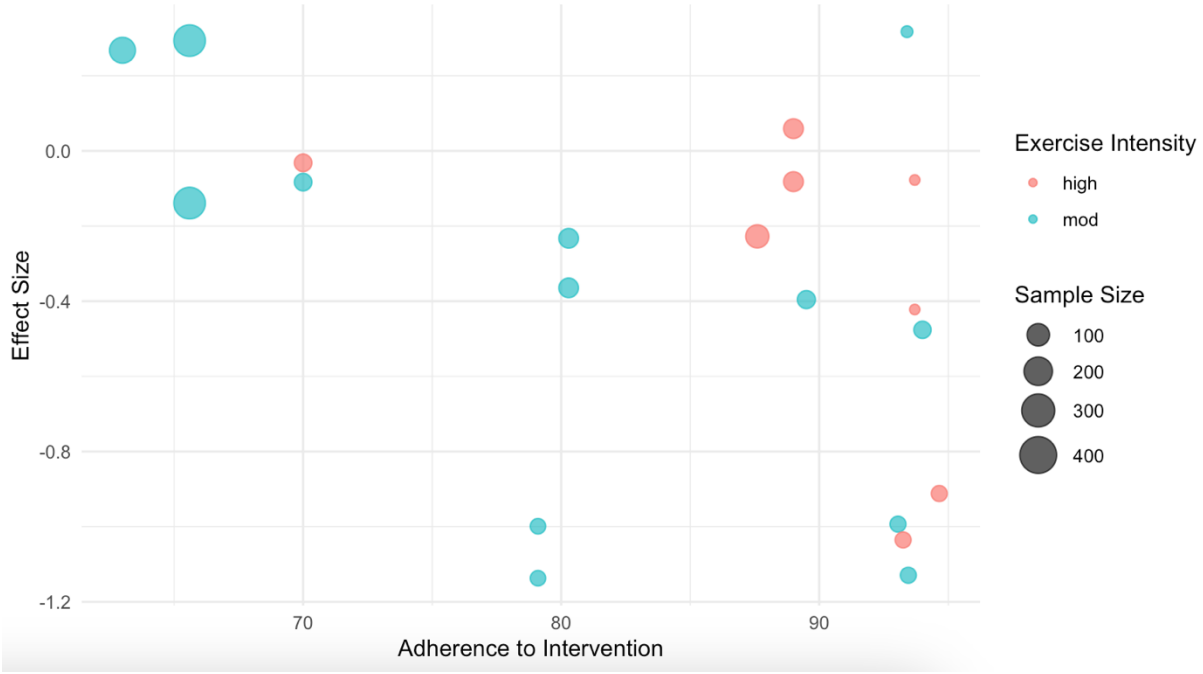
Figure 8

Bubble Plots of the Effect that Minutes of Exercise has on the Effect Size for Post-Intervention versus Pre-Intervention Cognition Scores

Adherence to Exercise Intervention. The study investigated the potential influence of treatment adherence on cognitive performance. Significant residual heterogeneity was observed across studies even after considering potential moderators, QE(19) = 379.86, p < .0001. Results revealed that adherence to the intervention did not significantly affect the outcome, QM(1) = 1.44, p = 0.231. Model estimates for the intercept and adherence shows that neither the intercept (estimate = 0.84, p = 0.372) nor the moderator (estimate = -0.01, p = 0.231) demonstrated statistical significance. These findings indicate that variations in treatment adherence levels do not appear to significantly influence cognitive performance in older adults with cognitive impairment. This effect is demonstrated in Figure 9.

Figure 9

Bubble Plots of the Effect that Adherence to the Exercise Intervention has on the Effect Size for Post-Intervention versus Pre-Intervention Cognition Scores



Type of Exercise. The effect that the type of exercise conducted within the intervention may have on cognition was investigated. Significant residual heterogeneity was observed across studies even after considering potential moderators, QE(21) = 590.62, p < .0001. A test of moderators was performed to assess the collective impact of exercise types on the outcomes. Results indicated that the set of moderator variables did not collectively significantly impact the outcomes (QM(5) = 3.43, p = 0.634), which suggests that variations in the types of exercise did not lead to significant differences in the observed outcomes across studies. Model estimates for each moderator variable and the intercept are provided. Among the different types of exercise provided none of the categories, including mind-body exercise, aerobic, cycling, sport, and walking, there were none that exhibited statistical significance. This is shown in Figure 10.

Figure 10

Bubble Plot of the Effect that the Type of Exercise has on the Effect Size for Post-Intervention versus Pre-Intervention Cognition Scores

Heterogeneity

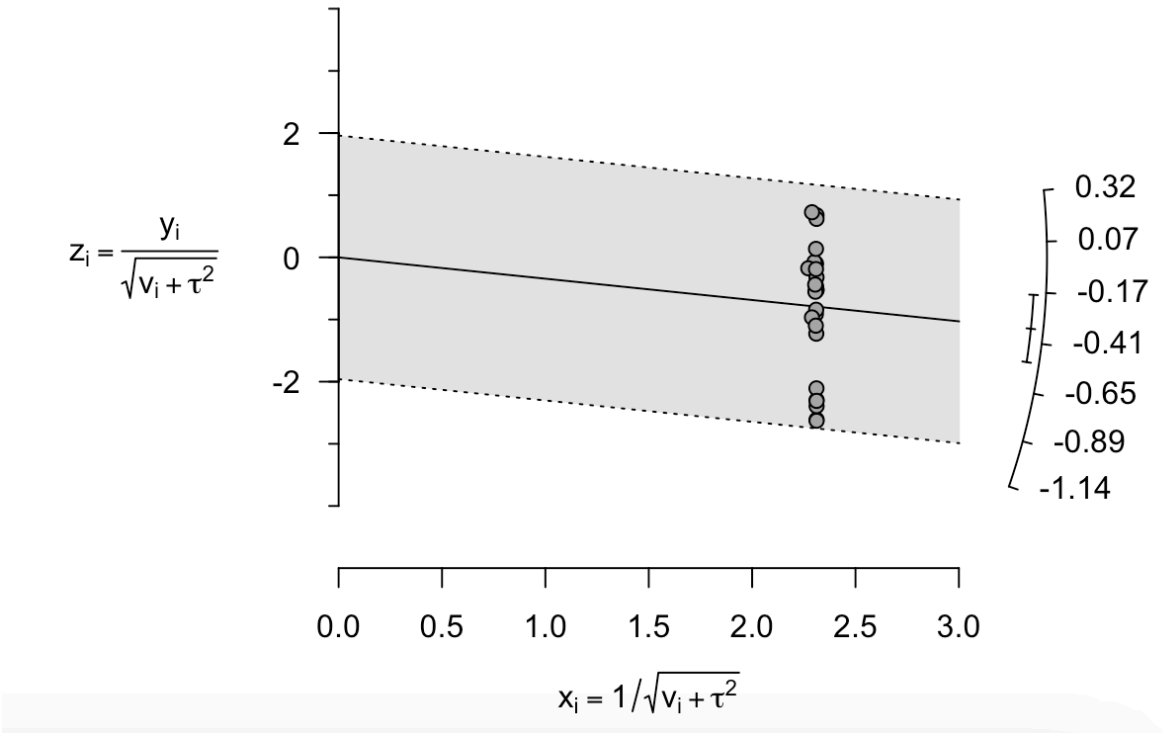
As significant variability was suggested, the I^2 statistic was calculated to assess the degree of heterogeneity across studies. This statistic quantifies the proportion of total variability in effect estimates that is attributable to true between-study heterogeneity, beyond what could be expected by chance. The I^2 statistic was computed in RStudio and was found to be $I^2 = 0.5306$, indicating that approximately 53.06% of the total variability observed across studies is due to true between-study heterogeneity beyond chance. This suggests a moderate level of heterogeneity among the included studies. It implies that a substantial portion of the variability in effect estimates can be attributed to differences between studies, such as variations in study populations, interventions, outcome measures, or study designs. Due to this, the potential sources of heterogeneity will be considered when

interpreting these results by subgroup and sensitivity analyses being performed to assess the robustness of the findings.

The Galbraith plot pictured in Figure 11 revealed a pattern wherein studies exhibited vertical alignment, which indicated consistent effect sizes across the included studies but varying levels of precision in their estimates. Specifically, despite differences in sample sizes or measurement methodologies among studies, the estimated effect sizes remained remarkably consistent. This observation suggests a high degree of homogeneity in the estimated treatment effects across the included studies.

Figure 11

Galbraith Plot of the Assessment of Heterogeneity in the Comparative Efficacy of Exercise Intensity Meta-Analysis



Note. x-axis = the effect size estimate of the study. y-axis = the level of precision in the effect size estimate.

Subgroup Analyses

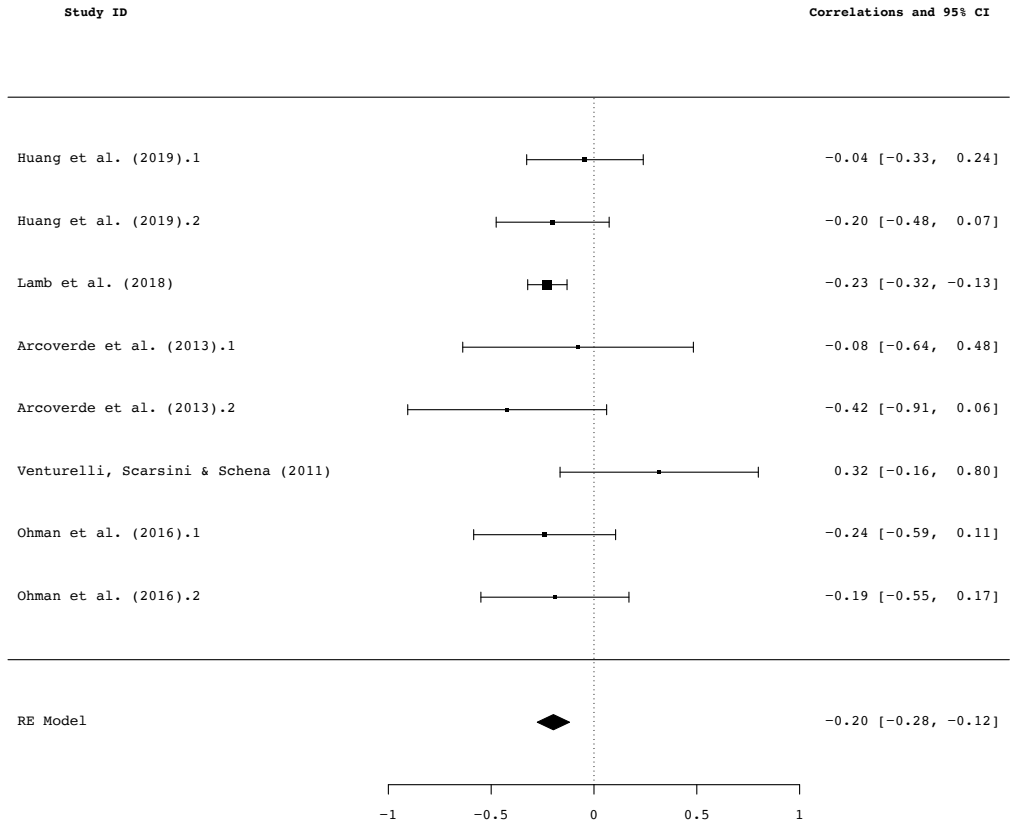
In addition to the main analysis, we conducted subgroup analyses to explore potential sources of heterogeneity and examine whether the effects vary across different diagnoses for cognitive impairment, ages, length of intervention, and the quality of the study. These analyses provide valuable insights into how effects may vary across different subpopulations or intervention characteristics within the meta-analysis.

Cognitive Impairment

An analysis that looked at dementia diagnoses as a subgroup and MCI diagnoses as a subgroup was conducted to determine if there are differing effects of cognition based on the cognitive impairment the individual is experiencing. This can help to determine whether there should be different recommendations for individuals based on their diagnosis. In the subgroup analysis looking into studies that focused on dementia a multivariate meta-analysis model with 8 effect sizes from a total of 5 studies, utilizing the REML method was used to estimate the variance components. The analysis of the dementia model revealed that the variance within studies was negligible. There was no fixed effect considered in this analysis. A test for heterogeneity indicated no significant heterogeneity among the studies included in this subgroup, $Q(7) = 6.93$, $p = 0.436$. Model results demonstrated a significant effect estimate for dementia of -0.20 (SE = 0.04), with a corresponding z-value of -4.94 and $p < .001$. The 95% confidence interval for this effect estimate ranged from -0.28 to -0.12. Overall, these finding suggest that exercise is associated with a significant improvement in cognitive functioning, or a significant reduction in cognitive decline, among individuals with dementia. This subgroup analyses can be seen in Figure 12.

Figure 12

Forest Plot: Studies that Considered Participants Diagnosed with Dementia Only

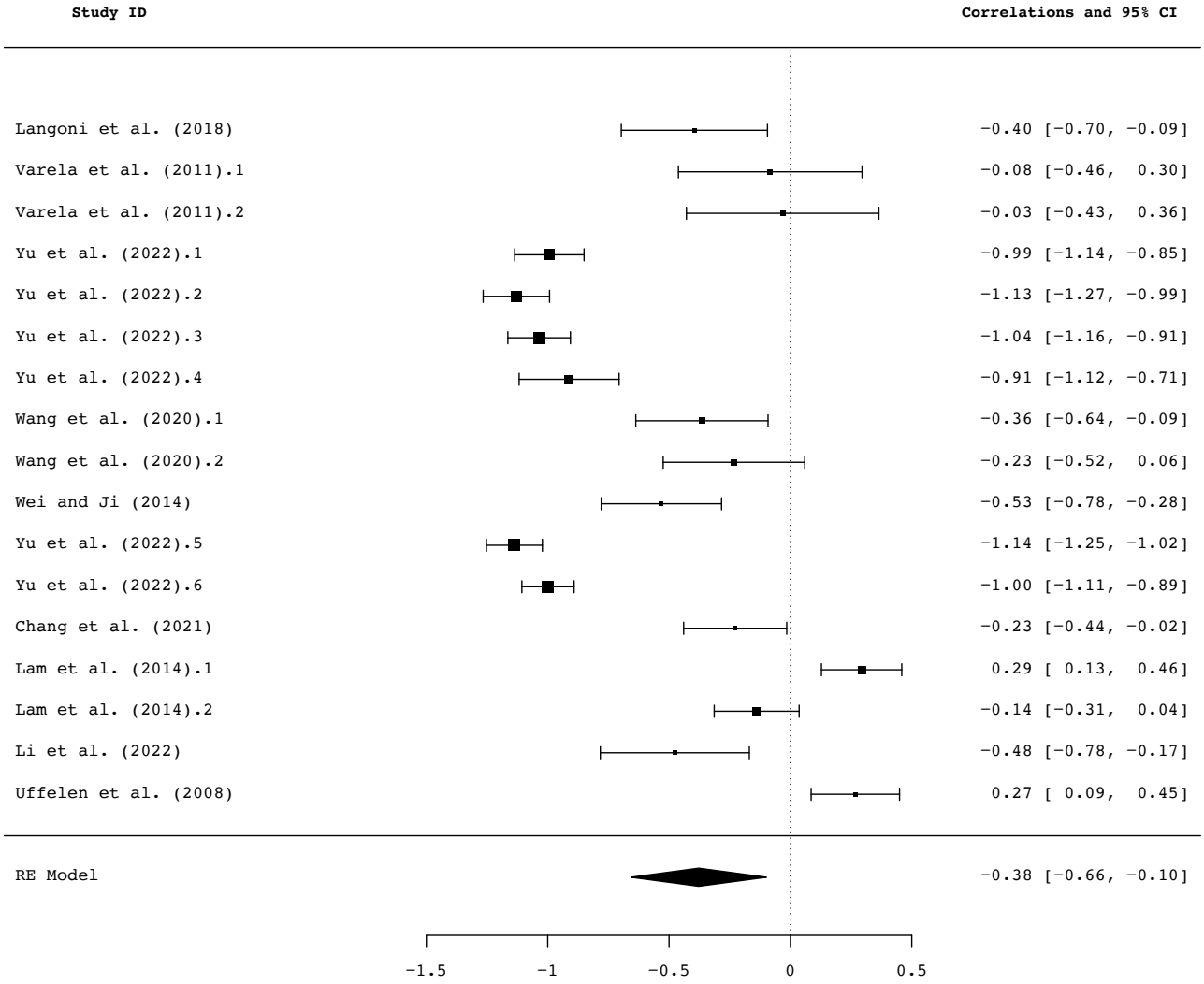


Note. Size of the square indicates sample size. Error bars indicate confidence interval. Diamond indicates overall effect estimate with the width indicating variability of this estimate.

For the MCI subgroup, the multivariate meta-analysis model incorporated 17 effect sizes from a total of 10 studies, utilizing the REML method. The analysis of variance revealed an estimate of 0.19 (SE = 0.43) and no fixed effect was assumed in this analysis. A test for heterogeneity indicated significant heterogeneity among the included studies, Q(16) = 518.65, $p < .001$. This suggests variability in effect sizes across the studies. The model shows a significant estimate of -0.38 (SE = 0.14), z = -2.66, $p < .01$. The 95% confidence interval ranged from -0.66 to -0.10. This indicated that exercise is associated with a significant improvement in cognitive functioning among individuals with MCI (Figure 13).

Figure 13

Forest Plot: Studies that Considered Participants Diagnosed with Mild Cognitive Impairment Only



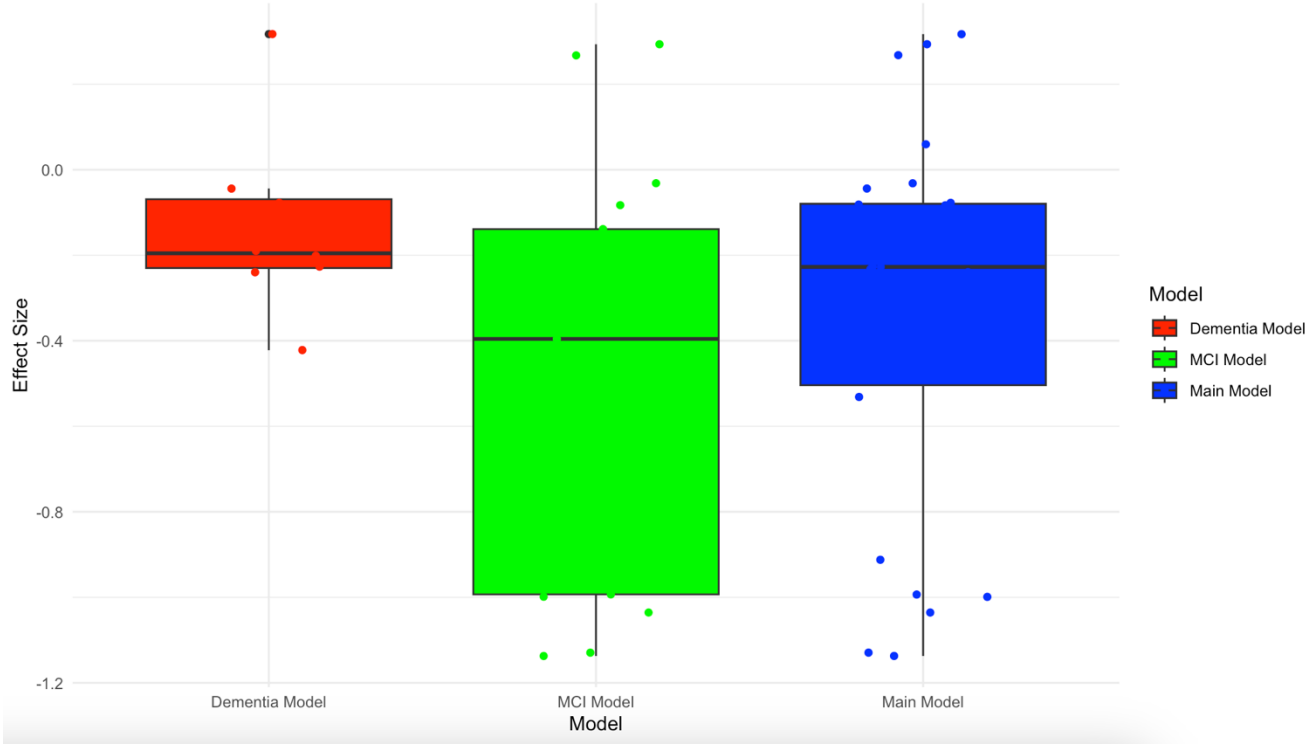
Note. Size of the square indicates sample size. Error bars indicate confidence interval. Diamond indicates overall effect estimate with the width indicating variability of this estimate.

Overall, whilst both models suggest a significant association between exercise and cognitive functioning, the MCI model demonstrates a larger effect size and higher heterogeneity compared to the dementia model. This suggests that the effect of exercise on

cognitive functioning may vary depending on the population being studied. Overall, whilst both subgroups showed significant effects of an exercise intervention on cognitive functioning within their respective populations, the main model reveals a broader scope of impact across a more diverse range of individuals (Figure 14). The main model has a slightly larger effect size (es = -0.28) than the dementia model (es = -0.20), but a smaller effect size than the MCI model (es = -0.38). However, the main model (Q = 676.95, p < .001) displays higher heterogeneity than both the dementia (Q = 6.93, p = 0.436) and the MCI (Q = 518.65, p <.001) models. This indicates greater variability in treatment effects across the included studies in the main model.

Figure 14

Comparison of Effect Sizes for Main Model, Dementia Model and MCI Model



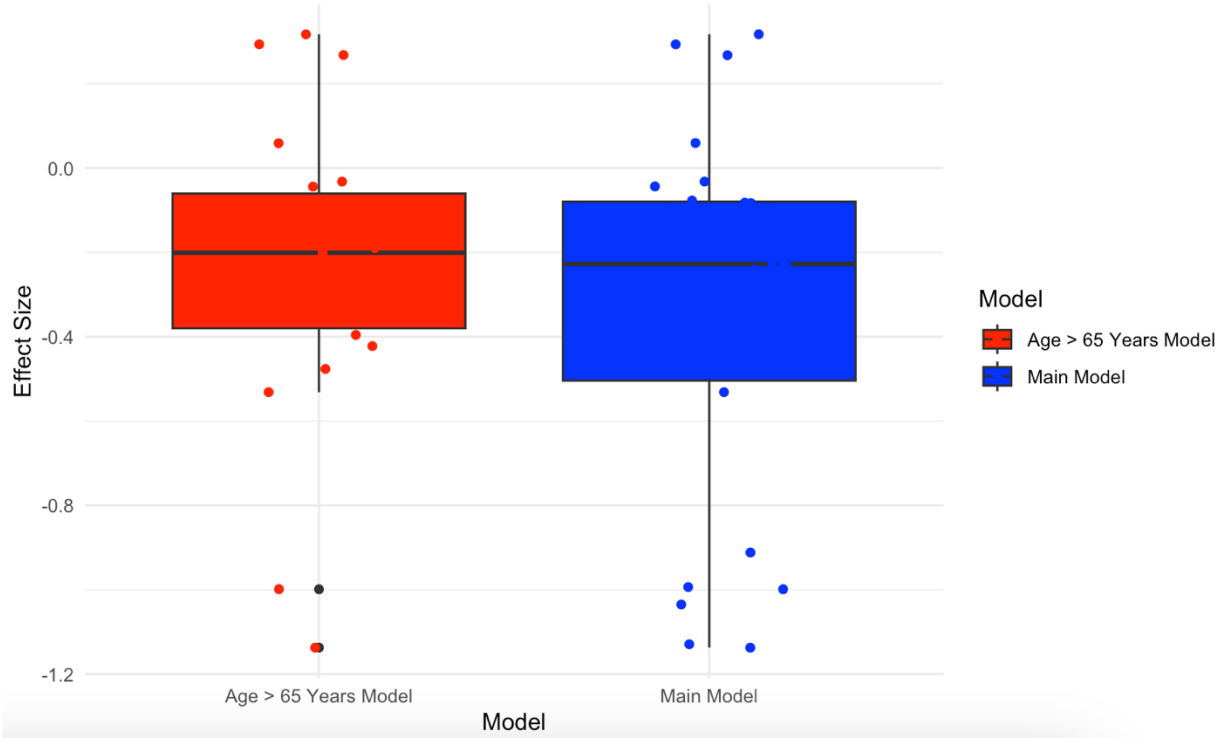
Note. Dots represent individual study effect sizes. Box plot shows the distribution of effect sizes.

Age of Participant

Age was considered as a subgroup to determine whether there is a specific age at which exercise is more beneficial, or to see if there may be a cutoff age where exercise no longer has an effect on cognition. The results of this subgroup analysis can be seen in Figure 15. A multivariate meta-analysis model was utilized to examine the effect of exercise on cognition specifically among participants aged over 65. The analysis included data from 23 samples from 15 studies and employed the REML method. The analysis of variance components indicated an estimate of 0.11 (SE = 0.33). No fixed effects were assumed in this analysis. A test for heterogeneity revealed significant heterogeneity among the included studies, $Q(22) = 461.72$, $p < .001$. This suggests variability in effect sizes across studies.

Figure 15

Comparison of Effect Sizes for Main Model and Participants Aged over 65 Model



Note. Dots represent individual study effect sizes. Box plot shows the distribution of effect sizes.

The model showed a significant effect estimate of -0.23 (SE = 0.09), z = -2.50, p < .05. The 95% confidence interval ranged from -0.40 to -0.05. Compared to the main model, both effect sizes are statistically significant and the 95% confidence intervals for the effect sizes overlap, indicating no statistically significant difference in the magnitude of the effect between the two analyses (Figure 15). The estimated effect sizes are consistent, which suggests that age does not significantly impact the effect of exercise on cognition.

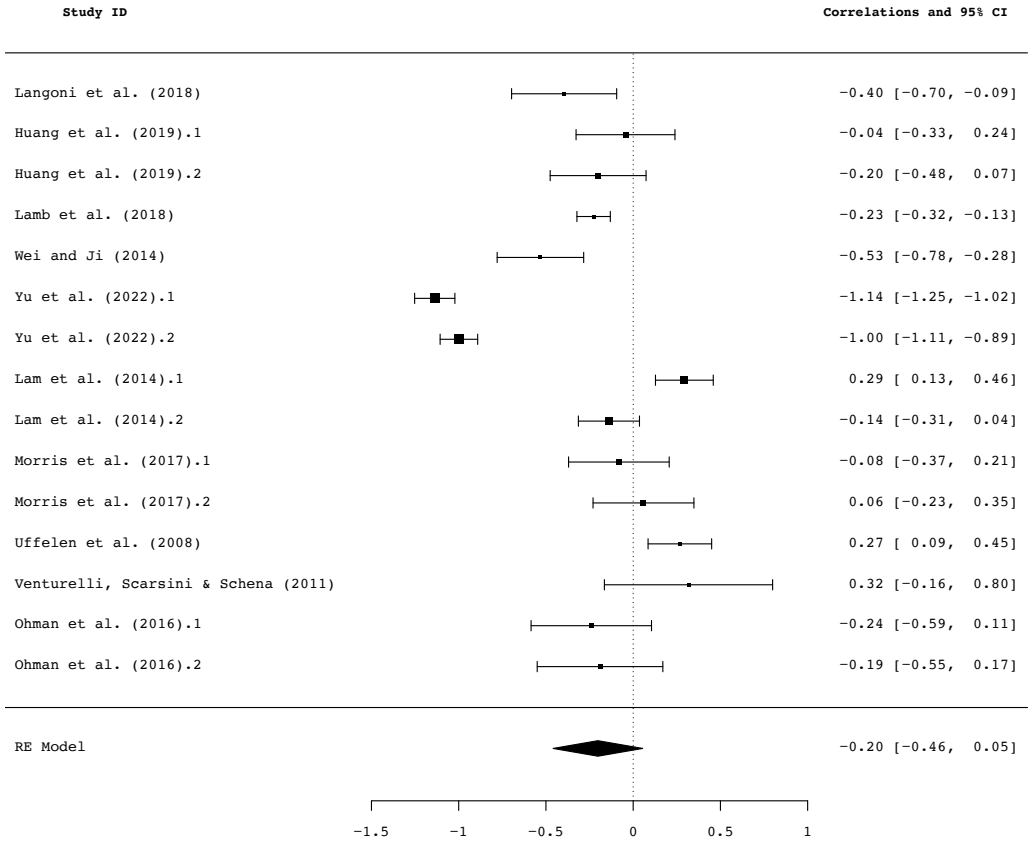
Length of Intervention

The length of the intervention is another important consideration to make when analysing the data. Two subgroups of data were made, one where the studies had employed interventions of 26 weeks or more, and one where the studies had employed interventions of less than 26 weeks total. This has been done to determine whether shorter-term chronic exercise interventions or longer-term chronic exercise interventions are more effective, which can also help to inform on the effects exercise can have on cognition over an extended period of time. As an exclusion criteria for the study, only studies that employed interventions that are longer than 8 weeks were included to fit with the literatures definition for a chronic exercise intervention.

A multivariate meta-analysis model was applied to a dataset consisting of 15 effect sizes across 10 studies examining interventions with a duration greater than 26 weeks (Figure 16). The REML method was utilised for estimation. The indicated estimated variance was 0.16 (SE = 0.40). A significant test for heterogeneity was observed, with Q(14) = 448.80, p < .001. The estimated effect size was -0.20 (SE = 0.13), CI 95% [-0.46, 0.05], p = 0.123. This indicates that there is no significant effect of exercise interventions on cognitive functioning for interventions that span more than 26 weeks.

Figure 16

Forest Plot: Studies with Interventions that Lasted Longer than 26 Weeks

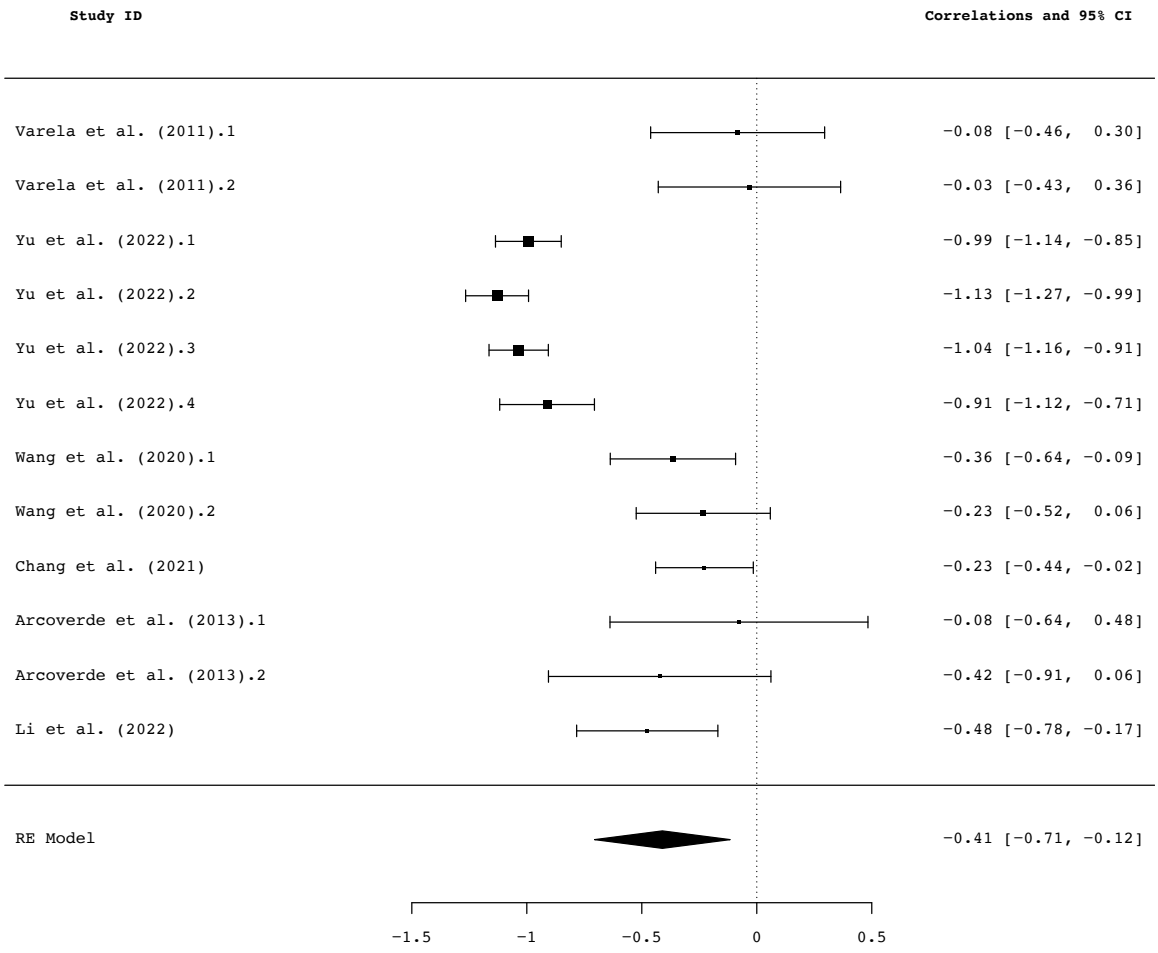


Note. Size of the square indicates sample size. Error bars indicate confidence interval. Diamond indicates overall effect estimate with the width indicating variability of this estimate.

Conversely, a multivariate meta-analysis model looked at a dataset of 12 effect sizes from 6 studies that employed interventions that were shorter than 26 weeks (Figure 17). Again, the REML method was used for estimation. The estimated variance component was 0.12 (SE = 0.35), with a significant test for heterogeneity observed, $Q(11) = 136.66$, $p < .001$. The estimated effect size was -0.41 (SE = 0.15), 95% CI [-0.71, -0.12], $p < .01$. This indicates that there is a statistically significant effect of exercise interventions on cognitive functioning for interventions that lasted less than 26 weeks but more than 12 weeks.

Figure 17

Forest Plot: Studies with Interventions that Lasted Less than 26 Weeks



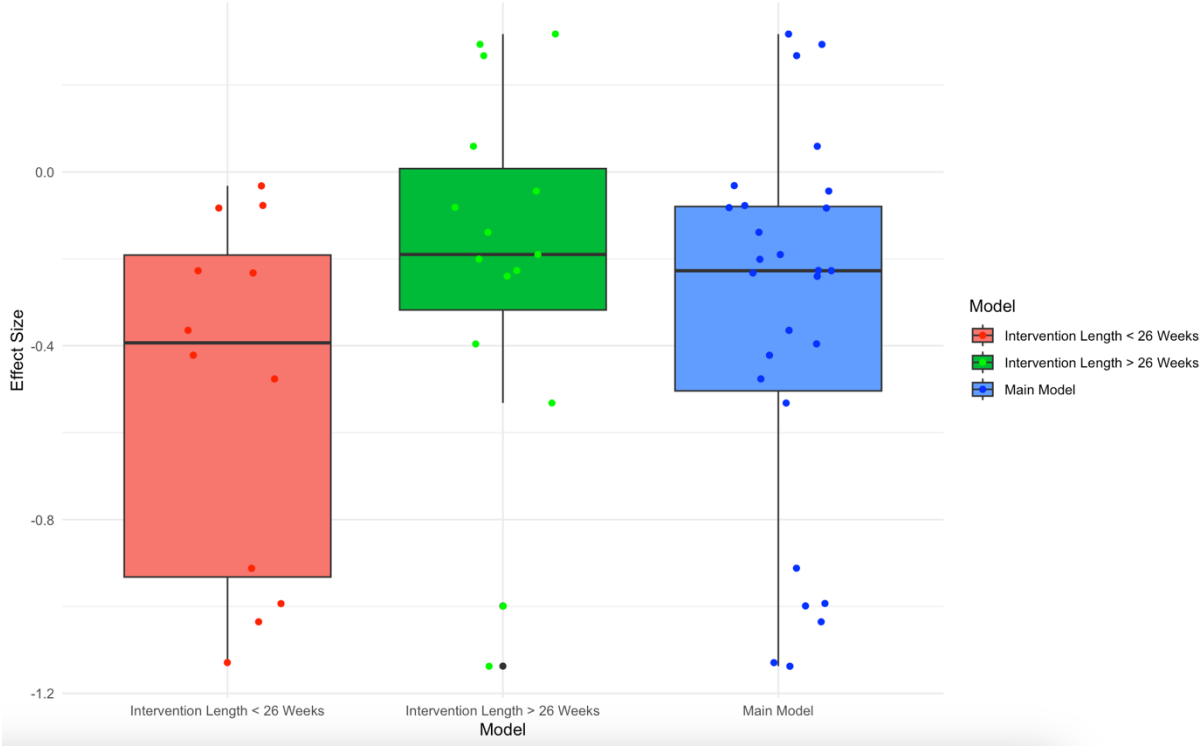
Note. Size of the square indicates sample size. Error bars indicate confidence interval. Diamond indicates overall effect estimate with the width indicating variability of this estimate.

When comparing the two models, it is evident that interventions with a duration of fewer than 26 weeks yielded a statistically significant effect, suggesting a beneficial impact on cognition. Conversely, interventions lasting longer than 26 weeks did not show a statistically significant effect. When comparing these models to the main model, an intervention length greater than 26 weeks exhibits a smaller effect size with a higher p-value, suggesting a weaker association between interventions of longer duration and cognition. However, an intervention of less than 26 weeks had a larger effect size estimate and a lower

p-value than the main model, indicating a stronger association. This is displayed within Figure 18.

Figure 18

Comparison of Main Model, Intervention Length > 26 Weeks Model, and Intervention Length < 26 Weeks Model



Note. Dots represent individual study effect sizes. Box plot shows the distribution of effect sizes.

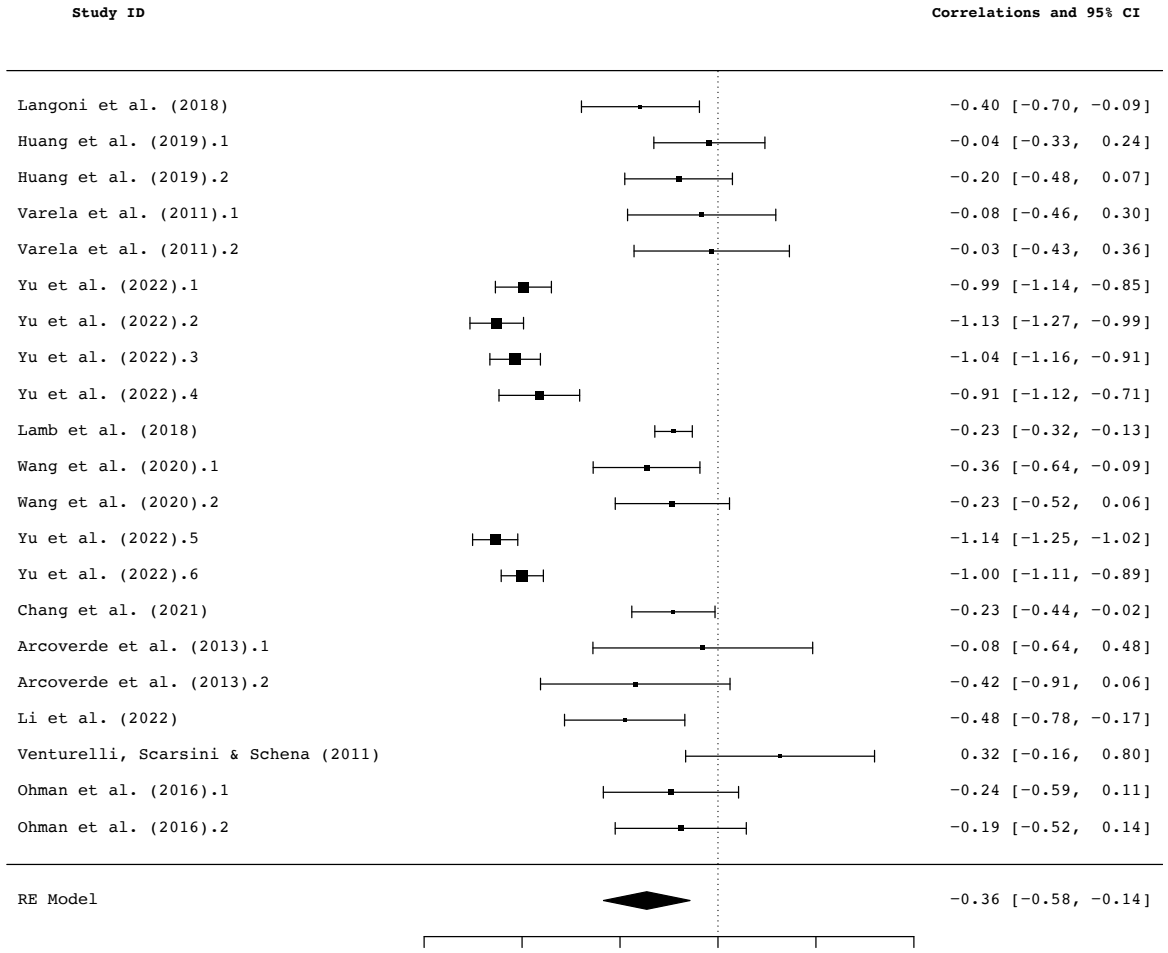
Study Quality

In the subgroup analysis, studies that were found to have high risk of bias were excluded from the dataset. This analysis can help to determine whether the quality of the studies involved in the meta-analysis have a significant effect on the outcome. There was a notable difference in effect size estimate when comparing this to the main model. In the model excluding studies with a high risk of bias, comprising of 21 effect sizes from 14 studies, the estimated effect size was found to be -0.36 (SE = 0.11), indicating a statistically

negative association for the effect of an exercise intervention on cognition ($p < .01$). The 95% confidence interval [-0.58 to -0.14] further supported the robustness of the effect estimate. This analysis can be seen in Figure 19.

Figure 19

Forest Plot: Excluding Studies that have a High Risk of Bias



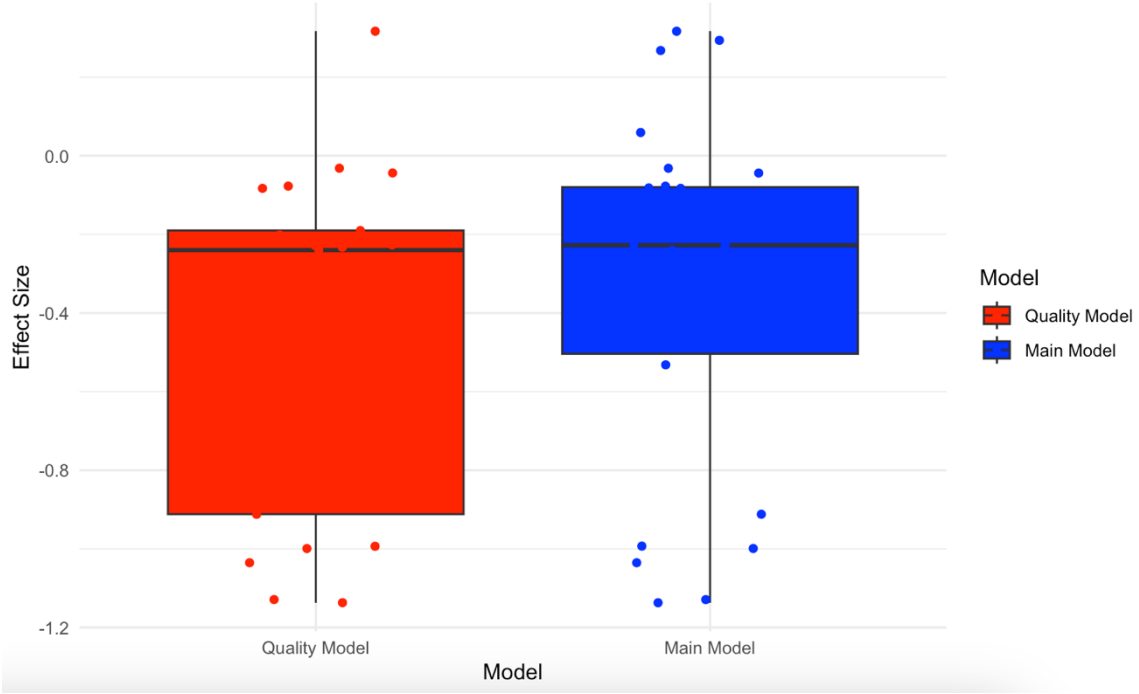
Note. Size of the square indicates sample size. Error bars indicate confidence interval. Diamond indicates overall effect estimate with the width indicating variability of this estimate.

Conversely, in the main model encompassing 27 effect sizes without excluding any studies based on quality, the effect size estimate was slightly smaller, measured at -0.28 (SE = 0.10). While this estimate remains statistically significant, the confidence interval ranged from -0.47 to -0.08, indicating a wider range of uncertainty around the effect estimate. The

difference in effect size estimates between the two models underscores the potential influence of study quality on the observed effect (Figure 20). Excluding studies with a high risk of bias in the subgroup analysis produced a more pronounced effect size estimate, suggesting that the inclusion of studies of varying quality levels may attenuate the observed effect. These findings highlight the importance of considering study quality.

Figure 20

Main Model Compared to Subgroup of Studies Excluding Those That Have a High Risk of Bias RoB.2 Assessment (N = 4)



Note. Dots represent individual study effect sizes. Box plot shows the distribution of effect sizes.

Additional Analyses

Some additional analyses were also run to determine whether the moderator variables had any effect on high-intensity exercise, or low- to moderate-intensity exercise interventions specifically. For these analyses the moderators were run against the high-intensity subgroup and then the low- to moderate-intensity subgroup. This can help to

better determine the differences between the intensities and help to inform on recommendations for best practice.

Frequency of Exercise and Exercise Intensity

When considering high-intensity exercise interventions, the amount of exercise sessions per week was considered as a moderator. Throughout the 18 effect sizes this varied from one to five times per week. A multivariate meta-analysis model using the REML method was used looking at 10 studies. The estimated variance components showed moderate variability among the studies. Six levels were considered for the moderator. A significant amount of variability among the studies was observed ($QE(8) = 51.85$, $p < .001$). The test of moderators approached but did not reach significance ($QM(1) = 2.80$, $p = 0.094$). The intercept was estimated at -0.57 (SE = -0.20, $p < .01$), indicating a significant negative effect. This suggests that, without any exercise sessions, cognitive performance tends to be lower. The coefficient for frequency of exercise sessions per week was 0.09 (SE = 0.05, $p = 0.094$), showing a positive trend although not statistically significant.

This suggests that for high-intensity interventions, the negative intercept estimate suggests that without any exercise sessions per week, the expected cognitive performance after the intervention tends to be worse than before as it represents the baseline cognitive performance level before the intervention. The positive estimate for the coefficient, although not statistically significant, suggests that, on average, there is a trend towards post-intervention cognition scores to be higher (or less improved) with an increase in the frequency of exercise sessions per week. This implies that more high-intensity exercise sessions per week may be associated with less improvement or even deterioration in cognitive performance following the intervention.

When looking at low- to moderate-intensity exercise interventions, a multivariate meta-analysis model using the REML method looked at 17 effect sizes across 12 studies. There was a substantial level of variability among the studies. Significant heterogeneity among the studies was also observed (QE(15) = 555.60, p < .001). The test of moderators did not reach significance (QM(1) = 1.42, p = 0.234), indicating that the frequency of exercise sessions per week does not overall have an effect on cognitive performance for low- to moderate-intensity interventions. Both the intercept estimate (estimate = -0.15, SE = 0.19, p = 0.419) and the coefficient for the moderator (estimate = -0.06, SE = 0.05, p = 0.234) were found to have non-significant results also.

Now it becomes pertinent to consider the minutes spent exercising per week as a moderator. The minutes per week across the 18 studies ranged from 60 to 180 minutes. For the high-intensity subgroup, a multivariate meta-analysis model using the REML method looked at 10 effect sizes across 6 studies. The estimated variance components showed moderate variability among the studies. A significant amount of heterogeneity was also observed (QE(8) = 37.35, p < 001). The test of moderators did not reach overall statistical significance, QM(1) = 1.78, p = 0.182. The intercept estimate showed a trend towards significance (estimate = -0.97, SE = 0.51, p = 0.06), and there was also a non-significant effect for the coefficient for minutes of exercise per week (estimate = 0.01, SE = 0.01, p = 0.182).

In the low- to moderate-intensity subgroup the model looked at 17 effect sizes across 12 studies. There was again substantial variability and significant heterogeneity (QE(15) = 237.07, p < .001). The test of the moderator overall showed statistical significance, QM(1) = 7.62, p < .01. The intercept was estimated at 0.78 (SE = 0.41, p = 0.058), showing a trend towards significant, whereas the coefficient for minutes of exercise per week showed a significant negative effect (estimate = -0.01, SE = 0.003, p < .01). This suggests that in the

low- to moderate-intensity subgroup, increased minutes of exercise per week were associated with significantly better cognitive performance, while in the high-intensity subgroup this association was not statistically significant.

Adherence and Exercise Intensity

When considering high-intensity exercise interventions, a multivariate meta-analysis model was employed comprising of 8 effect studies, utilizing the REML method. The estimate variance was moderate for residual heterogeneity, with 5 studies under consideration for the moderator of adherence. A test for residual heterogeneity revealed significant heterogeneity, $QE(6) = 62.75$, $p < .001$. The test of the moderator adherence showed no significant effect for high-intensity exercise ($QM(1) = 0.61$, $p = 0.433$). This suggests that how well a participant stuck to the exercise plan did not have a significant impact on the outcomes.

When looking at low- to moderate-intensity exercise interventions, a multivariate meta-analysis model comprised of 13 effect sizes utilized the REML method. Similar to the high-intensity group, there was a lot of variability among the studies ($QE(11) = 246.85$, $p < .001$), and adherence to the exercise plan did not have a significant impact on outcomes ($QM(1) = 2.27$, $p = 0.132$). Within this subgroup also, adherence to the intervention did not seem to strongly affect the overall effectiveness of the intervention.

Exercise Type and Exercise Intensity

For the high-intensity subgroup, a multivariate meta-analysis model was employed using the REML method for 10 effect sizes. When considering type as a moderator there were five different types across the 18 studies: walking, cycling, mind-body, aerobic and sport. The estimated variance components indicated a moderate level of variability among the studies. Six studies were considered for the type of exercise moderator. A test for

residual heterogeneity revealed significant variability among the studies (QE(7) = 18.70, p < .01). For the test of moderators, only the coefficients walking and cycling were found within high-intensity interventions. Overall, there was no significant effect (QM(2) = 4.82, p = 0.090). The intercept was estimated at -0.15 (SE = 0.17, p = 0.382), indicating a non-significant result, however the walking coefficient showed a significant negative effect with the estimate -0.55 (SE = 0.27, p < .05). This suggests that when the type of exercise for a high-intensity exercise intervention is walking it has a significant impact on cognitive functioning, however this analysis only includes 6 studies which needs to be considered when interpreting the results.

In the analysis of the low- to moderate-intensity subgroup consisting of 17 effect sizes, a multivariate meta-analysis model was again applied using the REML method. The estimated variance components indicated considerable variability among the studies. Twelve studies were considered for the moderator. A test for residual heterogeneity indicated significant variability among the studies (QE(11) = 530.32, p < .001). The test of moderators did not show a significant overall effect (QM(5) = 3.14, p = 0.678). The intercept was estimated at -0.48 (SE = 0.57, p = 0.401), indicating a non-significant result, and none of the specific types of exercise showed significant effects on outcomes as evidenced by non-significant coefficients and wide confidence intervals.

Overall, in both intensity groups, the type of exercise did not consistently affect the outcomes across all studies. However, this analysis shows that walking as a type of exercise had a significant negative effect on outcomes, therefore a significant improvement in cognitive functioning post-intervention, when employed within a high-intensity exercise intervention. Other types of exercise did not have an impact on the outcome for high-

intensity exercise, and none of the specific types of exercise showed significant effects for low- to moderate-intensity exercise.

Small-Study Bias

Small-study bias represents a critical consideration in meta-analytic research, as it can significantly impact the validity and generalizability of study findings. Various methods were used to assess small-study bias, including the trim-and-fill method, funnel plots, Egger's regression test, and the utilization of a p-curve. Through the application of these methods, this study aims to provide a comprehensive assessment of small-study bias, enhancing the rigor and reliability of the meta-analytic findings.

Trim-and-Fill Method

The trim-and-fill analysis was performed to evaluate the potential impact of small-study bias on the meta-analysis findings. The analysis suggested that there were an estimated 4 missing studies on the left side, with a standard error of 3.47. this indicates potential asymmetry in the distribution of studies, possibly due to small-study bias favoring studies with positive results.

This trim-and-fill analysis was analysed using a random-effects model with a total of 31 effect sizes included. The estimated amount of total heterogeneity (tau^2) was found to be 0.23 (SE = 0.06), indicating substantial variability among the study effect sizes. The square root of the estimated tau^2 value (tau) was 0.48, and the I^2 statistic indicated that 95.69% of the total variability was attributed to heterogeneity across studies. The H^2 statistic suggested that 23.19% of the total variability was due to sampling variability. The trim-and-fill model estimated an overall effect size of -0.46 (SE = 0.09), with a corresponding z-value of -5.14 ($p < .001$). The 95% confidence interval for the effect size ranged from -0.63 to -0.28. The significance of this effect size suggests a statistically significant negative association,

therefore a significant improvement or slowing of cognitive decline in older adults with cognitive impairment after undergoing an exercise intervention.

Funnel Plot

The funnel plot can be used as a graphical tool to assess small-study bias in meta-analysis (Figure 21). Ideally, the plot should resemble an inverted funnel shape, where studies with smaller sample sizes, and therefore potentially larger standard errors, scatter widely at the bottom and larger studies with smaller standard errors cluster closer to the combined effect estimate. The trim-and-fill method was used within this funnel plot to impute potentially missing studies to achieve symmetry. It estimates the number of missing studies that may exist due to small-study bias and recalculates the effect size accounting for these imputed studies. A wide spread of points, as can be seen in Figure 21, indicates heterogeneity among the included studies beyond what can be expected due to chance alone. This heterogeneity could arise from various sources, such as differences in the study design, intervention protocols or population characteristics. The dots that fall outside of the funnel suggest the presence of small-study bias or some other form of bias that affect the distribution of the study results. Studies with statistically significant findings are more likely to be published, leading to an overrepresentation of positive or significant results in the literature, which may be why there is asymmetry in the plot. This can distort the pooled effect estimate and lead to an over or underestimation of the true effect size. The presence of heterogeneity and potential bias highlights the importance of sensitivity analyses and exploration of sources of heterogeneity.

Egger's Test

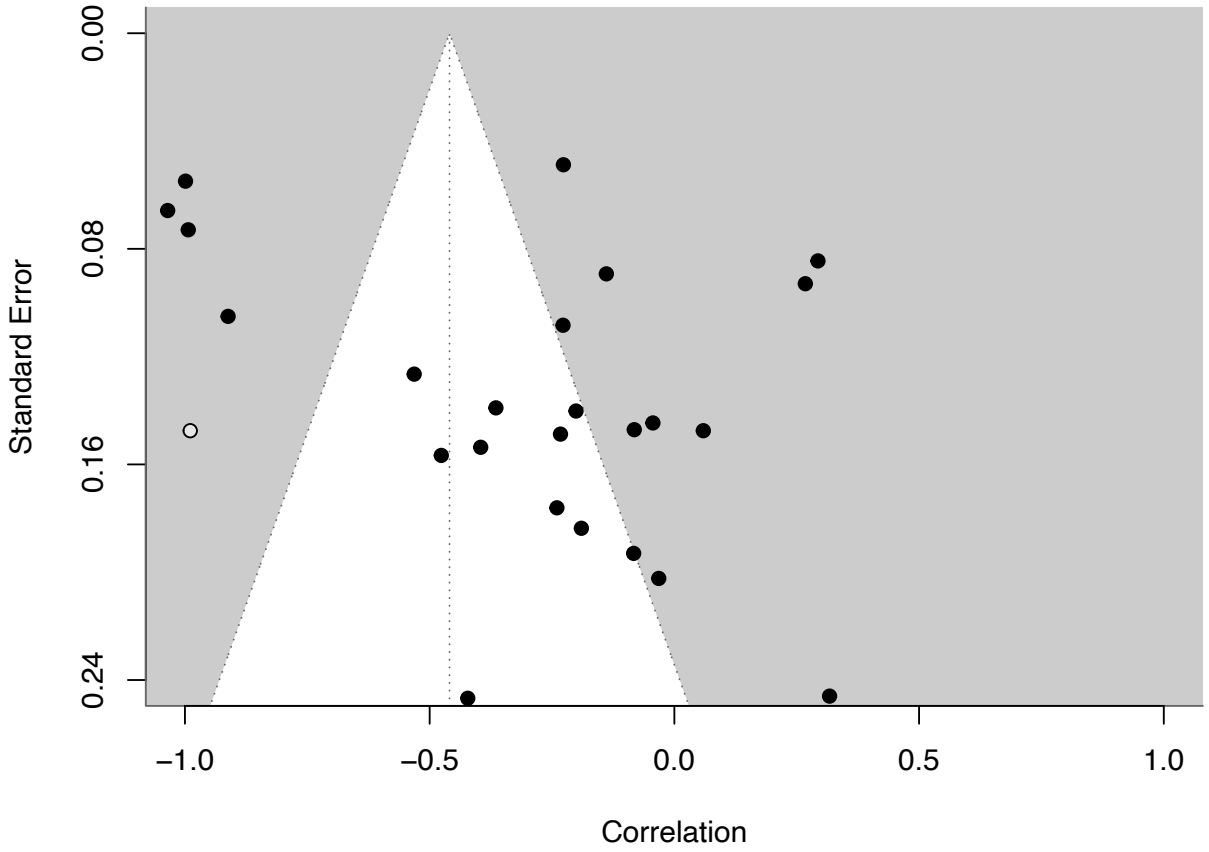
The results of the Egger test for funnel plot asymmetry indicated potential small-study bias within the meta-analysis. The analysis utilised a mixed-effects meta-regression

model to account for both fixed and random effects. The predictor variable examined was the standard error, which is commonly used to assess precision in meta-analyses.

The results are displayed in Table 3. There is a statistically significant result, suggesting the presence of funnel plot asymmetry, and the negative confidence interval values suggest that there is potential bias favouring the publication of studies with smaller standard errors.

Figure 21

Funnel Plot for the Main Model Considering Post-Intervention versus Pre-Intervention Cognitive Functioning Scores



Note. Dots that fall outside of the funnel indicate studies that potentially have small-study bias.

Table 3

Eggers Test Results

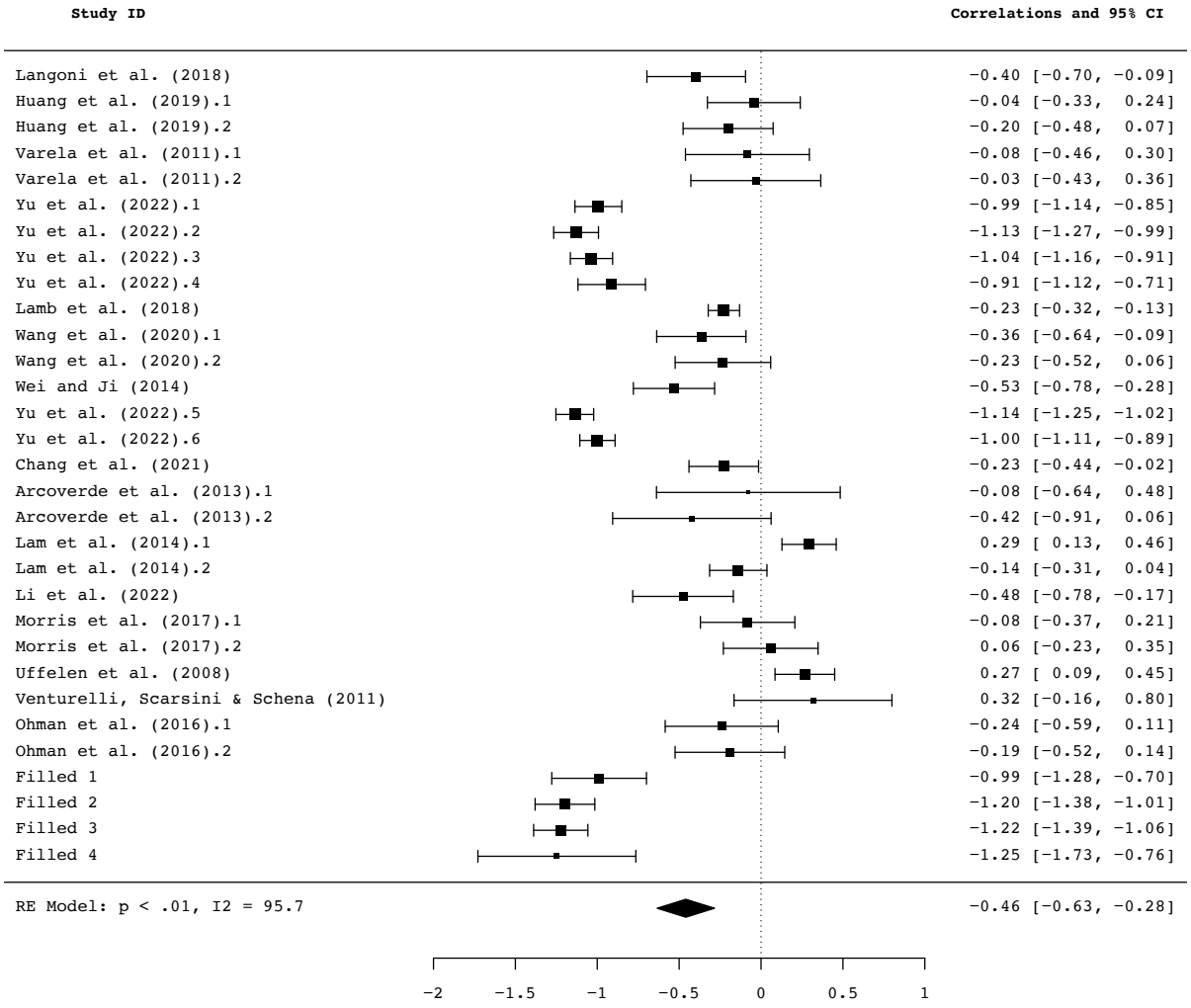
Variable		Test for Funnel Plot Asymmetry		Limit Estimate (as sei -> 0)	
Model	Predictor	z-value	p-value	Coefficient (b)	95%CI
Mixed-effects meta-regression model	Standard error	2.796	0.005	-0.844	-1.214, -0.474

The trim-and-fill model was also compared to the main model to see the extent to which they agree with or deviate from each other. The main model estimated an effect size of -0.36, while the trim-and-fill model estimated a slightly larger effect sizes of -0.46. This suggests that after accounting for potential small-study bias through the trim-and-fill analysis, the effect size estimate increases indicating a potentially more conservative estimate in the main model. In the main model, the confidence interval for tau^2 ranged from 0.10 to 0.34, while in the trim-and-fill model it ranged from 0.14 to 0.41. Similarly, the confidence interval for tau in the main model was narrower (0.32 to 0.58) compared to the trim-and-fill model (0.37 to 0.64). This indicates that the uncertainty surrounding the estimates of heterogeneity increased slightly in the trim-and-fill model. The p-value associated with the effect size in the main-model indicated statistical significance ($p < .001$). The p-value in the trim-and-fill model was also statistically significant ($p < .001$), however it was also much smaller, indicating even greater statistical significance when accounting for potential small-study bias. This trim-and-fill model can be seen in Figure 22 in comparison to the main model which has been re-shown in Figure 23 (also in Figure 4).

In summary, these results imply there is a likelihood of small-study bias within the meta-analysis, with studies exhibiting smaller standard errors potentially being overrepresented in the literature. The slightly larger effect size estimate and increased statistical significance in the trim-and-fill model suggest that accounting for small-study bias led to a more conservative estimate of the effect size. This shows the importance of considering the possibility of small-study bias when interpreting the findings of a meta-analysis.

Figure 22

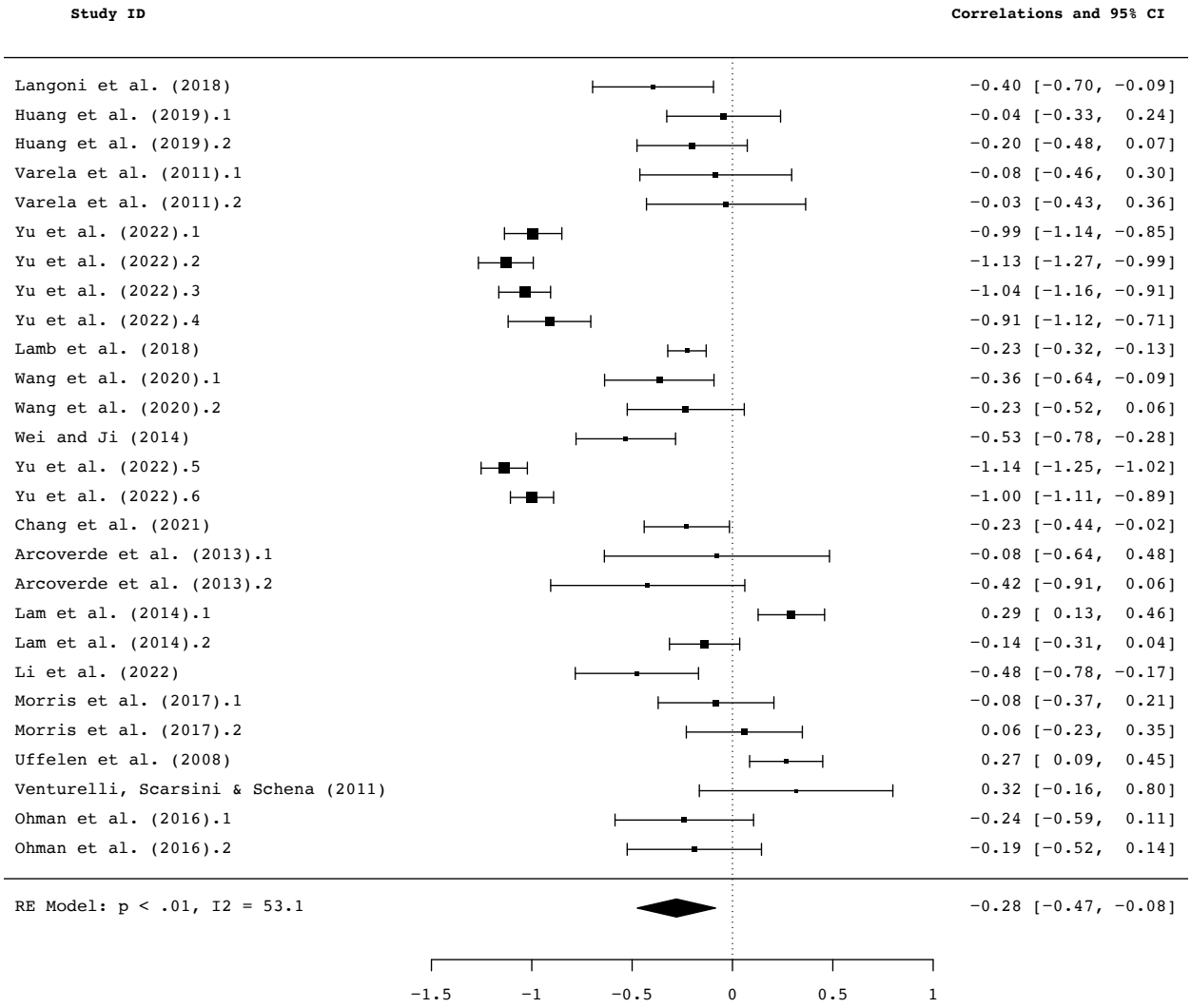
Forest Plot: Exhibiting the Effect Sizes and Confidence Intervals of Studies Included in the Trim-and-Fill Model Comparing Post-Intervention Scores to Pre-Intervention Scores



Note. Size of the square indicates sample size. Error bars indicate confidence interval. Diamond indicates overall effect estimate with the width indicating variability of this estimate.

Figure 23

Re-Showing of the Forest Plot Exhibiting the Effect Sizes and Confidence Intervals of Studies Included in the Meta-Analysis Comparing Post-Intervention Scores to Pre-Intervention Scores in the Intervention Groups



Note. Size of the square indicates sample size. Error bars indicate confidence interval. Diamond indicates overall effect estimate with the width indicating variability of this estimate.

P-Curve Analysis

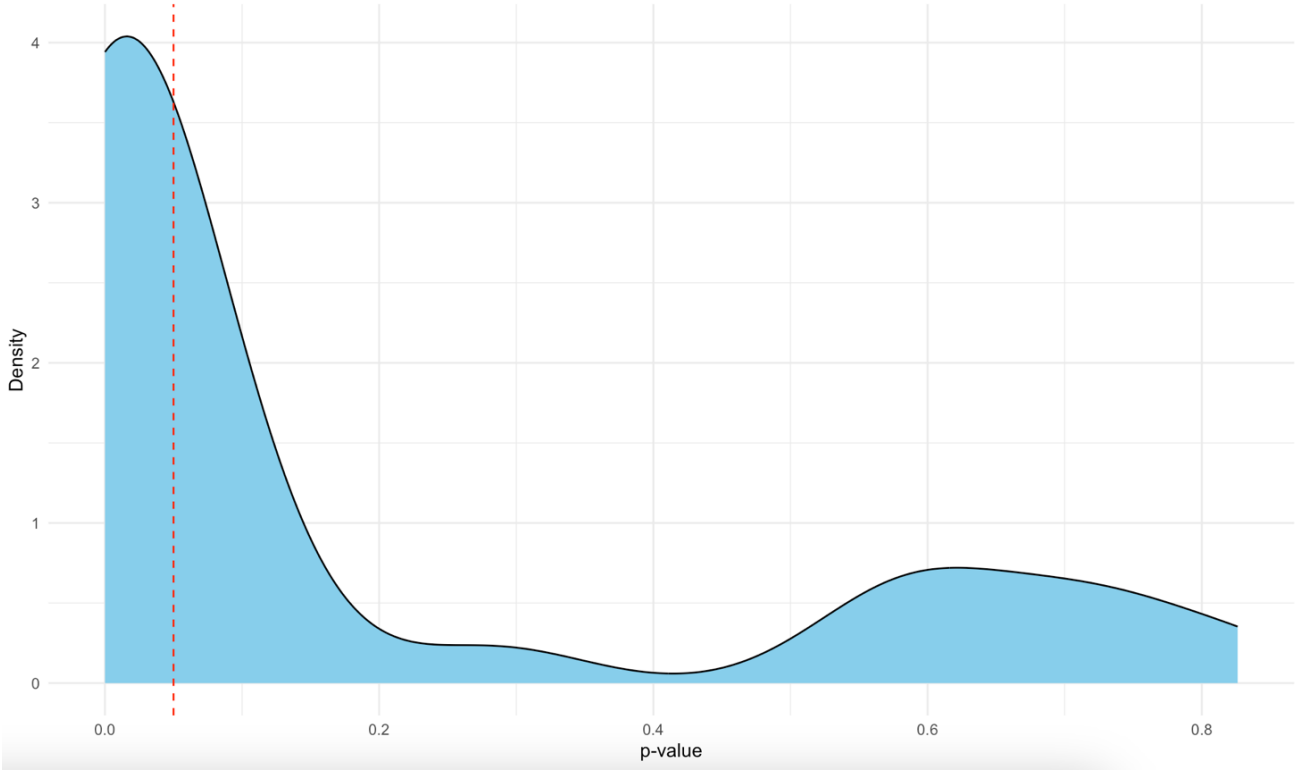
The p-curve analysis was conducted to assess the evidential value of the included studies. The p-curve plot, displayed in Figure 22, illustrates the distribution of p-values derived from the aggregated study outcomes. The shape of the p-curve provides insight into

the presence or absence of evidential value. A right-skewed distribution, characterised by a higher frequency of smaller p-values, typically suggests robust evidential value. Conversely, a flat or left-skewed distribution may indicate a lack of evidential support.

In this analysis, the p-curve revealed distinctive patterns in the distribution of p-values derived from the meta-analysis results. Initially, there is a substantial drop in density indicating a pronounced concentration of statistically significant results. The steep decline in density, accompanied by a concentration of statistically significant results below the conventional significance threshold (p = .05), suggests evidential support for the presence of genuine effects in the meta-analysis findings. This initial drop indicates a higher proportion of smaller p-values, indicating strong evidence against the null hypothesis.

Figure 22

P-Curve Plot Illustrating the Distribution and Density of P-Values Derived from the Meta-Analysis Results



Following the initial drop, the p-curve exhibits a narrow and relatively straight section to suggest a relative paucity of statistically significant results within this range of p-values. This suggests a lack of statistically significant results within this range and may indicate a less conclusive body of evidence or a potential plateau in the strength of evidence within this range. However, an intriguing pattern emerges thereafter, characterised by a rise in density followed by a subsequent fall. This indicates variability in the strength of evidence within this range. The rise may suggest an increase in the proportion of statistically significant results or the presence of selective reporting bias or p-hacking. Conversely, the fall suggests a decrease in the proportion of statistically significant results or potential regression to the null.

While the initial drop below the convention significance threshold provides some evidence for genuine effects, the presence of variability and fluctuations in density across different ranges of p-values underscores the nuanced nature of the meta-analysis findings. It highlights the need for cautious interpretation and further exploration of potential sources of bias or heterogeneity within the included studies.

Discussion

This systematic review aimed to investigate the effect of different intensities of exercise interventions on global cognitive performance for older adults with diagnosed cognitive impairments. Overall, exercise was shown to improve cognition post intervention for individuals with cognitive impairment, however this effect was more pronounced when the exercise intervention was low- to moderate-intensity. Moderator variables did not have an effect overall on the cognitive outcomes, however when controlling for intensity some of these moderator variables had a significant effect. Additional subgroup analyses were considered, such as the diagnosis of the individual or the length of the intervention, and

these results help to inform best practice for this population when engaging in an exercise intervention. The following subsections detail these results and their implications, as well as some overall limitations and directions for future research.

Included Studies

Eighteen studies employing a randomised controlled or intervention design were included in this meta-analysis, with a total number of 47 independent samples and 29 different effect sizes. As some studies employed a high-intensity and a low- to moderate-intensity exercise intervention for two separate samples, and other studies had both a dementia sample and an MCI sample, there are more effect sizes than studies in this meta-analysis. Some studies also had differing methodologies, such as frequency of the intervention or type of exercise, which meant there were additional effect sizes to consider. All of these studies had participants that were older than 50 years of age and had been diagnosed with either MCI or dementia, alongside a control group that was either not receiving any intervention at all or they were receiving a non-exercise intervention. Cognitive function was the main outcome for all of these studies, and they all used a validated neuropsychological test, such as the MMSE, ADAS-Cog or MoCA, to assess cognition pre-intervention and post-intervention. Across the 18 studies there was a total of 2360 participants.

Of the 18 studies included in the meta-analysis, six employed a high-intensity exercise intervention, ten considered a low- to moderate-intensity exercise intervention and two studies looked at both high-intensity and low- to moderate-intensity exercise. A third of the studies employed aerobic exercise as their intervention (6/18), with mind-body interventions (such as tai chi) making up five of the 18 of the studies. The studies came from a range of different countries which allows for further generalisability of the findings from

this meta-analysis. All of the studies except for two (F. Yu, Salisbury, et al., 2021; F. Yu, Vock, et al., 2021) had pre-intervention and post-intervention means and standard deviations allowing for an effect size to be calculated, or had provided an effect size. The two papers that did not provide this information instead provided change scores which were able to be converted into effect sizes. Moderator information about frequency, duration and type was available for all of the included studies. Adherence rates was not available for all of the studies but was extracted for 75% of the included studies.

Exercise Interventions

The findings from the meta-analysis shed light on the significant impact of exercise interventions on cognitive performance among older adults with cognitive impairment. Through the synthesis of data from 18 studies comprising 29 effect sizes, a multivariate meta-analysis model was applied to investigate the aggregated outcomes. The effect size estimate indicated a substantial improvement in cognitive performance among individuals in the intervention group compared to those in the control groups, and this effect was statistically significant. This magnitude of improvement, equivalent to approximately 2.6 standard deviations, underscores the clinical significance of exercise as a potent intervention for cognitive impairment in older adults. Notably, the effect size surpasses thresholds indicative of meaningful clinical change, emphasizing the practical relevance of exercise-based interventions in slowing cognitive decline. The presence of heterogeneity across the studies underscores the need to interpret these findings cautiously, however subsequent subgroup and sensitivity analyses take this heterogeneity into account.

Neurobiological Explanations

This meta-analysis aligns with and extends upon the theoretical frameworks and empirical evidence outlined in the existing literature regarding the association between exercise interventions and cognitive functions in older adults with cognitive impairment.

The cardiovascular fitness hypothesis posits that improvements in cerebrovascular fitness induced by exercise may enhance cognitive function. While this meta-analysis did not directly assess cardiovascular fitness, the observed enhancement in cognitive performance supports this hypothesis. Previous research has documented associations between exercise-induced modifications in cerebral vasomotor reactivity and enhancements in memory and executive function, implying that cardiovascular adaptions stimulated by exercise may contribute to cognitive benefits (Barnes et al., 2003; Etnier et al., 2006; Tomoto et al., 2021). Exercise has additionally been shown to mitigate cardiovascular risk factors, such as hypertension and diabetes. These risk factors have been associated with cognitive decline and were also identified as part of the 12 modifiable risk factors by Livingstone et al. (2020), leading to 3% of worldwide dementias. This all works together to reduce neuropathological damage, and demonstrates the links and connections between these risk factors, whereby altering one can have a subsequent effect on another and so on and so forth like a cascade. These results also support the evidence seen that exercise may induce alterations in cerebral vasomotor reactivity (Tomoto et al., 2021). Cerebrovascular dysfunction is one potential underlying mechanism behind AD, and changes in reactivity within this region can be associated with improved memory and executive functioning, which are areas that feature within the cognition measures used in this meta-analysis. The relationship between exercise and cardiovascular fitness is an important one, especially when it has been posited that an

increase in cardiovascular fitness is the first event in a cascading series of events that will promote cognition (Etnier et al., 2006).

Likewise, the oxygen saturation and angiogenesis hypothesis proposes that exercise-induced elevations in cerebral blood flow and oxygenation may facilitate cognitive functioning by augmenting nutrient delivery to brain regions implicated in executive functioning (Lautenschlager et al., 2008; Moriarty et al., 2019). This heightened metabolic activity may foster synaptic plasticity and neuronal resilience. Our findings of improved cognitive performance in the intervention group align with this hypothesis, highlighting the potential role of enhanced oxygenation and blood flow in mediating the cognitive benefits of exercise. Whilst it is still undetermined whether these increases in cerebral blood flow is the main reason for increased cognitive performance after exercise, it is evident that there is some benefit to this process and that the adaptations of how oxygen is utilised in the brain during exercise may have the ability to influence brain functioning during ageing.

Furthermore, the upregulation of neurotropins hypothesis suggests that exercise-induced elevations in neurotropic factors, such as BDNF, may underpin the cognitive benefits of exercise interventions (Foster et al., 2011; Moriarty et al., 2019; Vaynman et al., 2004). Studies have shown that exercise can elevate BDNF levels in the hippocampus, fostering neuronal growth and synaptic plasticity. Elevated BDNF may also foster neurogenesis and synaptic remodelling in brain regions implicated in learning and memory. This mechanism provides a plausible explanation for the observed enhancements in cognitive performance among older adults following exercise interventions, suggesting that exercise may exert its cognitive benefits through neurobiological pathways.

Psychological and Social Explanations

Exercise can provide psychological benefits, such as reduced stress and improved mood, which may indirectly enhance cognitive function. Psychological wellbeing is closely intertwined with cognitive performance, and interventions that promote mental health, such as exercise, may confer cognitive benefits through mechanisms beyond purely neurobiological pathways. This is particularly true for improvements in mood and the ability to cope with stress (Plante et al., 2007). Exercise has additionally demonstrated large to moderate effect sizes for improving depressive symptoms and other mood disorders such as bipolar disorder (Hearing et al., 2016). This represents another modifiable risk factor identified by Livingstone et al. (2020) that leads to 4% of worldwide dementias. Individuals who have major depressive disorder (MDD) or bipolar disorder also have a higher incidence of cardiovascular disease, diabetes and metabolic syndromes, which are additional modifiable risk factors for dementia (Hearing et al., 2016; Livingston et al., 2020). Despite there being some promising pharmacological advances in the area of mood disorders, many do not achieve remission and these medications can be associated with weight gain or poorer physical health (Hearing et al., 2016). Due to this, exercise represents a cost-effective and easily providable intervention to help reduce these factors that lead to a higher dementia risk. Accounting for hypertension, diabetes, cardiovascular risk and depression amounts to 8% of worldwide dementia cases (Livingston et al., 2020).

Moreover, social engagement inherent in group-based exercise interventions may provide cognitive stimulation and social support, which are conducive to cognitive health in older adults. The burden of social isolation for older adults has become a considerable concern within the healthcare community, and it has also been identified as a risk factor for dementia leading to 4% of worldwide dementia cases (Livingston et al., 2020). Higher levels

of participation in household physical activity has been associated with older adults being less socially isolated (Robins et al., 2018). The interactive nature of group exercise sessions fosters cognitive engagement and may mitigate social isolation. In fact, it is possible that the psychological improvements associated with exercise may have at least some relationship with social factors, where there is increased calmness and enjoyment for the individual when exercising with a friend or in a group (Plante et al., 2007). These psychological benefits can have an impact on cognitive functioning. In a large population of older adults, higher levels of psychological wellbeing has been associated with better cognitive functioning, and this pattern has been observed across all cognitive domains (Llewellyn et al., 2008).

These findings additionally corroborate previous research looking into social engagement and social connectedness (Fratiglioni et al., 2004; Kelly et al., 2017; Schwartz & Litwin, 2019; Zunzunegui et al., 2003). Social interaction is often fostered when engaging in physical activity programs, and this social contact may contribute to the improvement in cognition seen after an exercise intervention (Jenkins et al., 2002). This shows that there are pathways other than neurobiological where exercise can be seen to indirectly influence cognitive functioning, and it could be part of the reason why we see improved cognition for older adults with cognitive impairment after participating in an exercise-based intervention.

Multifaceted Approach

The key takeaway from this meta-analysis and previous research is that physical activity for older adults can have a wide-ranging and multifaceted impact on cognition and dementia risk. Of the 12 modifiable risk factors for dementia that have been identified by Livingston et al. (2020), six of them are affected by participation in physical activity: hypertension, obesity, depression, social isolation, physical inactivity and diabetes. This means that of the potentially modifiable 40% of worldwide dementia that those 12 risk

factors amount to, 14% of it can be directly impacted by engaging in exercise. This is only one part of the impact that exercise may have as it does not factor in the added neurobiological benefits that exercise can bring. Exercise can promote oxygenated blood flow to executive functioning areas of the brain, areas that are critical for those with dementia or MCI. It can also strengthen cognitive reserve and protect neurons and synapses that would otherwise deteriorate from the effects of tau or Aβ. Whilst there is uncertainty around the strength of the independent effects of each of these aspects, what is known is that exercise has a positive impact on all of them as well as having its own independent effect on cognition. This means that it may be one of the most effective tools that can be used when trying to slow or stop the progressive decline that is seen with neurodegenerative disorders like dementia and MCI.

The observed enhancements in cognitive performance following exercise interventions among older adults with cognitive impairment may be attributed to a multifaceted interplay of neurobiological, cardiovascular, psychological, social, and cognitive factors. Future research should further explore the specific mechanisms through which exercise exerts it's cognitive benefits and look into personalised approaches to exercise interventions tailored to the unique needs of individuals with cognitive impairment. Longitudinal studies are warranted to examine the long-term effects of exercise interventions on cognitive function and dementia risk reduction, paving the way for targeted interventions aimed at promoting healthy ageing and preserving cognitive function in older adults.

Exercise Intensity

The main goal of this meta-analysis was to shed light on the impact of exercise intensity on cognitive performance among older adults with cognitive impairment. This was

done by looking at pre and post-intervention scores and considering intensity as a moderator within the meta-analytic model. It was also assessed by looking at high-intensity as a separate subgroup, and low- to moderate-intensity as a separate subgroup and comparing the models. By employing a multivariate meta-analytic approach, we systematically compared the effects of high-intensity and low- to moderate-intensity exercise interventions on cognitive outcomes. The results revealed intriguing insights into the differential effects of exercise intensity. Overall, both high-intensity and low- to moderate-intensity exercise interventions demonstrated significant heterogeneity in effect sizes across studies. However, the significance and magnitude of the effect varied between the two intensity levels.

High-intensity exercise interventions exhibited a trend towards a negative association, or an improvement in cognitive functioning by the end of the exercise intervention compared to the beginning, however this trend did not reach statistical significance. In contrast, low- to moderate-intensity exercise intervention demonstrated a statistically significant negative association with cognitive functioning, supported by a robust effect estimate and a confidence interval excluding zero. This suggests that low- to moderate-intensity exercise interventions led to a significant improvement in cognitive functioning of older adults with cognitive impairment when comparing their post-intervention cognition scores to their pre-intervention cognition scores. These findings suggest that while both high-intensity and low- to moderate-intensity exercise intervention may impact cognitive functioning, the effect may be more reliably observed with low- to moderate-intensity exercise regimens.

Contextualising within Prior Research

The observed differential effects of high-intensity and low- to moderate-intensity exercise interventions on cognitive functioning among older adults with cognitive impairment resonate with and extend the existing literature. The literature presents a complex landscape, with mixed findings regarding the optimal intensity level for maximising cognitive benefits. High-intensity exercise has been postulated to elicit superior cognitive benefits compared to low- to moderate-intensity exercise, owing to its potential to induce greater physiological adaptations and neural plasticity (K. Broadhouse et al., 2020; Kovacevic et al., 2020). Studies have reported enhancements in memory, executive function, and brain health following high-intensity exercise interventions, suggesting a dose-dependent relationship between exercise intensity and cognitive outcomes. Conversely, research also underscores the potential cognitive benefits of low- to moderate-intensity exercise, particularly in domains such as executive function and attention. Moderate-intensity exercise has been associated with improved executive function and memory performance, attributed to its ability to enhance cerebral blood flow and oxygenation in the brain regions crucial for cognitive processing (Y.-K. Chang & Etnier, 2009; C.-C. Wang et al., 2013). Moreover, low- to moderate-intensity exercise may mitigate the risk of cognitive fatigue or overexertion associated with high-intensity exercise, promoting sustained engagement in physical activity among older adults with cognitive impairment.

Several factors may contribute to these differential effects. One potential explanation is the differential impact of exercise intensity on neurophysiological pathways implicated in cognitive function. High-intensity exercise may induce transient hypofrontality, leading to temporary reductions in neural activation and oxygenation in non-motor areas of the brain (Jung et al., 2022). This may result in decrements in cognitive performance reliant on

executive function, counteracting the potential long-term benefits of increased oxygenation to executive function areas (C.-C. Wang et al., 2013). In contrast, low- to moderate-intensity exercise may optimise oxygenation to both executive function areas, and motor and sensory cortices, promoting sustained cognitive engagement and enhancing cognitive outcomes over time. This relates to the oxygenation saturation and angiogenesis hypothesis. Increased flow of oxygenated blood to areas of the brain that are non-motor related, such as executive functioning and memory areas, will promote the distribution of the nutrients and resources to these areas that promote cognition and lead to improved functioning (Moriarty et al., 2019). Transient hypofrontality means that high-intensity exercise will not reap the benefits of oxygenated blood in executive functioning areas, as it will be drawn to motor regions in order to reach the high level of physical activity that needs to be maintained during high-intensity exercise. This supports evidence that there is a significant quadratic relationship between exercise intensity and higher-order cognitive measures (Hains & Arnsten, 2008; C.-C. Wang et al., 2013; Yuen et al., 2009). High-intensity exercise may lead to decrements in cognitive performance that relies on executive functioning, whereas low- to moderate-intensity exercise does not demonstrate the same drop off in cognitive abilities.

Another consideration is the possible connection between the upregulation of neurotropins hypothesis and the oxygenation and angiogenesis hypothesis. BDNF is stored within the blood, mainly in platelets but it could also be diffused through blood plasma (Brigadski & Leßmann, 2020). Blood BDNF levels is particularly influenced by activity-dependent release of BDNF, as in this instance BDNF is released from hypothalamic neurons that are not shielded from the bloodstream by the blood brain barrier (Brigadski & Leßmann, 2020). This opens up a connection with the oxygen saturation and angiogenesis hypothesis, where it logically follows that increased blood flow to executive functioning

areas of the brain also means increased levels of BDNF being transported to those same areas. Both of these hypotheses point to low- to moderate-intensity exercise being more beneficial, with this intensity leading to increased oxygenation and nutrients for executive functioning areas of the brain, and the extended period of time at this low level of intensity allowing for the effects of BDNF to strengthen neurons. This could be due to the interplay between these two hypotheses, where increased oxygenated blood flow in these areas transports increased levels of BDNF and allows for long-term cognitive benefits through extra nutrients, support and synaptic plasticity.

It is also possible that low- to moderate-intensity exercise promotes more relaxation and positive mood states, leading to enhanced cognitive performance, whereas high-intensity exercise can induce significant stress on the body. Cortisol is the principal glucocorticoid in humans and it plays an important role in immune function and metabolism. Acute exercise can induce changes in cortisol concentrations, and the amount in which it changes is dependent on the type of exercise that has been performed (McGuigan et al., 2004). Studies have shown that after a bout of high-intensity exercise, salivary cortisol levels are significantly elevated, compared to low-intensity exercise which does not elicit any significant changes in cortisol levels or moderate-intensity exercise that shows lower levels of cortisol (Hackney & Viru, 1999; McGuigan et al., 2004). Why this is important is because higher levels of cortisol have been associated with worse performance in a number of cognitive domains, particularly for older adults (Lee et al., 2007). The ageing brain may be more vulnerable to the effects of stress, and chronic overactivation or underactivation of cortisol may lead to dysregulation and adverse health outcomes (Lee et al., 2007; McEwen & Stellar, 1993). This suggests that high-intensity exercise for an older population may lead to

increased cortisol levels and subsequently increased stress, potentially leading to poorer cognitive outcomes.

Moreover, individual differences in cognitive reserve, baseline fitness levels, and exercise adherence may modulate the effects of exercise intensity on cognitive functioning. Older adults with lower baseline fitness levels or limited cognitive reserve may experience greater cognitive benefits from low- to moderate-intensity exercise, which may be more tolerable and sustainable for this population. Additionally, adherence to high-intensity exercise regimens may be challenging for older adults with cognitive impairment, leading to suboptimal engagement and limited cognitive benefits. These may all be potential explanations for why low- to moderate-intensity exercise interventions were found to significantly impact cognitive functioning for older adults with cognitive impairment when high-intensity exercise did not. However, high-intensity exercise was still found to be trending towards significance, and it is possible that the sample size within this meta-analysis was not large enough to elicit a more significant effect. Further research into the effects of high-intensity exercise specifically within this population is warranted to determine whether it is or is not beneficial for cognition.

Translation into the Real World

In the real-world context, the choice between high-intensity and low- to moderate-intensity exercise interventions for older adults with cognitive impairment should consider individual preferences, capabilities and health status. Tailoring exercise prescriptions to individual needs and preferences may optimise engagement and adherence, maximising the cognitive benefits of physical activity interventions. Furthermore, integrating multimodal interventions that combine elements of both high-intensity and low- to moderate-intensity exercise, along with cognitive training and social engagement, may offer a more

comprehensive approach to promoting cognitive health and overall wellbeing in this population. It is clear that exercise in general has a positive effect on cognition. Whilst this meta-analysis shows that low- to moderate-intensity exercise may be more beneficial for older adults with cognitive impairment, what the results also show is that high-intensity exercise was trending towards a significant effect. There is potential for a combination of the two intensities being the most valuable, and future research should consider looking into interventions that combine these intensities to further investigate this possibility.

Moderators and Additional Analyses

Four different moderators were considered within this meta-analysis: the amount of exercise sessions per week (frequency) and the amount of minutes spent exercising per week (duration), adherence to the exercise intervention, and the type of exercise that was used within the intervention. This can help to provide some information on the factors that may influence the effectiveness of exercise interventions in enhancing cognitive abilities for older adults with cognitive impairment. Additional analyses were also run where these moderators were considered within the context of the high-intensity subgroup and the low-to moderate-intensity subgroup. This can help to see if these moderators influence effectiveness not only for exercise interventions in general, but also to determine whether they can have unique effects on different intensities of exercise.

Frequency and Duration of Exercise

One of the key variables examined was the frequency of exercise sessions per week that the individual was engaging in as part of the intervention. The moderator variable ranged from one session a week to five sessions a week. The findings revealed that, despite significant residual heterogeneity across studies, variations in the frequency of exercise did not yield any significant differences in cognitive performance outcomes. This suggests that

for exercise interventions in general, increasing the number of sessions per week may not necessarily translate into greater improvements in cognitive functioning among older adults with cognitive impairment. This same trend was also seen with the total number of minutes spent exercising per week. The results of this meta-analysis indicated that differences in the duration of exercise throughout the week did not lead to significant differences in cognitive functioning, suggesting that it may not be a decisive factor in determining the effectiveness of an exercise intervention.

However, when considering this moderator alongside exercise intensity some different results start to appear. When examining the frequency of exercise sessions per week as a moderator for high-intensity exercise interventions, the test of moderators did not reach statistical significance. This suggests that the frequency of exercise sessions per week did not significant impact cognitive performance in this subgroup. While the intercept estimate indicated a significant negative effect, which implies that there is a consistent effect across the studies even without considering any additional factors, the coefficient for the frequency of exercise sessions per week showed a positive trend, although not statistically significant. This suggests that more frequent high-intensity exercise sessions per week may be associated with lower cognitive performance. For the potential moderating effects of the duration of exercise, the test of moderators did not reach overall significance. While the intercept estimate showed a trend towards significance, the coefficient was not statistically significant. This could potentially be related to the aforementioned higher levels of stress associated with high-intensity exercise. One or two sessions per week of high-intensity may promote cognitive functioning, but extended periods of time at high-intensity could lead to excess cortisol levels and significant stress on the body.

Conversely, when examining low- to moderate-intensity exercise interventions, the test of moderators for frequency did not reach statistical significance, indicating that this does not significantly affect cognitive performance in this subgroup. Both the intercept estimate and the coefficient for the frequency of exercise were found to be non-significant. In contrast, the duration was found to significantly affect cognitive performance for this subgroup. The intercept estimate showed a trend towards significance, and the coefficient for minutes of exercise per week had a significant negative effect on cognitive performance. This suggests that increased minutes of exercise per week were associated with significantly better cognitive performance in the low- to moderate-intensity subgroup. This could be related to the upregulation of neurotropins hypothesis, where extended periods of time at a low- to moderate-intensity can foster neuronal growth and neuroplasticity. Exercise has been shown to upregulate the production of BDNF in the brain, which plays a prominent role in the survival, growth and maintenance of neurons, as well as modulating synaptic plasticity in older adults (Vaynman et al., 2004). A significant element of this hypothesis is that cognitive benefits from exercise upregulating BDNF can be long-term and become more enhanced over time. The greatest effects are seen in highly transformable areas responsive to environmental stimuli, and it is possible that extended time in these environments allows for more benefits to occur (Foster et al., 2011). This theory suggests a possible explanation for why longer durations of low- to moderate-intensity exercise throughout the week leads to significantly better cognitive outcomes.

These results highlight that there is an importance of duration for low- to moderate-intensity exercise, but the opposite effect for high-intensity exercise. It seems that for low- to moderate-intensity exercise, the number of sessions per week matters less than the total amount of time taken each week to exercise. Conversely, high-intensity exercise is less

subject to duration, but more sessions per week exercising at this high-intensity can lead to poorer cognitive outcomes. This suggests that if high-intensity exercise is the intervention choice, less is more, but for low- to moderate-intensity the more the better.

Adherence to Exercise Intervention

Adherence rates varied across studies, but the analysis revealed that differences in these adherence levels did not significant influence cognitive performance outcomes in the main model. Despite significant residual heterogeneity, these findings suggest that maintaining high levels of adherence to the exercise intervention may not be essential for achieving the improvements seen in cognitive functioning. However, it is important to note that all studies included within this meta-analysis had 60% or more of their participants adhere to the entire intervention, indicating that there was moderate to high levels of adherence across the meta-analysis. It is possible that studies with lower adherence rates would see a significant impact of adherence on cognitive outcomes, as it logically follows that if individuals do not complete the majority of the exercise intervention they will not reap the cognitive benefits of it. Therefore, while adherence remains an important consideration for the overall success of any intervention, these results imply that even a moderate level of adherence may still be able to yield meaningful cognitive benefits within this population.

Examining the moderating effects of adherence to the exercise program on cognitive outcomes within each intensity subgroup, we found that adherence did not have a significant impact on outcomes for either high-intensity or low- to moderate-intensity exercise interventions. There was considerable variability among the included studies, but the overall effectiveness of the interventions was not affected by adherence. It is likely that these subgroup analyses were similar to the main model for the same reason seen within

the main model: that there was moderate to high adherences across all of the studies. There was also no significant difference between the adherence rates of these two subgroups, with adherence in the high-intensity subgroup ranging from 70% - 95%, and adherence in the low- to moderate-intensity subgroup ranging from 63% - 94%.

Type of Exercise

The impact of the type of exercise on exercise interventions ability to improve cognitive performance was also found to be non-significant. The results for the main model showed that variations in exercise modalities, including aerobic exercise, mind-body exercise, cycling, sports, and walking, did not result in any significant differences in cognitive outcomes across studies. This suggests that the type of exercise used may not be a crucial determinant, and that while certain types of exercise may offer unique physiological or psychological benefits, their differential impact on cognitive functioning in this population appears to be limited.

However a different trend is seen within the additional subgroup analyses. For high-intensity exercise interventions, the analysis revealed significant variability among the studies, with walking as a type of high-intensity exercise showing a significant negative effect on cognitive functioning. This suggests that when walking is used within a high-intensity exercise intervention for this population, it has a significant impact on and enhances cognitive functioning by the end of the intervention period. This could potentially be due to the specific characteristics of walking exercise. In the context of adults aged over 50 years, and particularly those with some form of cognitive impairment, walking may be one of the simplest and most effective ways to exercise. The environmental demands associated with mobility for older adults with disabilities is an important consideration, and walking may be the best possible way for individuals to reach a higher intensity workout without putting too

much physical strain on their body. There is also the social opportunity that is available with walking that is not seen in cycling or other activities, where the social connectedness seen within walking groups can help to sustain more consistent exercise and potentially more benefits (O'Regan et al., 2020). Other types of exercise did not have a significant impact on cognitive outcomes in the high-intensity subgroup.

In the low- to moderate-intensity subgroup, none of the specific types of exercise showing significant effects on outcomes. This suggests that the type of exercise employed in low- to moderate-intensity interventions may not consistently affect cognitive outcomes across all studies.

Implications

These moderator analyses help to inform how different factors may interplay with the exercise intervention to effect cognitive outcomes. For the main model, none of the moderator variables showed a significant impact on the cognitive outcomes demonstrated, however when considering them in the context of different exercise intensities they did have significant effects. The additional analyses provide valuable insights into the nuanced relationships between exercise intensity, specific exercise-related variables, and cognitive outcomes among older adults with cognitive impairment. While some variables, such as adherence to the intervention, may not significantly impact cognitive performance across all intensity levels, others, such as the type or duration of exercise, may have differential effects depending on the intensity of the intervention.

Understanding how these moderating variables influence the cognitive benefits of exercise interventions can inform the development of more targeted and effective exercise prescriptions for older adults with cognitive impairment. By tailoring exercise interventions

to individual needs and preferences, healthcare providers can optimise cognitive outcomes and enhance overall quality of life for this vulnerable population.

Heterogeneity

The observed heterogeneity in the meta-analysis results, as indicated by a moderate level of the I^2 statistic (I^2 = 53.06%), underscores the need for careful consideration of potential sources of variability when interpreting the studies. Heterogeneity refers to the degree of variability in effect estimates across studies that cannot be explained by chance alone. In this context, it suggests that differences between studies, such as variations in study populations, interventions, outcome measure, or study designs, contribute significantly to the observed variability in effect sizes.

The presence of heterogeneity highlights the complexity of the relationship between exercise interventions and cognitive outcomes among older adults with cognitive impairment. While the overall effect estimate provides valuable insights into the average effect of exercise interventions on cognitive functioning, the variability across studies suggests that certain factors may influence the effectiveness of these interventions in different contexts. One possible explanation for the observed heterogeneity is the diversity of intervention protocols and participant characteristics among the included studies. Variations in the duration, frequency, intensity, and type of exercise interventions, as well as differences in the severity of cognitive impairment among participants, may contribute to the observed variability in effect sizes.

The inclusion of multiple effect sizes from the same studies may have contributed to the heterogeneity within this meta-analysis. Variability in effect sizes across studies may be influenced by factors such as differences in study design, participant characteristics, intervention protocols, and outcome measures. However, when multiple effect sizes are

derived from the same studies, the inherent correlations between effect sizes from the same study may artificially inflate the overall heterogeneity observed in the meta-analysis. To properly account for the correlations between these effect sizes, multilevel modelling was used to control for the clustering within studies to obtain a more accurate estimate of heterogeneity.

Despite this presence of heterogeneity, the Galbraith plot revealed a pattern of vertical alignment, indicating consistent effect sizes across the included studies but varying levels of precision in their estimates. This suggests that, whilst the magnitude of treatment effects may vary between studies, the direction of their effects remains consistent across the literature. This observation provides some reassurance regarding the reliability and consistency of the observed treatment effects across different study findings. Subgroup analyses and sensitivity analyses were conducted to be able to examine these potential reasons for heterogeneity. By identifying these factors that influence the effectiveness of exercise interventions on cognitive outcomes, healthcare professionals and policymakers can tailor interventions to better meet the needs of older adults with cognitive impairment. Moreover, a better understanding of the sources of variability in treatment effects can inform the design of future research studies and contribute to the development of more effective interventions for this population.

Subgroup Analyses

The subgroup analyses conducted in this meta-analysis help to identify potential variations in the effects of exercise interventions on cognitive functioning across different subpopulations and intervention characteristics. The subgroups explored within this meta-analysis were the diagnosis of cognitive impairment (MCI or dementia), the age of the

participant (50+ or 65+), the length of the intervention (12-26 weeks or 26+ weeks), and the quality of the study based on its RoB.2 assessment.

Clinical Diagnosis

When examining the effect of exercise interventions on cognitive functioning among individuals with dementia, the analysis revealed a statistically significant improvement in cognitive outcomes. This finding suggests that engaging in exercise can improve cognitive functioning even for those that are showing the profound deficits seen in executive functioning and memory that come with a dementia diagnosis. However, in comparison to the main model including all of the studies, this positive effect seen within dementia individuals was smaller. Therefore, whilst there is still significant improvement, it is not to the same degree as what is seen across studies including both dementia and MCI participants. By demonstrating a positive effect on cognition in individuals with dementia, this subgroup analysis provides valuable evidence supporting the inclusion of exercise interventions in dementia management programs.

Similarly, individuals with MCI also showed significant improvements in cognitive functioning following exercise interventions, although this model demonstrated a larger effect size than the dementia model. Additionally, this effect size was larger still than the effect seen within the main model. This indicates that, whist exercise has a positive effect on cognitive functioning regardless of the cognitive impairment that is being demonstrated, there is more room for improvement when the intervention is capturing the MCI population. An explanation for this may be seen within the upregulation of neurotropins hypothesis. This theory promotes long-term and slow promotion of cognitive benefits over an extended period of time, with an upregulation of BDNF playing a prominent role in the survival and growth of neurons during development (Foster et al., 2011; Vaynman et al., 2004). For an

individual with dementia, who is already showing significant loss of neurons or neuron functionality, this process may not have a large effect. However, for individuals with MCI that do not have the same atrophy or loss of important areas within the brain, the upregulation of a neurotropin like BDNF could significantly slow the progression from MCI to dementia, and strengthen the neurons and connections that were showing decline but had not completely lost function. This suggests that exercise may play a crucial role in delaying or attenuating cognitive decline within this population, and highlights the potential for exercise to be used as a preventative measure for individuals at risk of progressing to dementia.

The difference in these effect sizes underscores the importance of tailoring interventions to specific cognitive impairment conditions. Exercise may be particularly beneficial for individuals with MCI in preserving or improving cognitive functioning. For individuals with dementia, exercise is still shown to be an effective intervention, and promoting physical activity for this population may help to slow the decline seen with dementia by protecting unaffected neurons and brain regions. However, the changes seen within cognitive functioning may be less pronounced than what could be seen when utilising exercise as a preventative measure for individuals with MCI.

Age of Participant

When considering the age of the participant, exercise interventions were associated with significant improvements in cognitive functioning among individuals over the age of 65, however this effect was similar to what was seen within the main model that includes participants from aged 50+. This indicates that exercise is an effective intervention to employ at any point within this age range, which is important for identifying what interventions could be employed to mitigate age-related cognitive decline. This additionally supports findings that exercise can be used at a later stage in life and still have a significant effect on

cognitive functioning (Livingston et al., 2020). Unlike other risk factors for dementia that are imperative to consider early in life, such as education level, exercise is a measure that can be begun at a much later stage and still will work to reduce neuropathological damage.

This is important information to have to support older adults in engaging in behaviours that can promote cognitive health and stability. These results show that age does not diminish the effectiveness of these interventions, and that older adults can benefit from exercise even if cognitive decline has already begun. Additionally, the similarity of effects between participants over 50 years of age and those over 65 years of age underscores the potential universality of exercise as an intervention. These results align with existing literature that exercise remains effective later in life (Livingston et al., 2020), and provide valuable insights into the importance of interventions in later life stages as a part of comprehensive dementia prevention or mitigation strategies.

Length of the Exercise Intervention

The length of the intervention emerged as a significant factor influencing the effectiveness of exercise interventions on cognitive outcome. Interventions that last less than 26 weeks demonstrated a statistically significant improvement in cognitive functioning, whereas interventions that spanned more than 26 weeks did not show a significant effect. This suggests that there may be a cut-off point around the 6 month mark where exercise interventions stop having as much of an effect on cognition.

There are a number of reasons why this may be the case. Firstly, it is possible that there is a limit to how much improvement can be gained for an individual's cognition through exercise. There may be only so many ways that exercise can protect against neurodegenerative diseases. Engagement in regular physical activity has been seen to maintain the integrity of the BBB, preserve hippocampal volume or neural plasticity, and

lower cardiovascular risk (Aarsland et al., 2010; Cotman & Berchtold, 2002; Erickson et al., 2009, 2011; Vecchio et al., 2018). All of these benefits can provide the brain protection and allow for better resilience against neurodegenerative diseases, but it is also possible that these benefits for an individual with dementia or MCI can only help in a limited capacity. There is also a possibility that, within this population, it is difficult for individuals to maintain the exercise regime to the same ability over longer periods of time. Older adults have physiological considerations to make, particularly when it comes to falls. For adults aged over 65 in the United States, 27.5% report falling at least once in the past year, and 10.2% reported an injury because of that fall (Moreland et al., 2020). Whilst exercise can help to reduce the incidence of falls in older adults that lead to injury, maintaining an exercise regime consistently for more than 6 months at a time may be difficult within this population due to elevated risk of injury or physical limitations.

The finding that shorter-term interventions elicit better cognitive outcomes may be more fitting when considering the real-world context. It is possible that for an ageing population, especially a population that has more dependence upon support from healthcare professionals or relatives, there are significant barriers to maintaining an intervention for longer than six months at the same authenticity or energy. If the individual is residing in a care facility, there may be more support for older adults with cognitive impairment to engage in these interventions and for them to become part of a routine. But the costs of this healthcare is high, and healthcare professionals are often underpaid and overworked. This makes longer-term interventions more difficult to maintain. Similarly, in a community-dwelling situation where the individual is being taken care of by a relative or a friend, there are a number of limitations to implementing these interventions over a long term period. As mentioned previously, there are disparities in receiving and gaining access to

healthcare for ethnic minorities (Aranda et al., 2021), and caring for a person with dementia in particular leads to poorer mental and physical health (Allen et al., 2017; Fonareva & Oken, 2014; D. L. Roth et al., 2019; Schulz & Martire, 2004). Implementation of a long-term exercise intervention may be too difficult for caregivers and the individual. These are all important considerations to make when tailoring an exercise intervention to an individual.

This finding suggests that shorter-term exercise interventions may be more effective in improving cognitive outcomes than longer-term interventions, and this may result has important implications for the implementation of these interventions in the future. However, further research is needed to elucidate the optimal duration and intensity of exercise interventions for maximising cognitive benefits. Follow-up periods were also not considered within this meta-analysis, with the post-intervention cognitive results being assessed immediately after the conclusion of the exercise regime. It is possible that the improvements in cognition seen after an intervention do not maintain for a significant period of time following the intervention, or that longer interventions elicit better long term results. This is an area of research that would be interesting to consider when trying to determine what length of exercise intervention is most effective for older adults with cognitive impairment.

Quality of the Study

The subgroup analysis based on study quality provides valuable insights into the potential impact of methodological rigor on the observed effects of exercise interventions on cognitive functioning. By excluding studies with a high risk of bias, as assessed by the RoB.2, we aimed to look at the robustness of the effect estimates and determine whether methodological quality influences the observed treatment effects.

High-risk-of-bias studies typically exhibit methodological flaws that may compromise the validity and reliability of their findings. This could include issues such as inadequate blinding, incomplete outcome data, selective outcome reporting, or other sources of bias that could inflate or deflate the observed treatment effects. By excluding these from the subgroup analyses, we sought to minimise the influence of these methodological limitations on the overall effect estimates and provide a more accurate assessment of the true association between exercise interventions and cognitive functioning. Of the 18 studies included within this meta-analysis, 4 were found to have a high risk of bias when undergoing the RoB.2 assessment.

When excluding studies with a high risk of bias from the analysis, there was a more pronounced effect size estimate. This suggests that methodological rigor impacts the observed treatment effects, and excluding studies of higher risk results in a stronger and more consistent effect of exercise interventions on cognitive functioning. The implications of this finding are twofold. First, it suggests that exercise interventions may indeed have a more substantial effect on cognitive functioning when implemented under rigorous methodological conditions. This has important implications for the design and conduct of future exercise intervention studies, emphasising the need for robust methodological approaches to minimise bias and enhance the validity of study findings. Secondly, the stronger effect size observed when excluding high-risk-of-bias studies suggests that caution should be exercised when interpreting meta-analyses that include studies with these methodological limitations. Studies with higher methodological quality are more likely to provide reliable and valid estimates of treatment effects, thereby informing more accurate conclusions and recommendations.

This further emphasizes the need for transparency and thorough reporting of study methods and results to enable accurate interpretation and synthesis of evidence in meta-analytic reviews. By demonstrating the impact of study quality on effect estimates, this analysis shows the importance of adhering to rigorous methodological standards in exercise intervention research.

Small-study bias

Small-study bias is a critical consideration in meta-analytic research, impacting the validity and generalisability of study findings. Various methods were employed to assess small-study bias, including funnel plots, trim-and-fill analysis, Egger's regression test, and p-curve analysis, aimed at providing a comprehensive evaluation of bias and enhancing reliability of the meta-analytic results.

The results from the trim-and-fill analysis shed light on the potential impact of small-study bias within this meta-analysis. The results suggested 4 missing studies on the left side, indicating potential asymmetry in the distribution of studies. There was observed heterogeneity and variability, however the analysis yielded a statistically significant overall effect size estimate that indicated an improvement in cognitive function after an exercise intervention for older adults with cognitive impairment. This suggests that despite the potential influence of small-study bias, there is evidence to suggests a meaningful relationship between exercise and cognition. However, it is important to acknowledge certain limitations with the trim-and-fill method. Firstly, this method assumes that missing studies are due to small-study bias, which may not always be the case. It also relies on certain assumptions about the distribution of the studies which may not hold true in all circumstances. Therefore, while the analysis provides an estimated of missing studies, it does not offer definitive evidence of small-study bias.

The funnel plot, a graphical tool for assessing small-study bias, displayed a wide spread of points, indicating heterogeneity among the included studies beyond chance variation. However, asymmetry in the plot, with some studies falling outside the funnel, suggested potential small-study bias favouring the publication of studies with significant results. This bias could distort the pooled effect estimate, emphasising the importance of sensitivity analyses and exploration of heterogeneity sources. The results of Egger's regression test supported the presence of this funnel plot asymmetry, indicating potential small-study bias within the meta-analysis. Statistically significant results suggested bias favouring studies with smaller standard errors, potentially inflating the apparent effect size. This underscores the need for cautious interpretation of the meta-analytic findings and consideration of potential sources of bias.

The p-curve analysis provided further insight into the evidential value of the included studies. The initial drop in density below the conventional significance threshold suggested strong evidence for genuine effects in the meta-analysis findings. However, subsequent fluctuations in density across different ranges of p-values indicated variability and potential selective bias reporting or p-hacking, highlighting the nuanced nature of the evidence and the need for careful interpretation.

However, it is important to note that some studies provided multiple effect sizes due to employing a high-intensity and a low- to moderate-intensity intervention, or perhaps two different samples. With this, there is a risk of duplication of data, as studies with significant findings may be more likely to report multiple effect sizes. This can lead to the overrepresentation of significant results in the meta-analysis, potentially biasing the overall effect estimate and influencing assessments of small-study bias. The presence of duplicate data may artificially inflate the apparent strength of evidence for the intervention's

effectiveness, leading to an overestimation of effect sizes and potentially masking the true variability across studies.

Implications

The presence of small-study bias in the meta-analysis has several implications for the interpretation and generalisability of the findings. First, the potential overrepresentation of significant results could lead to an inflated estimate of the true effect size, affecting the accuracy of conclusions drawn from the meta-analysis. Second, selective publication of studies with significant findings may skew the evidence base, leading to biased conclusions and inappropriate clinical recommendations. Thirdly, the presence of small-study bias underscores the importance of transparent reporting practices and preregistration of studies to mitigate bias and enhance the credibility of research findings.

In summary, the evaluation of small-study bias through various methods can reveal important insights in the reliability and validity of meta-analytic findings. While heterogeneity among studies beyond chance variation was observed, asymmetry in the funnel plot and significant results from Egger's regression test suggested the presence of small-study bias, potentially inflating the apparent effect size. The nuanced nature of the evidence uncovered by the p-curve analysis further underscores the need for cautious interpretation. Moreover, the inclusion of studies with multiple effect sizes introduces a risk of data duplication, potentially biasing the overall effect estimate and influencing assessments of small-study bias. However, it is worth noting that a multi-level approach was employed to combat the potential risk of data duplication, mitigating this concern to some extent. Careful consideration of these factors can help with informing evidence-based decision-making in clinical practice and policy formulation.

GRADE Assessment

The GRADE assessment has been employed as a framework to determine the quality of the meta-analysis. An overall GRADE quality rating is applied by taking the lowest quality of evidence from all the outcomes that are critical to the decision making, and the evidence is rated on a certainty scale. Certainty will be rated down for risk of bias, imprecision, indirectness, small-study bias and inconsistency. It will be rated up for a large magnitude of effect, a dose-response gradient and when all residual confounding would decrease the magnitude of effect.

Quality Rating

Risk of Bias. The studies included within this meta-analysis have been independently rated using the RoB.2 assessment (Sterne et al., 2019). Overall, 5 studies were considered to be low risk, 9 studies showed some concern and 4 studies showed a high risk of bias.

Inconsistency. The point estimates did vary in their level of precision, however they were consistent in regard to the direction of the effect. This suggests that while the magnitude of treatment effects varied, the direction of the effect did not. There was some overlap between confidence intervals, and the magnitude of statistical heterogeneity was moderate at 53.1%. the test for heterogeneity was statistically significant at $p < .01$.

Indirectness. The populations in the included studies were highly applicable to the decision context, as all populations were older adults aged over 50 years that had been formally diagnosed with either MCI or dementia. The interventions in the included studies were also highly applicable, as they were all either high-intensity or low- to moderate-intensity exercise interventions. The included outcome was not a surrogate outcome and has been pre-registered under PROSPERO (Appendix A). The outcome timeframe is sufficient and the conclusions are based on direct comparisons.

Imprecision. The confidence interval for the pooled estimate was consistent with exercise interventions inducing cognitive benefits, and the magnitude of the median sample size was intermediate at just over 100 participants. The number of included studies was 18 which is considered to be large, and there was no evidence in any of the studies of serious harm associated with the exercise interventions.

Small-study bias. A comprehensive search was conducted and grey literature was searched. Some restrictions were placed on the study selection as only studies that were available in English were considered. There was no industry influence on studies included within the review. However, there was evidence of funnel plot asymmetry, and it is unclear whether there was a discrepancy between published and unpublished findings as no unpublished studies met the full criteria for inclusion in this meta-analysis.

Overall Confidence

The original studies were well planned and executed, the results are precise, but there is some possibility of small-study bias as evidenced by the asymmetry in the funnel plot (Figure 19). There are some problems with inconsistency, as there was some overlap between the confidence intervals and, whilst the directionality of the effect was consistent, there was variation in the magnitude of this effect. Heterogeneity was also present throughout this meta-analysis, although this was considered to be at a moderate level. Unexplained heterogeneity in the results across studies reduces the quality of the evidence for all outcomes. The overall quality of evidence for this meta-analysis is considered to be moderate due to these reasons.

Methodological Considerations

It is important to note that this meta-analysis was undertaken by one researcher, which can mean that there are some cautionary approaches that need to be taken. Best

practice for the methodology of a meta-analysis would typically mean that two separate researchers have undertaken the task of identifying studies and data extraction. This would be done separately and then the researchers would come together to see if they have reached the same decisions, and if there were any disagreements a third researcher would be approached as a mediator. Due to the limitations of a masters project, this was not possible for this particular meta-analysis. However, this was controlled for and considered within the methodological approach. The risk of bias that can occur with an individual approach was mitigated to some extent through the supervision of a secondary independent researcher that monitored each stage of the meta-analytic process, and through the pre-registration of the meta-analysis on PROSPERO to formally document the steps that would be taken and the methodology plan. Whilst there is still some risk of bias due to the methodology of this meta-analysis, there have been efforts to mitigate this risk as much as possible within the limitations of the project.

Risk of Bias

Overall, the included studies were thought to have a low risk of bias. However, the domain of selection of the reported result presented a more significant challenge for out of the 18 studies compared to other domains. This was mostly due to a lack of pre-registration across the studies included, therefore it was difficult to determine whether the main outcome was pre-determined or decided after an analysis of the results. Additionally, the blinding of participants may be practically difficult in an exercise experiment, particularly when the control is a non-exercise intervention or no intervention at all. Due to this, it was considered to be consistent across all of the studies and therefore did not factor into the risk of bias assessment.

Future Research

While this meta-analysis provides valuable insights into the differential effects of exercise intensity on cognitive functioning, several avenues for future research warrant exploration.

Firstly, further investigation into the specific mechanisms underlying the observed effects of exercise intensity on cognitive outcomes is needed. Longitudinal studies incorporating neuroimaging techniques can elucidate the neurobiological pathways through which exercise intensity influences cognitive function, shedding light on potential targets for intervention. Studies that further explore the moderating effects of individual factors would also be warranted, particularly when it comes to things like cognitive reserve, genetic predispositions or baseline fitness levels. Understanding how these individual differences shape the response to exercise interventions, and differing intensities in particular, can inform personalised approached to promoting cognitive health in aging populations.

Research looking into the sustainability of high-intensity exercise versus low- to moderate-intensity exercise, and the long-term effects of them, is also crucial. The findings from this study have suggested that short-term interventions are more beneficial for cognition when looking at older adults with cognitive impairment, but it did not consider follow-ups for cognitive ability after the exercise intervention had been finished. Gaining more information about the ongoing effects of exercise may further our understanding, and it would also help guide knowledge around what intensities and types of exercise older adults with cognitive impairment will be capable of sustaining after the intervention has concluded. Longitudinal studies tracking cognitive trajectories over extended periods can provide insight the durability of cognitive benefits conferred by different exercise regimens,

guiding the development of evidence-based interventions for preventing cognitive decline and dementia in later life.

Future research could also consider different measures of cognition to better ascertain if there are specific regions or areas that are affected by specific intensities. This study considered overall cognition, but it would be interesting to research the areas of cognition that are most affected by cognitive decline to determine whether personalised approaches can be taken. Dementia is associated with significant brain atrophy in areas of executive function, therefore looking into what intensities or types of exercise that promote plasticity and neuronal protection in executive functioning areas could be key for slowing dementia progression. It would also help on an individual level, where certain types or intensities of exercise could be suggested for particular areas of decline such as memory or decision-making.

Conclusion

Overall, the studies in this meta-analysis show that exercise interventions in later life lead to improved cognitive functioning, or a slowing of cognitive decline, for older adults with cognitive impairment. Exercise interventions compared to control groups was shown to have significantly greater change over the course of the intervention period, and when looking into the direction of this change the results indicate that post-intervention cognition scores are lower than pre-intervention cognition scores. As lower scores on the cognitive measures used across all the studies in the meta-analysis mean better cognitive functioning, this shows that exercise interventions improve cognitive functioning for older adults experiencing cognitive impairment. Frequency, duration, adherence and type of exercise was not shown to effect overall cognitive functioning.

Only low- to moderate-intensity exercise showed a significant improvement in cognition after the intervention period, however high-intensity exercise interventions were trending towards significance. Both of these intensities also had the same estimated effect size, even though the significance differs, which implies whilst both have an effect on cognition there may be more consistent effects when conducting a low- to moderate-intensity exercise intervention. There were also more studies in this meta-analysis that used a low- to moderate-intensity exercise intervention than high-intensity, which may have contributed to this finding. The effect of differing intensities on cognition was moderated by frequency and duration. Longer duration of low- to moderate-intensity exercise is shown to elicit greater cognitive benefits, whereas higher frequency of high-intensity exercise leads to poorer cognitive outcomes.

The subgroup analyses were able to provide a more nuanced account of the effect exercise interventions has on cognitive performance. Individuals that had been diagnosed with MCI showed greater improvement in cognition after undergoing an exercise intervention. Whilst individuals with dementia still showed some improvement, this was not as pronounced as what was seen for people diagnosed with MCI. Longer-term intervention periods were also not shown to significantly effect cognitive performance for this population, with interventions lasting between twelve to twenty-six weeks having a significant effect. This helps to formulate a better understanding on what is best practice on both an individual and a methodological level. More knowledge around how cognitive trajectories over a long period of time fluctuate after undergoing an exercise intervention would be beneficial in understanding the long-term impact of these changes. Ultimately, these findings have the potential to help design personalised interventions for older adults to slow or mitigate the effects of cognitive decline seen within dementia and MCI.

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Appendices

Appendix A: Pre-Registration for PROSPERO

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Comparative efficacy of exercise intensity on cognitive function for older adults with cognitive impairment: A systematic review with meta-analysis

Citation

Olivia Avery, David Moreau. Comparative efficacy of exercise intensity on cognitive function for older adults with cognitive impairment: A systematic review with meta-analysis. PROSPERO 2023 CRD42023433569 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023433569

Review question

Do chronic high-intensity or moderate-intensity exercise interventions have greater cognitive benefits for older adults with dementia-related cognitive impairment?

Searches

The systematic literature search for work published before August 2023 will be performed on the following electronic databases: PsycINFO, Web of Science, ScienceDirect, ProQuest, PubMed, SPORTDiscus, Cochrane Central Register of Controlled Trials (CENTRAL) and Scopus. Additionally, Google Scholar, PsyArXiv, medRxiv and bioRxiv will be searched to identify potential gray literature. The initial search is planned to be conducted in August 2023. Articles must be in English.

Types of study to be included

This meta-analysis will include studies that follow a randomised controlled trial or intervention study design, and that include effect sizes or the information necessary to calculate effect sizes. Articles will be excluded if they are prospective or retrospective cohort studies, case reports, conference abstracts, or have not written in English.

Condition or domain being studied

As of 2015 there were around 47 million people living with dementia, and this number is projected to triple by the year 2050 under the expectation that no cure or way of slowing the disease is identified (Livingston et al., 2017). Clinically recognizable Alzheimer's dementia is seen within all ethnic groups and the prevalence increases with age, with about 80% of all dementia seen in individuals aged 75 or older (Livingston et al., 2017). Whilst there is no current in vivo technique for confirming dementia, it is characterized by a decline in cognitive functioning that significantly affects daily living or social functioning, and significant brain atrophy in areas of executive function, such as the hippocampus (Kirk-Sanchez & McGough, 2014). Significant decline in executive functioning tasks such as attention-switching, inhibitory control, response times, information process and memory are indicative of this (Kirk-Sanchez & McGough, 2014). The progression to dementia usually includes a transition through the pre-clinical stage of mild cognitive impairment (MCI), which increases the risk of dementia by five- to ten-fold and exhibits the same decline in previously attained cognitive level (Petersen et al., 1999).

Participants/population

The population being considered in this review consists of older adults who have been diagnosed with dementia-related cognitive impairment, such as mild cognitive impairment or Alzheimer's. Due to this, studies will be included if the participants are human's over 50 years of age that have received a dementia-related cognitive impairment diagnosis.

Intervention(s), exposure(s)

For a study to meet the inclusion criteria the primary intervention of the study must be either high-intensity exercise or moderate-intensity exercise that has been defined using a validated measure of intensity. Some examples of a validated measure include: the heart rate reserve (%HRR) method defined by the American College of Sports Medicine (ACSM) where high-intensity is 60-89 %HRR and moderate-intensity is 40-59 %HRR; or the Borg Rating of Perceived Exertion (RPE) where high-intensity is scored between 15-17 on the 6-20 scale or 7-8 on the 10-item scale, and moderate-intensity is scored between 12-14 or 4-6 on either of the two RPE scales. Studies will be excluded if the intervention includes low-intensity exercise or any non-exercise intervention as the primary intervention.

Comparator(s)/control

Studies will be included in the review if they have a control group who has not participated in the exercise intervention (passive control), participated in a non-exercise intervention (active control) or consisted of healthy individuals of a similar age (cohort control). Studies will be excluded if there is no control group.

Main outcome(s)

To meet inclusion criteria the primary outcome of the study must be cognitive function that has been assessed using validated neuropsychological or cognitive tests (e.g., MMSE, ADASCog).

Measures of effect

Standardised mean difference (SMD; e.g., cohen's d/g) is the main effect measure, and studies included that are not using SMD will be converted into SMD

Additional outcome(s)

Not applicable

Data extraction (selection and coding)

After uploading all articles that appear in the searches across all platforms onto Rayyan, duplicates will be identified and then excluded from the screening process. The title and abstracts of all articles will then be screened for whether they fit the inclusion criteria for the review. After this screening process, all articles that have been included will be read thoroughly to determine whether they meet all inclusion criteria and no exclusion criteria. Articles that have been included after this process are then included within the meta-analysis. This process for selecting studies will initially be completed by one researcher, however this will be reviewed by a second independent researcher. The second researcher will assess a random sample of articles and determine which articles would be included in the review and which ones would be excluded, and then these decisions will be compared with the decisions made by the first researcher. If there is high agreeability on what articles meet the inclusion criteria and what articles don't then it will be determined that the process has been conducted effectively. If there are differences in opinion, the inclusion criteria will be revisited and a consensus will be reached. This same process will be followed for data extraction.

Information about the authors, year of publication, population characteristics, intervention characteristics (e.g., high-intensity or moderate-intensity), measures used to determine cognitive function (e.g., MMSE, ADASCog) and effect sizes or information to calculate effect sizes (e.g., group means, standard deviations) will be extracted. Information about the main findings for each included study will also be extracted. Information on key moderator variables will also be extracted if part of the study, including information on frequency of exercise, type of exercise, and adherence to the exercise program.

Risk of bias (quality) assessment

This risk of bias will be assessed in each of the studies using the Cochrane Collaboration's Risk of Bias tool (RoB 2; Sterne et al., 2019). Each study will be independently rated, reliability will be calculated, and disagreements will be resolved through discussion. Study quality will be considered as a moderating variable. Publication bias will be examined by inspecting a funnel plot of obtained standard errors and effect sizes for each of the studies, and the trim-and-fill analysis will be used to determine the number of missing effect sizes (Duval & Tweedie, 2000). A p-curve will also be created (Simonsohn et al., 2014) to determine if the resulting p-value distribution for the studies that have been included is what would be expected for a true effect.

Strategy for data synthesis

A random effects meta-analytic model will be used for the data synthesis. Heterogeneity will be calculated via Q and I^2 statistics, and moderating variables will be assessed accordingly. The measure of effect size will be Cohen's d/g, based on means and standard deviations extracted for each cognitive test. We will be using an R script template for the meta-analysis. This template will be modified appropriately and uploaded to support the registration.

Analysis of subgroups or subsets

Subsequent analyses (subgroup analysis and mixed effects meta-analysis modelling) will be conducted following the initial random-effects meta-analysis and heterogeneity determination if necessary. The same R script will be modified accordingly and employed for this.

Contact details for further information

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Organisational affiliation of the review

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Review team members and their organisational affiliations

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Type and method of review

Meta-analysis, Systematic review

Anticipated or actual start date

04 August 2023

Anticipated completion date

28 February 2024

Funding sources/sponsors

No sources of financial or other support for this review.

Conflicts of interest

Language

English

Country

New Zealand

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Aged; Cognition; Cognitive Dysfunction; Dementia; Humans

Date of registration in PROSPERO

14 August 2023

Date of first submission

31 July 2023

Stage of review at time of this submission

The review has not started

Stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

14 August 2023

14 August 2023

Appendix B: Dataset for Meta-Analysis

study_id	es_id	ref	no_pages	country	tot_part_ran	tot_part_ana	diag_sample	ex_inten	sex	av_age	int_length	cog_func_test	int_n_pre	int_mean_pre	int_sd_pre	int_n_post	int_mean_post
1	1	Langoni et al. (2018)	8	Brazil	60	52	MCI	mod	77	72.6	26	MMSE	26	21.9	4.8	26	25
2	2	Huang et al. (2019)	10	China	80	74	dementia	mod	68	81.9	40	MMSE	40	20.75	6.56	36	21.17
2	3	Huang et al. (2019)	10	China	80	74	dementia	mod	68	81.9	40	MoCA	40	13.06	5.34	36	14.83
3	4	Varela et al. (2011)	9	Spain	68	48	MCI	mod	56	78.3	12	MMSE	27	19.86	5.12	17	20.66
3	5	Varela et al. (2011)	9	Spain	68	48	MCI	high	56	78.3	12	MMSE	26	20.81	4.69	15	21.06
4	6	Yu et al. (2022)	12	Hong Kong	50	37	MCI	mod	89	63.5	12	HK-MoCA	10	19.7	1.9	7	24.5
4	7	Yu et al. (2022)	12	Hong Kong	50	37	MCI	mod	89	63.5	12	HK-MoCA	10	18.9	1.9	7	25.4
4	8	Yu et al. (2022)	12	Hong Kong	50	37	MCI	high	89	63.5	12	HK-MoCA	10	20.1	1.7	8	25.7
4	9	Yu et al. (2022)	12	Hong Kong	50	37	MCI	high	89	63.5	12	HK-MoCA	10	19.6	2.5	8	23.9
5	10	Lamb et al. (2018)	11	England	494	418	dementia	mod	61	77.5	48	ADAS-Cog	329	21.2	9.5	281	25.2
6	11	Wang et al. (2020)	7	China	66	66	MCI	mod	71	81.1	12	MMSE	33	25.03	2.01	33	26.21
6	12	Wang et al. (2020)	7	China	66	66	MCI	mod	71	81.1	12	MoCA	33	19.39	3	33	20.55
7	13	Wei and Ji (2014)	5	China	60	60	MCI	mod	33	66	26	MMSE	30	24.33	1.65	30	25.53
8	14	Yu et al. (2022)	15	Hong Kong	37	34	MCI	mod	67	73.5	26	MoCA-HK	12	19.7	1.5	10	26.6
8	15	Yu et al. (2022)	15	Hong Kong	37	34	MCI	mod	67	73.5	26	MoCA-HK	13	19.3	2	12	25
9	16	Chang et al. (2021)	9	China	136	109	MCI	high	NA	76.3	18	MoCA	62	21.61	2.11	62	22.34
10	17	Arcoverde et al. (2013)	7	Brazil	20	20	dementia	high	55	78.8	16	MMSE	10	20.4	2.7	10	20.7
10	18	Arcoverde et al. (2013)	7	Brazil	20	20	dementia	high	55	78.8	16	CAMCOG-CAMDEX	10	69.9	10.8	10	76
11	19	Yu et al. (2021)	12	United States	96	79	dementia	high	45	77.4	26	ADAS-Cog	NA	NA	NA	NA	NA
12	20	Lam et al. (2014)	4	Hong Kong	389	265	MCI	mod	76	77.8	52	ADAS-Cog	96	12.7	4.9	96	10.4
12	21	Lam et al. (2014)	4	Hong Kong	389	265	MCI	mod	76	77.8	52	MMSE	96	24.7	3	96	25.4
13	22	Li et al. (2022)	13	United States	70	46	MCI	mod	57	74.6	16	MoCA	22	25.09	2.43	22	26.82
14	23	Morris et al. (2017)	9	United States	76	68	MCI & dementia	high	51	72.9	26	Composite battery memory	39	-2.5	1.4	34	-2.3
14	24	Morris et al. (2017)	9	United States	76	68	MCI & dementia	high	51	72.9	26	Executive function battery	39	-1.12	0.82	34	-1.2
15	25	Uffelen et al. (2008)	19	Netherlands	179	152	MCI	mod	44	75	52	MMSE	86	29	0.74	77	28.5
16	26	Venturelli, Scarsini & Schena (2011)	8	Italy	25	21	dementia	mod	86	84	26	MMSE	12	13	2	11	12
17	27	Yu. Salisbury & Mathiason (2021)	8	United States	78	78	dementia	high	41	77.4	26	ADAS-Cog	NA	NA	NA	NA	NA
18	28	Ohman et al. (2016)	8	Finland	210	161	dementia	high	39	78.1	52	MMSE	70	17.8	6.6	59	NA
18	29	Ohman et al. (2016)	8	Finland	210	161	dementia	high	39	78.1	52	MMSE	70	18.5	6.3	51	NA

int_sd_post	ch_score_int	con_n_pre	con_mean_pre	con_sd_pre	con_n_post	con_mean_post	con_sd_post	ch_score_con	cohen_int	cohen_con	es_calc	mod_freq_min	mod_freq_total	mod_adher	mod_type	pub	rob_2
4.7	NA	26	23.7	3.7	26	20.4	4.1	NA	0.657	0.85	means and sd	120	2	89.5	aerobic	Y	2
5.47	NA	40	20.79	5.16	38	19.47	5.73	NA	0.07	0.242	means and sd	60	3	NA	mind-body	Y	1
5.71	NA	40	13.32	4.56	38	12.16	4.72	NA	0.32	0.25	means and sd	60	3	NA	mind-body	Y	1
7.39	NA	15	21.8	3.23	15	19.53	5.5	NA	0.126	0.503	means and sd	90	3	70	cycling	Y	2
5.4	NA	15	21.8	3.23	15	19.53	5.5	NA	0.049	0.503	means and sd	90	3	70	cycling	Y	2
2.1	NA	10	19.9	3.5	7	20.7	3.1	NA	2.397	0.242	means and sd	150	1	93.05	walking	Y	1
1.4	NA	10	19.9	3.5	7	20.7	3.1	NA	3.895	0.242	means and sd	150	3	93.45	walking	Y	1
2.4	NA	10	19.9	3.5	7	20.7	3.1	NA	2.693	0.242	means and sd	75	1	93.25	walking	Y	1
1.6	NA	10	19.9	3.5	7	20.7	3.1	NA	2.099	0.242	means and sd	75	3	94.65	walking	Y	1
12.3	NA	165	21.4	7.8	137	23.8	10.4	NA	0.364	0.261	means and sd	150	2	NA	aerobic	Y	1
1.93	NA	33	24.36	3.32	33	24.06	3.88	NA	0.599	0.083	means and sd	120	3	80.29	mind-body	Y	2
3.23	NA	33	18.97	4.71	33	18.79	4.62	NA	0.372	0.039	means and sd	120	3	80.29	mind-body	Y	2
0.82	NA	30	25	1.29	30	24.67	1.42	NA	0.921	0.243	means and sd	150	5	NA	sport	Y	3
1.9	NA	12	18.2	3.8	12	18.9	5.2	NA	1.51	2.36	means and sd	180	3	79.1	mind-body	Y	1
2.5	NA	12	18.2	3.8	12	18.9	5.2	NA	3.88	2.36	means and sd	180	3	79.1	aerobic	Y	1
1.87	NA	47	21.49	2.39	47	21.21	2.13	NA	0.71	0.124	means and sd	120	3	87.6	aerobic	Y	2
2.4	NA	10	19.9	3.4	10	17.8	0.8	NA	0.117	0.85	means and sd	60	2	93.7	walking	Y	2
6.7	NA	10	68.4	12.2	10	62.3	4.3	NA	0.679	0.667	means and sd	60	2	93.7	walking	Y	2
NA	1	NA	NA	NA	NA	NA	NA	0.1	NA	NA	NA	180	3	NA	cycling	Y	1
4.7	NA	169	14.2	5.7	169	12.7	5.8	NA	0.479	0.261	means and sd	90	3	65.6	mind-body	Y	3
3.3	NA	169	24.3	2.9	169	24.2	3.4	NA	0.222	0.032	means and sd	90	3	65.6	mind-body	Y	3
1.84	NA	24	25.13	2.19	24	25.54	1.89	NA	0.803	0.2	means and sd	120	2	94	mind-body	Y	2
1.7	NA	37	-2.8	1.4	34	-2.7	1.7	NA	0.128	0.064	means and sd	150	5	89	aerobic	Y	3
0.9	NA	37	-1.34	0.85	34	-1.33	0.97	NA	0.093	0.011	means and sd	150	5	89	aerobic	Y	3
1.48	NA	93	29	0.265	75	28.5	0.343	NA	0.427	1.68	means and sd	120	2	63	walking	Y	3
2	NA	12	12	2	10	6	2	NA	0.5	3	means and sd	120	4	93.4	walking	Y	2
NA	1	NA	NA	NA	NA	NA	NA	0.1	NA	NA	NA	180	3	85.6	cycling	Y	2
NA	NA	70	17.7	6.2	51	NA	NA	NA	-0.24	-0.6	means and sd	120	2	NA	aerobic	Y	2
NA	NA	70	17.7	6.2	51	NA	NA	NA	-0.19	-0.6	means and sd	120	2	NA	aerobic	Y	2

Appendix C: Code Used for Meta-Analysis in RStudio

```
############ 1. Setting things up ############

# Install packages
if (!require("pacman")) install.packages("pacman")
pacman::p_load(tidyverse, metafor)
install.packages("ggplot2")
library(ggplot2)

# Import data
df <- read.csv("R_File1.csv",
         fileEncoding = "UTF-8-BOM",
         na.strings = "NA")


############ 2. Intervention vs control model ############

#Calculate change scores
df$change_score_control <- df$con_mean_post - df$con_mean_pre
df$change_score_intervention <- df$int_mean_post - df$int_mean_pre

# Input change scores already available from data set
df$change_score_control[19] <- 0.1
df$change_score_control[27] <- 0.1
df$change_score_intervention[19] <- 1.0
df$change_score_intervention[27] <- 1.0

# From means and SDs of change scores
es_from_mean_sd_change <- escalc(measure = "MD",
                    m1i = mean(change_score_control),
                    m2i = mean(change_score_intervention),
```

```
                    sd1i = sd(change_score_control),
                    sd2i = sd(change_score_intervention),
                    n1i = con_n_post,
                    n2i = int_n_post,
                    data = df,
                    slab = ref)

# Combine effect sizes and variances calculates
es_change <- coalesce(es_from_mean_sd_change$yi)
variance_change <- coalesce(es_from_mean_sd_change$vi)
df <- cbind(df, es_change, variance_change)

# Run the meta-analytic model
main_model_change <- rma.mv(yi = es_change,
                    V = variance_change,
                    data = df,
                    method = "REML",
                    level = 95,
                    digits = 7,
                    slab = ref,
                    random = ~ 1 |study_id)
main_model_change


############ 3. Calculate intervention model ############

# Calculate effect sizes and variances using escalc() function from metafor package
es_from_mean_sd <- escalc(measure = "RBIS",
                    m1i = int_mean_pre,
                    m2i = int_mean_post,
                    sd1i = int_sd_pre,
                    sd2i = int_sd_post,
```

```
                n1i = int_n_pre,
                n2i = int_n_post,
                data = df,
                slab = ref)

# Combine effect sizes and variances calculated above
es <- coalesce(es_from_mean_sd$yi)
variance <- coalesce(es_from_mean_sd$vi)
df <- cbind(df, es, variance)

# Add effect sizes given in studies to main data frame
df$es[28] <- -0.24
df$es[29] <- -0.19

# Calculate variances for these effect sizes
df$variance[28] <- (70 + 59) / (70 * 59) + (-0.24^2) / (2 * (70 + 59))
df$variance[29] <- (70 + 51) / (70 * 59) + (-0.19^2) / (2 * (70 + 51))



############ 4. Run the meta-analytic model ############

# Fit the random effects model with no moderators
main_model <- rma.mv(yi = es,
                     V = variance,
                     data = df,
                     method = "REML",
                     level = 95,
                     digits = 7,
                     slab = ref,
                     random = ~ 1 | study_id)
main_model
```

```
############ 5. Calculate heterogeneity ############

# Calculate the I^2 statistic for a multilevel model
n_studies <- nrow(df)
W <- diag(1/n_studies, n_studies, n_studies)
X <- model.matrix(main_model)
if (nrow(X) < n_studies) {
  missing_rows <- n_studies -nrow(X)
  X <- rbind(X, matrix(0, nrow = missing_rows, ncol = ncol(X)))
}
P <- W - W %*% X %*% solve(t(X) %*% W %*% X) %*% t(X) %*% W
I2_statistic <- 100 * sum(main_model$sigma2) / (sum(main_model$sigma2) +
                                    (main_model$k-main_model$p)/sum(diag(P)))
I2_statistic

# Generate Galbraith plot for heterogeneity
data_galbraith <- data.frame(effect_sizes = df$es,
                             variances = df$variance,
                             study_ids = df$study_id)

res <- rma.uni(yi = effect_sizes, sei = variances, data = data_galbraith)
galbraith(res)


############ 5. Check outliers ############
# Using standardised residuals of correlations
resid <- residuals(main_model) %>%
  scale(center=F, scale=T)

par(mar=c(6,6,4,4))
plot(resid, type="o", pch=19)
```

```
png(filename = "ResidualsPlot.png",
    width = 800, height = 640,
    pointsize = 12, red = 120)
plot(resid, type="o", pch=19)
dev.off()

outliers_resid <- resid %>%
  cbind(df$ref) %>%
  subset(resid > 3.0 | resid < - 3.0) %>%
  View()

# Using Cook's distance
cooks <- cooks.distance(main_model)
plot(cooks, type="o", pch=19)
png(filename = "CooksDistancePlot.png",
    width = 800, height = 640,
    pointsize = 12, res = 120)
plot(cools, type="o", pch=19)
dev.off()

# View outliers with Cooks > 3 * mean
outliers_cooks <- cooks %>%
  cbind(df$ref) %>%
  filter(cooks < 3.0*mean(cooks))


############ 6. Create a forest plot ############

# Save output as pdf
pdf("ForestPlot.pdf", family = "Courier", width = 10, height = 8.5)

# Decrease margins so the full space is used
```

```
par(mar=c(2.5,4,1,2.5), cex = .9, font = 1)

# Generate the forest plot
forest(main_model,
       xlim = c(-2.5, 1.8),
       order = "obs",
       addfit = T,
       annotate = T,
       width = 0,
       efac = .55,
       pch = 19,
       col = "gray40",
       clim = c(-1, 1),
       cex.lab = 1,
       cex.axis = 1,
       lty = c("solid",
               "solid",
               "solid"),
       xlab = "",
       mlab = "RE Model: p < .01, I2 = 53.1",
       showweights = F,
       steps = 5)

# Switch to bold font
par(cex = .9, font = 2)

# Add column headings to the plot
text(-2.5, 28, "Study name", pos = 4, cex = .9)
text(1.8, 28, "Correlation and 95% CI", pos = 2, cex = .9)

# Close off set par back to the original settings
dev.off()
```

```
op <- par(cex = .9, font = 1)
par(op)


########### 7. Run intensity analyses ###########

# Run as a moderator
intensity_moderator <- rma.mv(yi = es,
                              V = variance,
                              mods = ~ ex_inten,
                              data = df,
                              random = ~ 1 | study_id)
intensity_moderator

# Run as a subgroup
subgroup_high <- df %>%
  filter(df$ex_inten == "high")

subgroup_mod <- df %>%
  filter(df$ex_inten == "mod")

high_model <- rma.mv(yi = es,
                     V = variance,
                     data = subgroup_high,
                     method = "REML",
                     level = 95,
                     digits = 7,
                     slab = ref,
                     random = ~ 1 | study_id)
high_model
```

```
mod_model <- rma.mv(yi = es,
                    V = variance,
                    data = subgroup_mod,
                    method = "REML",
                    level = 95,
                    digits = 7,
                    slab = ref,
                    random = ~ 1 | study_id)
mod_model

# Generate forest plots for subgroup intensity analyses - do the same for each subgroup
pdf("ForestPlotHigh.pdf", family = "Courier", width = 10, height = 8.5)

par(mar=c(2.5,4,1,2.5), cex = .9, font = 1)

forest(
  high_model,
  ylim = c(0, nrow(subgroup_high) +1),
  refline = 0,
  main = "",
  xlab = "Effect Size"
)

title("Study ID", line = -1, adj = 0, cex.main = 0.8)
title("Correlations and 95% CI", line = -1, adj = 1, cex.main = 0.8)

dev.off()

op <- par(cex = .9, font = 1)
par(op)

# Generate box plot with individual data points
```

```
data <- data.frame(Model = c(rep("Main Model", length(df$es)),
                             rep("High-Intensity Model", length(subgroup_high$es)),
                             rep("Low- to Moderate Intensity Model", length(subgroup_mod$es))),
                   Effect_Size = c(df$es, subgroup_high$es, subgroup_shortmod$es),
                   Study = c(paste("Study", 1:length(df$es)),
                             paste("Study", 1:length(subgroup_high$es)),
                             paste("Study", 1:length(subgroup_mod$es)))
 )

ggplot(data, aes(x = Model, y = Effect_Size, fill = Model)) +
  geom_boxplot() +
  geom_jitter(aes(colour = Model), width = 0.2) +
  labs(
    x = "Model",
    y = "Effect Size") +
  theme_minimal() +
  scale_colour_manual(values = c("Main Model" = "blue",
                                 "High-Intensity Model" = "red",
                                 "Low- to Moderate Intensity Model" = "green"))


########### 8. Run moderator analyses ###########

# Frequency of exercise
moderator_frequency <- rma.mv(yi = es,
                              V = variance,
                              mods = ~ mod_freq_total,
                              data = df,
                              random = ~ 1 | study_id)
moderator_frequency

# Minutes per week of exercise
```

```
moderator_min <- rma.mv(yi = es,
                        V = variance,
                        mods = ~ mod_freq_min,
                        data = df,
                        random = ~ 1 | study_id)
moderator_min

# Adherence to intervention
moderator_adher <- rma.mv(yi = es,
                          V = variance,
                          mods = ~ mod_adher,
                          data = df,
                          random = ~ 1 | study_id)
moderator_adher

# Type of exercise
moderator_type <- rma.mv(yi = es,
                         V = variance,
                         mods = ~ mod_type,
                         data = df,
                         random = ~ 1 |study_id)
moderator_type

# Create data frame for moderator information
data_mods <- data.frame(moderator1 = df$mod_freq_total,
                        moderator2 = df$mod_freq_min,
                        moderator3 = df$mod_adher,
                        moderator4 = df$mod_type,
                        effect_size = df$es,
                        sample = df$tot_part_ana,
                        intensity = df$ex_inten)
```

```
# Create bubble plot for moderators - repeat for all 4 moderator variables
ggplot(data_mods, aes(x = moderator1, y = effect_size, size = sample, colour = intensity)) +
  geom_point(alpha = 0.7) +
  scale_size_continuous(range = c(2, 8)) +
  labs(title = "Bubble Plot: Effect of Frequency of Exercise on Effect Size",
       x = "Frequency of Exercise",
       y = "Effect Size",
       size = "Sample Size",
       colour = "Exercise Intensity") +
  theme_minimal() +
  theme(legend.position = "right")


############ 9. Run subgroup analyses ############

# Create the subgroups
subgroup_dementia <- df %>%
  filter(df$cog_func_test == "dementia" & df$cog_func_test == "MCI & dementia")
subgroup_MCI <- df %>%
  filter(df$cog_func_test == "MCI" & df$cog_func_test == "MCI & dementia")

subgroup_age <- df %>%
  filter(df$av_age > 65)

subgroup_length <- df %>%
  filter(df$int_length > 25)
subgroup_shortlength <- df %>%
  filter(df$int_length < 25)

subgroup_quality <- df %>%
  filter(df$rob_2 != 3)
```

```
# Run subgroup analyses, and generate forest plots and comparison box plots - do this step for all subgroups
## analyses
dementia_model <- rma.mv(yi = es,
                         V = variance,
                         data = subgroup_dementia,
                         method = "REML",
                         level = 95,
                         digits = 7,
                         slab = ref,
                         random = ~ 1 | study_id)
dementia_model

## forest plot
pdf("ForestPlotDementia", family = "Courier", width = 10, height = 8.5)
par(mar=c(2.5,4,1,2.5), cex = .9, font = 1)

forest(
  dementia_model,
  ylim = c(0, nrow(subgroup_dementia) + 1),
  refline = 0,
  main = "",
  xlab = "Effect Size',"
)

title("Study ID", line = -1, adj = 0, cex.main = 0.8)
title("Correlations and 95% CI", line = -1, adj = 1, cex.main = 0.8)

dev.off()

op <- par(cex = .9, font = 1)
par(op)
```

```
## box plot
data <- data.frame(
  Model = factor(c(rep("Dementia Model", nrow(subgroup_dementia)),
                   rep("MCI Model", nrow(subgroup_MCI)),
                   rep("Main Model", nrow(df))),
                 levels = c("Dementia Model", "MCI Model", "Main Model")),
  Study = c(paste("Study", 1:nrow(subgroup_dementia)),
            paste("Study", 1:nrow(subgroup_MCI)),
            paste("Study", 1:nrow(df))),
  Effect_Size = c(subgroup_dementia$es, subgroup_MCI$es, df$es)
  )

ggplot(data, aes(x = Model, y = Effect_Size, fill = Model)) +
  geom_boxplot() +
  geom_jitter(aes(color = Model), width = 0.2) +
  labs(
    x = "Model",
    y = "Effect Size") +
  theme_minimal() +
  scale_fill_manual(values = c("red", "green", "blue")) +
  scale_color_manual(values = c("red", "green", "blue"))


############ 10. Additional analyses ############

# Run moderator variables on intensity subgroups – this code for both high and mod
intensity subgroups and against all moderators
freq_high_moderator <- rma.mv(yi = es,
                              V = variance,
                              mods = ~ freq_mod_total,
                              data = subgroup_high,
```

```
                    random = ~ 1 | study_id)
freq_high_moderator


############ 11. Small-study bias analysis ############

# Trim-and-fill analysis
main_model <- rma(yi = es,
                  vi = variance,
                  data = df)
trimfill_result <- trimfill(main_model)

# Comparing trim-and-fill model to main model
trimfill_model <- trimfill(main_model)

## compare effect size estimates
main_effect <- coef(main_model)
trimfill_effect <- coef(trimfill_model)

## compare confidence intervals
main_ci <- confint(main_model)
trimfill_ci <- confint(trimfill_model)

## compare statistical significance
main_p <- summary(main_model)$pval
trimfill_p <- summary(trimfill_model)$pval

## visualise comparisons
forest(main_model)
forest(trimfill_model)

## forest plot for trim-and-fill model
```

```
pdf("ForestPlotTrimFill.pdf", family = "Courier", width = 10, height = 8.5)
par(mar=c(2.5,4,1,2.5), cex = .9, font = 1)
forest(
  trimfill_model,
  refline = 0,
  main = "",
  xlab = "Effect Size",
  mlab = "RE Model: p < .01, I2 = 95.7"
)
title("Study ID", line = -1.5, adj = 0, cex.main = 0.8)
title("Correlations and 95% CI", line = -1.5, adj = 1, cex.main = 0.8)
dev.off()
op <- par(cex = .9, font = 1)
par(op)

# Create funnel plot
model_trim_fill <- rma(yi = es,
                       vi = variance,
                       data = df)

pdf("FunnelPlot.pdf", width = 7, height = 5)
par(mar=c(4.5,4.5,1,1))
taf <- trimfill(model_trim_fill)
funnel(taf,
       xlim = c(-1,1),
       xlab = "Correlation",
       ylim = c(.24, 0),
       steps = 4,
       digits = c(1, 2))
par(mar=c(2.5,3.6,0,1.5))
dev.off()
```

```
# Run Egger's test
standard_errors <- sqrt(df$variance)
random_effects_model <- metafor::rma(yi = df$es,
                                     vi = standard_errors^2,
                                     method = "REML")
egger_test <- metafor::regtest(random_effects_model)

# Generate a p-curve
p_values <- numeric(length(df$es))
p_curve_data <- character(length(df$es))
for (i in seq_along(df$es)) {
  t_stat <- df$es[i] / sqrt((1 - df$es[i]^2) / degrees_freedom[i])
  p_values[i] <- 2 * (1 - pt(abs(t_stat), degrees_freedom[i]))
  p_curve_data[i] <- paste("R(", degrees_freedom[i], ")=", df$es[i], ", p=", p_values[i], sep="")
}
print(p_curve_data, row.names = FALSE)
write.table(p_curve_data, "p-CurveData.csv", sep = ",", row.names = FALSE, col.names =
FALSE)
print(p_values)

## sort p-values in ascending order
sorted_p_values <- sort(p_values)

## convert p-values to a data frame
p_data <- data.frame(p = sorted_p_values)

## create a kernel density estimate of the p-values
p_density <- density(p_data$p)

## plot the kernel density estimate
ggplot(p_data, aes(x = p)) +
  geom_density(fill = "skyblue", color = "black") +
```

```
geom_vline(xintercept = 0.05, linetype = "dashed", color = "red") +
labs(x = "p-value", y = "Density") +
theme_minimal()
```