Physiological and Cognitive Responses to Isometric Resistance Training in Individuals Experiencing Memory Difficulties or With Mild Cognitive Impairment

Nicole Catherine Lincoln Hess
BPsych (Hons), University of New England, 2013

A thesis submitted for the degree of Doctor of Philosophy
to the University of New England
September 2016

Certification

I certify that the substance of this thesis has not already been submitted for any degree and is not currently being submitted for any other degree or qualification.

I certify that any help received in preparing this thesis and all sources used have been acknowledged in this thesis.

Candidate Signature

Dedication

This body of work is dedicated to my beautiful daughter Adrienne who died so suddenly and so very tragically 18 months after I began my PhD, and to my beautiful son Zacchary who is the light of my life and the strength that keeps me going.

Acknowledgements

I thank my supervisors, Neil Smart, Debra Dunstan, Jim McFarlane, and Gudrun Dieberg for being so giving of their time and their expertise, and for their concern and support through very difficult times. Thankyou Eliza Kent and the HDR team who gave me incredible support and helped me navigate my PhD journey through to completion. I wholeheartedly thank Debra Carlson for taking over the reins of my randomised trial after my daughter passed away; I am forever grateful for your support and kindness Debra. In this regard, I also thank Jodie Inder and Emmanuel Jesulola for their roles in assisting Debra to coordinate the study and finalise the data collection. Thank you, Bridgette Campbell for your all-round assistance helping with the coordination of the pilot studies. Thank you, Margaret and Michael Hill, managers of Sunny Cove Village, for allowing me to conduct my research with the Sunny Cove residents and utilising your facilities to do so. I thank the staff and provisional psychologists from the University of New England psychology clinic for coordinating and administering neuropsychological testing for the pilot case-studies; specifically, I would like to thank, Debra Dunstan, Warren Bartik, Natalya O'Keefe, Reese Lavender, Kerryn Rowe, Tommy Janovski, and Pam Roberts. Anna Terentieva, thank you for all of the artwork that you created.

Thank you to my dear friends Martin Collins and Katrina Grasby for their unwavering support, valuable advice, intellectual counsel, and superb formatting skills. To my beautiful Mother and Sister, your love, strength, and support have buoyed me. Thank you.

Preface

This thesis is by publication. The thesis is composed of an introductory chapter, which outlines and provides context on the topic and purpose of the subsequent papers, a methods chapter, a main body which is composed of four manuscripts, either accepted, submitted and in review, or in preparation to submit to a journal. For each of these chapters the author's contribution and statement of originality are provided. The concluding chapter links together the manuscripts, highlights the contribution of the body of work and discusses future research directions. Cited works are referenced at the end of the chapter in which they are cited.

Publications arising from thesis:

Chapter 3:

The effect of exercise intervention on cognitive performance in persons at risk of, or with, dementia: A systematic review and meta-analysis. (2014). *Healthy Aging Research*. doi: 10.12715/har.2014.3.3

Chapter 4:

HESS, N., CARLSON, D., INDER, J., JESULOLA, E., MCFARLANE, J., & SMART, N. (2016). Clinically Meaningful Blood Pressure Reductions With Low Intensity Isometric Handgrip Exercise. A Randomized Trial. *Physiological Research*, 461-468. doi: 10.33549/physiolres.933120

Chapter 5:

Hess, N., & Smart, N. (2017). Isometric Exercise Training for Managing Vascular Risk Factors in Mild Cognitive Impairment and Alzheimer's Disease. *Frontiers In Aging Neuroscience*, *9*. doi: 10.3389/fnagi.2017.00048

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Abbreviations

AACD = Age-associated cognitive decline

AAMI = Age-associated memory impairment

ACE = Angiotensin converting enzyme

ACTH = Adrenocorticotrophin hormone

AD = Alzheimer ’s disease

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

ADS 6 = Amsterdam Dementia Screening Test

aMCI = Amnestic mild cognitive impairment

ANCOVA = Analysis of co-variance

ANOVA = Analysis of variance

APOPε = Appolipo protein epsilon genotype

APP = Amyloid precursor protein

Aβ = Amyloid beta

BA = Brodmann area

BBB = Blood brain barrier

BDNF = Brain derived neurotrophic factor

BMI = Body mass index

BP = Blood pressure

CAD = Cardiovascular arterial disease

CBF = Cerebral blood flow

CDR = Clinical Dementia Rating scale

CDT = Clock drawing test

CI = Confidence interval

CNS = Central nervous system

CRP = Acute phase C reactant protein

CVD = Cardiovascular disease

DBP = Diastolic blood pressure

eNO = Endothelial nitric oxide

EPC = Endothelial progenitor cell

ERFC = Rapid Evaluation of Cognitive Function- French version

F/UP = Follow up

FMD = Flow mediated dilation

GDS = Geriatric Depression Scale

HAAS = Honolulu Asia Aging Study

HIF-1α = Hypoxia-inducible factor-α

HR = Heart rate

HREC = Human Research Ethics Committee

IET = Isometric exercise training

IGF-1 = Insulin-like growth factor 1

IHG = Isometric handgrip training

IL-1= Interleukin-1

IL-10 = Interleukin-10

IL-1ra = Interleukin-1ra

IL-1β = Interleukin-1β

IL-6 = Interleukin-6

IRD = Improvement Rate Difference

M = Mean

MAP = Mean arterial pressure

MCI = Mild cognitive impairment

MD = Mean difference

mmHg = Millimetres of mercury

MMSE = Mini Mental State Exam

MRI = Magnetic resonance imaging

MVC = Maximal voluntary contraction

NFT's = Neurofibrillary tangles

NO = Nitric oxide

NT's = Neuropil threads

PEM = Percentage of Data Points Exceeding the Median

PIT = Physiological ischemic training

PP = Pulse pressure

p-tau = Tau protein

RBANS = Repeatable Battery for the Assessment of Neurological Status

RCT = Randomised controlled trial

RDBP = Resting diastolic blood pressure

RIC = Remote ischemic conditioning

RNS = Reactive nitrogen species

ROS = Reactive oxygen species

RSBP = Resting systolic blood pressure

SBP = Systolic blood pressure

SCR = Initial screening prior to research intervention

SD = Standard deviation

TNF-α = Tumor necrosis factor-α

VaD = Vascular dementia

VEGF = Vascular endothelial growth factor

VO_{2max} = Maximum volume of oxygen

VRF = Vascular risk factors

WAIS-R = Wechsler Adult Intelligence scale revised

Abstract

Dementia is the second leading cause of death in Australia and the greatest cause of disability in people aged 65 years or older. On a global scale, it is estimated that there are more than 46.8 billion people living with dementia at an estimated cost of $815 billion USD. Alzheimer's disease (AD) is the most common form of dementia diagnosed amongst the elderly and Mild cognitive impairment (MCI) is a condition often indicative of the earliest symptomology of AD. Recent investigations report that individuals with a history of vascular risk factors (VRF) such as hypertension are high risk candidates for cognitive decline in later life, and that VRF promote progression from MCI to AD. Research suggests that isometric exercise training (IET) promotes anti-hypertensive effects and improved vascular endothelia functioning. It may be the case that IET has the potential to prevent, reduce, or attenuate the adverse effects that VRF have on cognitive performance outcomes and progression to AD. This thesis investigates cognitive and physiological responses to IET in elderly individuals experiencing memory impairment, MCI or AD. **Methods**: First, a meta-analysis was conducted to review the impact of exercise on cognitive performance outcomes. Second, in consideration of the frail and elderly who might struggle with IET at 30% maximal voluntary contraction (MVC), a randomised study was conducted in an attempt to determine the minimum anti-hypertensive threshold intensity for IET. Finally, we ran a small pilot-case-study to assess the impact of IET at 20% MVC on cognitive performance outcomes in elderly individuals experiencing memory impairment or diagnosed with AD. **Outcomes:** Physical activity provides significant improvements in some domains of neurocognitive functioning. The results of a randomised trial indicated that 6 weeks of low intensity (5% and 10% MVC) IET elicited reductions in systolic blood pressure (BP) similar to the antihypertensive effects observed in monotherapy of 5 – 7 mmHg. The results of four pilot case-studies reported that overall cognitive functioning remained stable for all but one participant; however, IET did not reduce resting BP after 3, 5 or 6 weeks of IET at 20% MVC. **Conclusions:** Physical activity improves neurocognitive function in people with cognitive impairments. In Individuals unable to complete isometric exercise at 30% MVC, our results suggest both 5% and 10% MVC may offer clinically relevant anti-hypertensive effects. Isometric exercise at 20% MVC does not reduce resting BP in elderly medicated hypertensives after 3, 5 or 6 weeks of training. Improvements in cognitive performance measures were not attributed to the anti-hypertensive effects of IET and may be attributed to increased social interaction or neurohormonal pathways not necessarily associated with BP reduction.

Chapter 1 : The Holistic Effects of Alzheimer's Disease: Socio-Economic, Physiological and Neurophysiological Etiology and Staging

1.1 Alzheimer's disease

Dementia is not a term that is unique to any one specific disease, instead it is an overarching term that encompasses a wide array of symptoms, and functional and cognitive deficits such as learning, memory, attention, motivation, executive function, motor function, global cognition, and activities of daily living [1,2]. Dementia occurs as a direct result of neuronal cell damage and most cases are irreversible. Whilst some cases of dementia may arise due to factors such as depression, excessive alcohol consumption, vitamin deficiencies, thyroid problems, and medication side effects, for the most part, dementia is caused by progressive neurodegenerative nervous system diseases such as Parkinsons, Huntingtons, Pickings, Alzheimers, and Lewy bodies [3,4]. In terms of both neural location and pattern of neurodegenerative progression, each different type of dementia is hallmarked by its own unique neuropathological fingerprint.

The most common form of dementia is Alzheimer's disease (AD) which accounts for 50–80% of all dementia cases [4,5]. Alzheimer's is a progressive, neurodegenerative dementing disorder that initially presents as a subtle decline in memory and manifests over time in the deterioration of global cognitive functioning, including personality changes, deterioration in language function, visuospatial awareness, and motor system function [5,6]. The pathological substrate responsible for these devastating debilities is extensive cerebral deterioration resulting from the progressive loss of synapses and neurons [5-7]. The time course of the disease is variable between individuals; however, the general prognosis is death within 3–9 years of receiving a clinical diagnosis [5]. Despite this seemingly rapid progression, long preclinical and prodromal phases of between 10–40 years are estimated prior to the onset of clinical symptoms and the subsequent diagnosis of AD [6-8].

Although clinical symptoms are not observed during the preclinical phase of AD, neuropathological changes are already evident within specific regions of the allocortex [6-8] (the allocortex includes the entorhinal and hippocampal). The clinical course of the disease may be defined in three stages: a preclinical/asymptomatic phase; prodromal/symptomatic phase, and dementia [7,9]. The preclinical phase is characterised by neuropathological changes with no functional or cognitive deficits [7,10]. Because there is no evidence of remission of Alzheimer-related neuropathological alterations [6,8], it is presumed that individuals with preclinical alterations, who live long enough, will develop symptomatic AD [7,8]. In the prodromal phase, intensifying neuropathological changes are accompanied with the first clinical expressions of the disease [7]. The prodromal/symptomatic phase may be further divided into mild or severe cognitive impairment according to clinical diagnoses and observation. This phase is commonly referred to as mild cognitive impairment (MCI) [7,11]. The final phase in the development of clinical AD is dementia; this phase can be further broken down as mild, moderate, and severe AD.

1.2 Prevalence and socio-economic impact of dementia

1.2.1 Prevalence

Ranging across the spectrum from MCI to AD, cognitive decline is one of the greatest health threats facing elderly Australians today [12]. Currently dementia is the second leading cause of death in Australia [13] and the greatest cause of disability in people aged 65 years or older [14]. Every 6 minutes in Australia someone is diagnosed with dementia [15]. This equates to more than 1,800 new cases of dementia being diagnosed in Australia each week [15]. In a comprehensive report on dementia, the Australian Institute of Health and Welfare [14] reported that in 2012 approximately 353,800 people were living with dementia and that this figure had more than doubled since 2004. In the absence of any significant medical breakthroughs, and

if this trend in growth continues, by 2050 more than 900,000 Australian people will be living with dementia [14]. Whilst dementia is not considered to fall within the normative spectrum of aging, age does appear to be a major contributor to this disease. Sporadic (late-onset) dementia affects close to one in ten individuals over the age of 65 and approximately three in ten individuals over the age of 85. Early-onset dementia (dementia diagnosed under the age of 65, with some of the youngest cases diagnosed at 30 years of age) currently affects almost 25,100 Australian people [14]. By 2050 it is predicted that worldwide, 131.5 billion people will be living with dementia [16].

1.2.2 Financial economic costs

Across 2009 to 2010, direct expenditure on health and aged care on individuals living in Australia with dementia was gauged at $4.9 billion [14]. By 2060 these costs are forecast to reach $83 billion and will reflect the greatest expenditure on any one health condition [15]. Currently, more than 50% of aged care persons residing in Australian government subsidised facilities have dementia [17]. On a world-wide scale it is predicted that there are more than 46.8 billion people living with dementia at an estimated cost of $815 billion USD [16].

1.2.3 Social costs

Whilst caring for a person with any type of disability or chronic condition can be physically, mentally and economically demanding, there is research to suggest that the burden of caregiving is particularly high for those caring for a person with dementia [18]. There are a number of factors that may affect the level of caregiving burden, including personal characteristics of carers and care recipients, living arrangements, employment and financial situations, and level of support available from formal services, family and friends [18].

A 2009 Australian survey [14] on disability, aging, and carers found that 34% of co-resident, primary carers of a person living with dementia reported feeling weary or lacking energy, 33% reported frequently feeling worried, and 66% reported some extent of sleep disturbance. The same survey reported that being a primary carer did not only affect the relationship of the carer to the care recipient but it also affected the carer's relationship to others; 34% of co-resident primary carers of a person living with dementia reported that the care giving role had placed strain on their relationship with the care recipient; 39% reported that they had lost touch or were losing touch with existing friends due to the caring role. For caregivers in the paid workforce, the demands of caring for a person with dementia may have implications for their employment; of the co-resident primary carers who were surveyed, 74% cited the main reason for having to leave paid employment was that there were no alternative care arrangements available.

Many of these social costs will translate directly to economic costs, for example increasing medical and mental health care costs for struggling carers, greater pressures on the healthcare system to meet the increased demands of healthcare workers to support carers, and increased pressures on the social welfare system as a result of carers being unable to hold down full time work. The current and bourgeoning socio-economic costs of dementia are frightening and highlight the importance of health and medical research to search for new treatments that might prevent, ameliorate, or attenuate this devastating disease.

1.3 Mild cognitive impairment due to AD

Cognitive impairment without dementia, such as age-associated cognitive decline (AACD) and age-associated memory impairment (AAMI), is considered to fall within the normative realms of brain aging [19,20]. Whereas MCI is a condition that is characterised by a deterioration in cognitive abilities and memory beyond that expected for a person's age and level of

education, but without notable loss of global cognition or activities of daily living [2,11,20,21]. Depending on the cognitive functions that are affected, MCI is further classified into either nonamnestic MCI or amnestic MCI [20]. Nonamnestic MCI affects cognitive domains other than memory such as the sequencing of complex tasks, judgement and decision making skills, and visual perception, whereas amnestic MCI primarily affects memory [2,11,20]. In many cases MCI is considered to be indicative of the early-stages of AD.

While not all cases of MCI will progress to a clinical diagnosis of dementia [22], within the space of 12 months 10–15% of MCI cases will progress to a clinical diagnosis of AD [11,22]. Subsequently, MCI is considered to represent the earliest symptomatic indications of AD [11,22-24]. MCI due to AD is a subset of cognitive impairment whereby the underlying pathophysiology is AD. As with AD, MCI due to AD cannot be identified nor distinguished from MCI that is not due to AD in laboratory tests and must be diagnosed by a clinician on the basis of clinical, cognitive, and functional criteria [25]. Consequently, MCI is viewed as a prodromal, pathological condition rather than as a consequence of the normative aging process [25,26].

1.4 Neuropathology of AD

Extracellular amyloid beta (Aβ) plaque formation and cytoskeletal neuropil threads (NT) and neurofibrillary tangles (NFT) are the hallmark pathological features of AD. Aβ peptides are a naturally occurring metabolite of the proteolysis of amyloid precursor protein (APP). When an imbalance between Aβ production and clearance occurs Aβ accumulation will result. This excess has been postulated as the initiating factor in AD driving both tau protein (p-tau) hyper-phosphorylation and aggregation, and Aβ plaque aggregation [5,6]. Neuronal cytoskeleton alterations (p-tau hyper-phosphorylation) resulting from an over accumulation of Aβ is thought to be the primary lesion that develops in AD. Tau proteins that would

normally stabilise the microtubules of a healthy neuron become hyper-phosphorylated, leading to the production of dense bundles of intra- and extracellular fibrils (NT and NFT) [5,6].

1.4.1 Staging Alzheimer's disease

Post mortem examinations have identified that AD related intraneuronal abnormal p-tau changes follow a predictable pattern of destruction and demonstrate little variation among individual suffers of the disease [6,27-30]. The disease begins in the subcortical regions of the brain and radiates outwards extending into the neocortex (an external map of the neocortex is provided in Figure 1.1 and various iterations of subcortical neural views are provided throughout the manuscript in Figures 1.2–1.4). This predictability has allowed scientists to identify six stages in the pathological evolution of abnormal cytoskeletal alterations that are the hallmark of AD. Braak and Braak [31] describe six neuropathological stages of the progression of AD; the transentorhinal stages I and II, the limbic stages III and IV, and the neocortical stages V and VI.

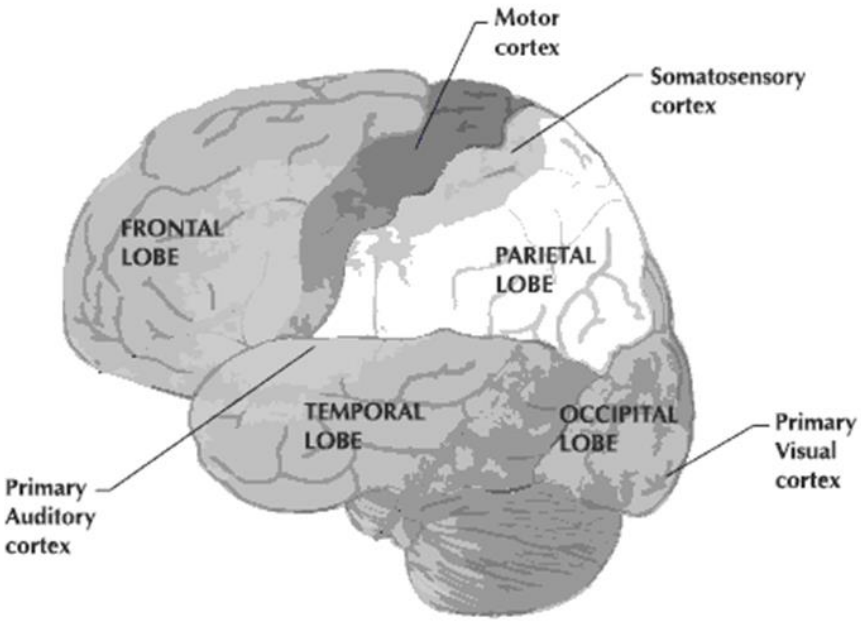


Figure 1.1 Lateral view of external regions of the left cerebral/neo cortex.

The transentorhinal stages I and II

Stage I: The development of lesions in the transentorhinal region, Figure 1.2. This is the first neural region to fall victim to intraneuronal AD related p-tau formation. These abnormal alterations will eventually formulate NFTs and NTs [6,27].

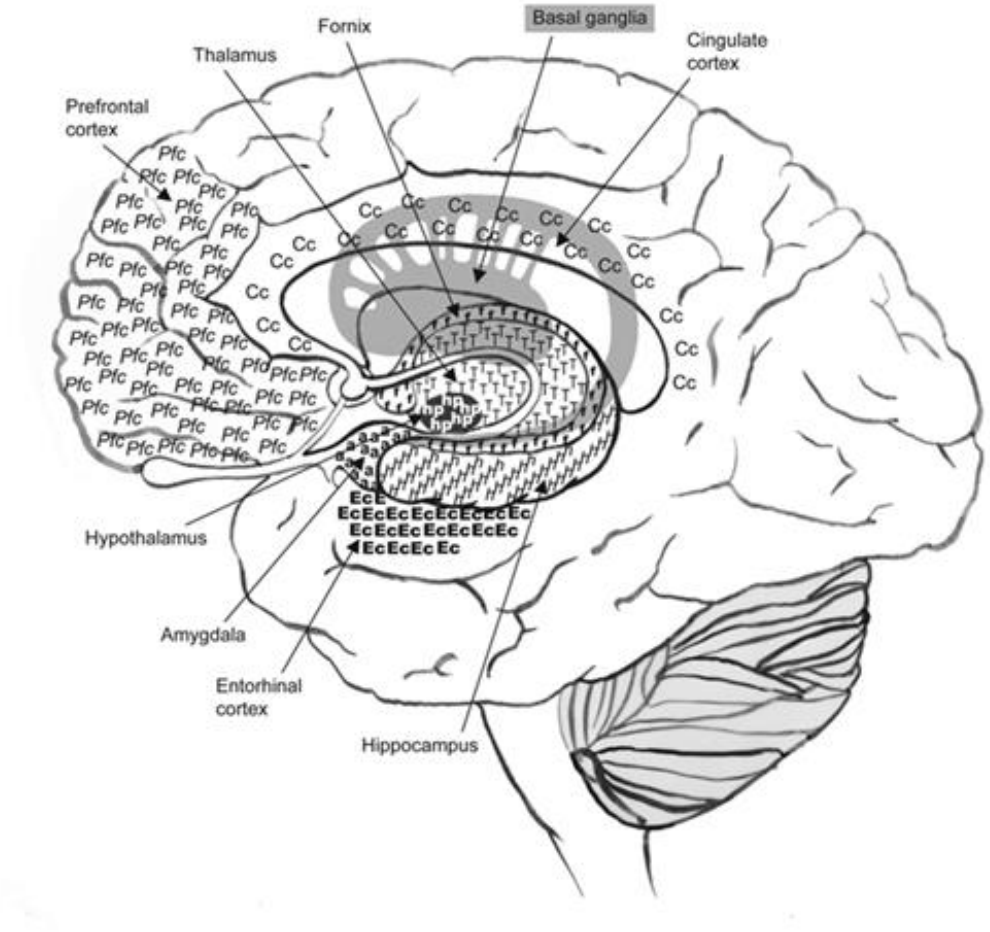


Figure 1.2. Sagittal view of the brain.
Alzheimer's disease (AD) is responsible for severe cortical atrophy in selective regions of the brain such as the frontal and prefrontal cortex, and the temporal, medial-temporal and limbic areas. Neural structures associated with these regions include the thalamus, basal ganglia, cingulate cortex, fornix, hypothalamus, amygdala, hippocampus and entorhinal cortex. The first neural region succumb to intraneuronal AD related tau protein formation is the entorhinal cortex.

Stage II: Density of lesions increase in the transentorhinal region and project into the entorhinal region proper. Abnormal p-tau appear in the regions CA1 and CA2 of Ammon's horn in the hippocampus [6,27], Figure 1.3.

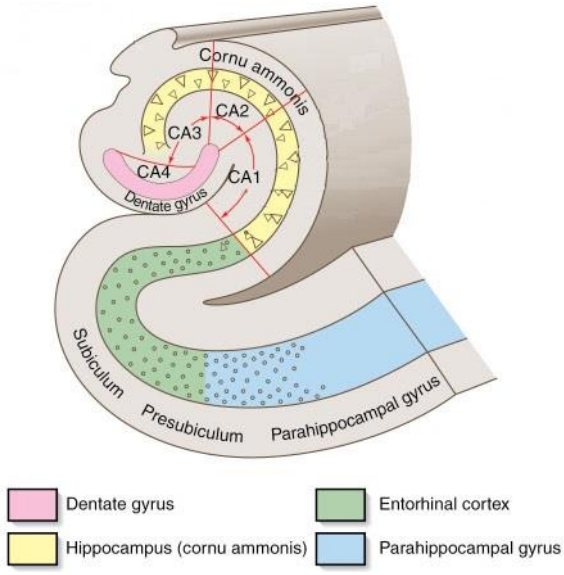


Figure 1.3. Ammon's horn in the hippocampus.
In Stage II of the neuropathological changes in Alzheimer's disease, abnormal tau proteins appear in the regions CA1 and CA2 of Ammon's horn in the hippocampus.

The neuronal destruction that occurs in stages I–II causes minor impediment to the transmission of information from the neocortex (cerebral cortex) through the entorhinal cortex to the hippocampal formation. However, at this stage of the disease there is insufficient neural destruction to manifest in clinical symptomology [6,27].

The limbic stages III and IV

Stage III: NFTs worsen in the transentorhinal and entorhinal regions, and the lesions extend into the neocortical association areas of the fusiform gyrus and calcarine fissure (occipito-temporal). Slight neurofibrillary changes progress in the hippocampal formation and begin to occur in the temporal and insular proneocortical areas and in a few subcortical nuclei [6,27].

Stage IV: The disease extends broadly into neocortical association areas (such as the frontal association areas Brodmann area (BA) 9 and 10, pre-motor association area BA6, primary motor cortex BA4, somatosensory cortex BA1 to BA3, sensory association areas BA7, and primary visual cortex BA17 to BA19) and the medial temporal gyrus, and lesion density increases in the transentorhinal and entorhinal regions [6,27]. Neuroanatomical locations of stage III and IV disease progression are shown in Figure 1.4.

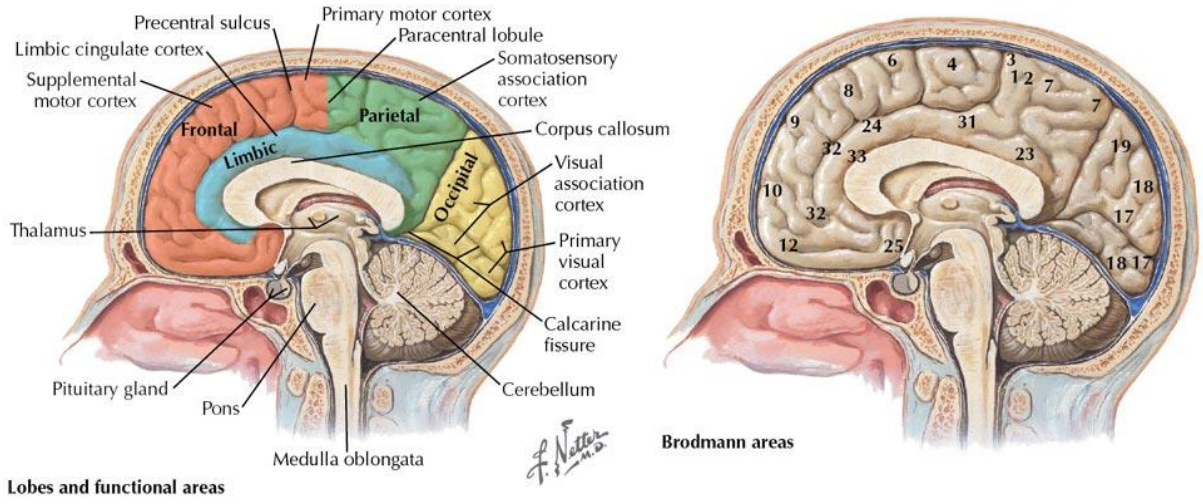


Figure 1.4. Neuroanatomic regions and Brodmann areas (BA) of the neocortex.
During stage III of the neuropathological progression of Alzheimer's disease, lesions extend into the occipito-temporal gyrus (located next to the calcarine fissure). During Stage IV pathological insult extends broadly into neocortical regions (frontal association areas BA9 and BA10, pre-motor association area BA6, primary motor cortex BA4, somatosensory cortex BA1 to BA3, sensory association areas BA7, and primary visual cortex BA17 to BA19).

Symmetrical affliction of the two cerebral hemispheres is the normal course of the pathology [6]. Because data exchange between the sensory association fields (which receive and process information from the senses), components of the limbic system (involved in long-term memory, emotion, behaviour, motivation, and smell), and the prefrontal cortex (involved in planning and sequencing complex tasks, judgement and decision making, behavioural

inhibition, expression of personality characteristics, and motivation) are hampered by the pathological insult characteristic of stages III and IV, the first noticeable functional disturbances may now become obvious [6]. Subtle mental deterioration and personality changes will present in many patients, in others symptoms may remain obscured due to individual cognitive reserve capacities (predominately correlated to years of education and occupation) [6]. Because it is most common for clinical symptoms to manifest in either of these stages, stages III or IV are considered to represent the morphological phase of preclinical AD [6].

The neocortical stages V and VI

Stage V: Neocortical insult proceeds fanlike superolaterally (the superolateral aspect of the brain involves areas of the cortex that lay in contact with the flat bones of the skull; this includes parts of the frontal, temporal, parietal, and occipital lobes) and lesions begin to infiltrate high order association areas of the frontal, parietal, and occipital neocortex (peristriate region) [6,27].

Stage VI: Lesions penetrate secondary and primary neocortical areas and extend into the striate area of the occipital cortex [6,27]. This stage is accompanied by macroscopic cortical atrophy, enlarged ventricular cavities due to cortical atrophy, and a marked loss in brain weight [6,27]. Severe dementia and gross disturbances of autonomic functions occur as a result of this devastating cortical atrophy [6].

1.5 Hypotheses of Alzheimer's disease

1.5.1 Amyloid hypothesis of AD

The analysis of cerebrovascular amyloid in patients with Down's syndrome in 1984 by Glenner and Wong [32] is considered to have initiated the Amyloid hypothesis of AD [33]. This hypothesis purports genetic causation and proposes that the Aβ peptide initiates a cascade of

events that result in neuronal injury and loss, and ultimately, AD. According to this theory tau protein develops primary to amyloid beta injury [5,34].

1.5.2 Vascular hypothesis of AD

The vascular hypothesis of AD dementia was first proposed in 1993 by de la Torre and Mussivand [35]. The vascular hypothesis of AD recognises that vascular dysfunction and neuronal dysfunction are intimately linked and highlights the importance of the circulatory system to brain functions [35,36]. The hypothesis proposes that sporadic (late-onset) AD is a multifactorial disease fuelled by vascular risk factors (VRF) such as hypertension, atherosclerosis, cardiac disease, stroke, and diabetes that contribute to chronic brain hypoperfusion (reduced neural blood flow) [37]. Chronic brain hypoperfusion, present during normal aging, is exacerbated by the influence of VRF. Obstructed cerebral blood flow (CBF) prevents the efficient delivery of nutrients such as oxygen, glucose, and micronutrients to the brain compromising energy metabolism and neural activity. De la Torre [36] suggested that the ability to couple obstructed CBF with VRF indicates that chronic brain hypoperfusion is a preclinical condition for MCI and a predictor of the later development of AD.

1.5.3 The two-hit vascular hypothesis of AD

More recently, the two-hit vascular hypothesis for AD has been proposed [34]. Similar to the vascular hypothesis, the two-hit hypothesis also proposes a non-amyloidogenic pathway of AD, which is driven by VRF. Subsequently, according to the two-hit theory vascular damage (hit one) leads to dysfunction of the blood brain barrier (BBB) and a reduction in CBF (oligaemia). Vascular injury inhibits the clearance of Aβ at the BBB; this in turn mediates increased production of Aβ and results in the accumulation of neurotoxic levels of this peptide. Both the aggregation of toxic levels of Aβ, and cerebral hypoperfusion promote early

neuronal dysfunction. Continuing increases in Aβ accumulation (hit two) exacerbates neuronal dysfunction, is a catalyst for neurodegeneration and AD, and promotes self-propagation of the disease, Figure 1.5. Contrary to the amyloid beta hypothesis, the two-hit theory proposes that Aβ and/or cerebral hypoperfusion will induce the hyperphosphorylation of p-tau resulting in the formation of neurofibrillary tangles. This theory suggests that p-tau is secondary to Aβ injury.

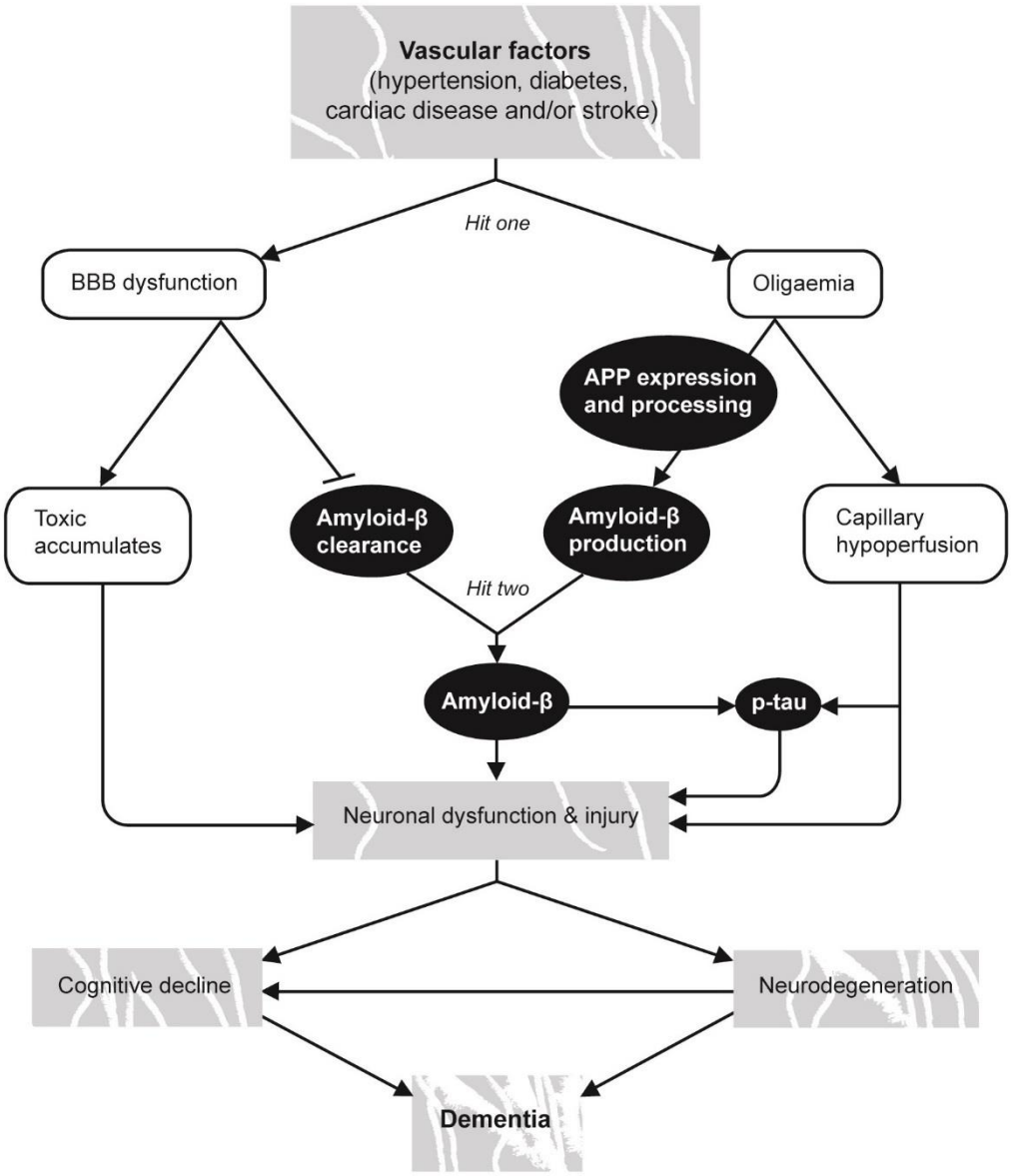


Figure 1.5. Two hit vascular theory of Alzheimer's disease.

Hit one, dysfunction of the blood brain barrier leads to oligaemia. Vascular injury inhibits the clearance of Aβ at the BBB; this in turn mediates increased production of Aβ and results in the accumulation of neurotoxic levels of this peptide. Both the aggregation of toxic levels of Aβ, and cerebral hypoperfusion promote early neuronal dysfunction. Hit two, continuing increases in Aβ accumulation exacerbates neuronal dysfunction, is a catalyst for neurodegeneration and AD, and promotes self-propagation of the disease.

1.6 Risk factors

Whilst dementia is not considered to be a part of the normal aging process, age does appear to be the principle risk factor with the majority of people diagnosed with AD 65 years or older [5,38,39] and the incidence of the disease doubling every 5 years thereafter [5]. After the age of 85 years the likelihood of being diagnosed with AD is greater than one in three [5], in fact, most cases of dementia are diagnosed in this age category [40]. However, for some people old age alone is a dispensable factor; despite extreme old age some people never develop dementia even in the presence of neuropathological changes that are associated with AD [10,39]. An autopsy of 3508 non-selected cases [8] revealed that the development of neurofibrillary changes pertaining to transentorhinal stages I/II (equivalent to preclinical dementia) can occur surprisingly early in life. Braak and Braak found that of the 3508 autopsies approximately 20% of stage I and II cases occurred within the 25–30 year age bracket. Although these individuals were reportedly cognitively healthy at the time of death, the stage I and II lesions observed in autopsy were hypothesised to more than likely signify the beginning stages of AD. These findings suggest that even though neuropathological and disease development will evolve over the fullness of time, old age alone is not sufficient criteria for the development of AD; lifestyle choices early in life may alter the trajectory of the disease overtime.

AD is believed to have a long preclinical phase of between 10–40 years [6,7,27]. By the time that clinical symptoms present cortical atrophy has progressed to neocortical levels including, neocortical primary, secondary, and association regions. MCI and dementia are associated with a number of modifiable risk factors such that early diagnosis and treatment of these conditions may stabilise or halt the progress of the disease and possibly improve neurocognitive functioning, quality of life and other activities of daily life. Consequently, early detection of the potential precursors of AD, such as VRF and MCI, and the attenuation

of these modifiable risk factors through interventions such as physical activity and diet may reduce the prevalence of these neurodegenerative pathologies [11,21]. AD is an irrevocable condition, subsequently, there is a tremendous need for therapeutic treatments that may prevent, attenuate, or slow down the progression of MCI to AD, and from early stage AD to more advanced stages. Preventative actions and treatments are believed to most likely be effective in the early stages of AD and other dementing disorders [21].

1.6.1 Vascular risk factors

AD and vascular dementia (VaD) are the two most common forms of dementia diagnosed amongst older adults, with AD being most common [41]. AD is hallmarked by severe cortical atrophy in selective regions of the brain such as the temporal, medial temporal, limbic, frontal and prefrontal cortices [1,5,27]. The functional and cognitive attributes affected by the deterioration of these brain structures include learning, memory, attention, motivation, executive function, motor function, global cognition, and activities of daily living [1,2]. MCI, a prelude to dementia [11,22], is also associated with disproportionate atrophy in the medial temporal and temporal cortices [2,27]. The severity and extent of AD related neurodegenerative atrophy grows as a function of time, destroying cognitive and functional abilities at each stage, whereas the presentation of dementia in VaD is attributed to dysfunctional vascular mechanisms alone [42]. In VaD memory remains intact with attentional and executive functioning disproportionately impaired [42,43], Figure 1.6 maps the different courses of AD and VaD. Traditionally these two diseases have been studied separately; however, increasingly over the past decade investigators have been able to link the contribution of VRF, such as hypertension, atherosclerosis, and cerebrovascular disease, to MCI and AD [34,37,44-46]. Recent studies report that individuals with a history of VRF and vascular disease are high risk candidates for developing cognitive impairment in later life and that untreated VRF promote

progression from MCI to AD. [44,47,48]. The results of 'The Honolulu Asia Aging Study' (HAAS) [47] suggest that hippocampal atrophy is linked to untreated hypertension in midlife, and that a positive correlation exists among systolic blood pressure (SBP), diastolic blood pressure (DBP), and burden of neural AD pathology.

Hypertension is chronically elevated blood pressure and is associated with increased peripheral arterial resistance. High blood pressure within the artery promotes dysfunctional shear wall stress, the impact of this type of shear stress results in damage to the endothelial lining of the vessel promoting the formation of atherosclerotic plaques [49]. Atherosclerosis (hardening of the arteries) is a pathological condition hallmarked by the deposition of calcium and lipid deposits below the vascular endothelium. These plaques harden overtime narrowing arteries and restricting blood flow to organs and other regions of the body [49]. One hypothesis is that the increased arterial peripheral resistance observed in hypertensive patients may occur due to a lack of nitric oxide (NO). NO is a signalling molecule that mediates blood vessel relaxation (vasodilation) [50]; furthermore, low concentrations of this vasodilator offer neuroprotective benefits [51]. Under physiological conditions NO assists in the genesis, nurturance, and differentiation of neurons; it is involved in memory function, synaptic activity, and neural plasticity [51]. Subsequently the significance of its role in cerebrovascular dysfunction in neurodegenerative diseases such as AD may warrant further investigation and qualification.

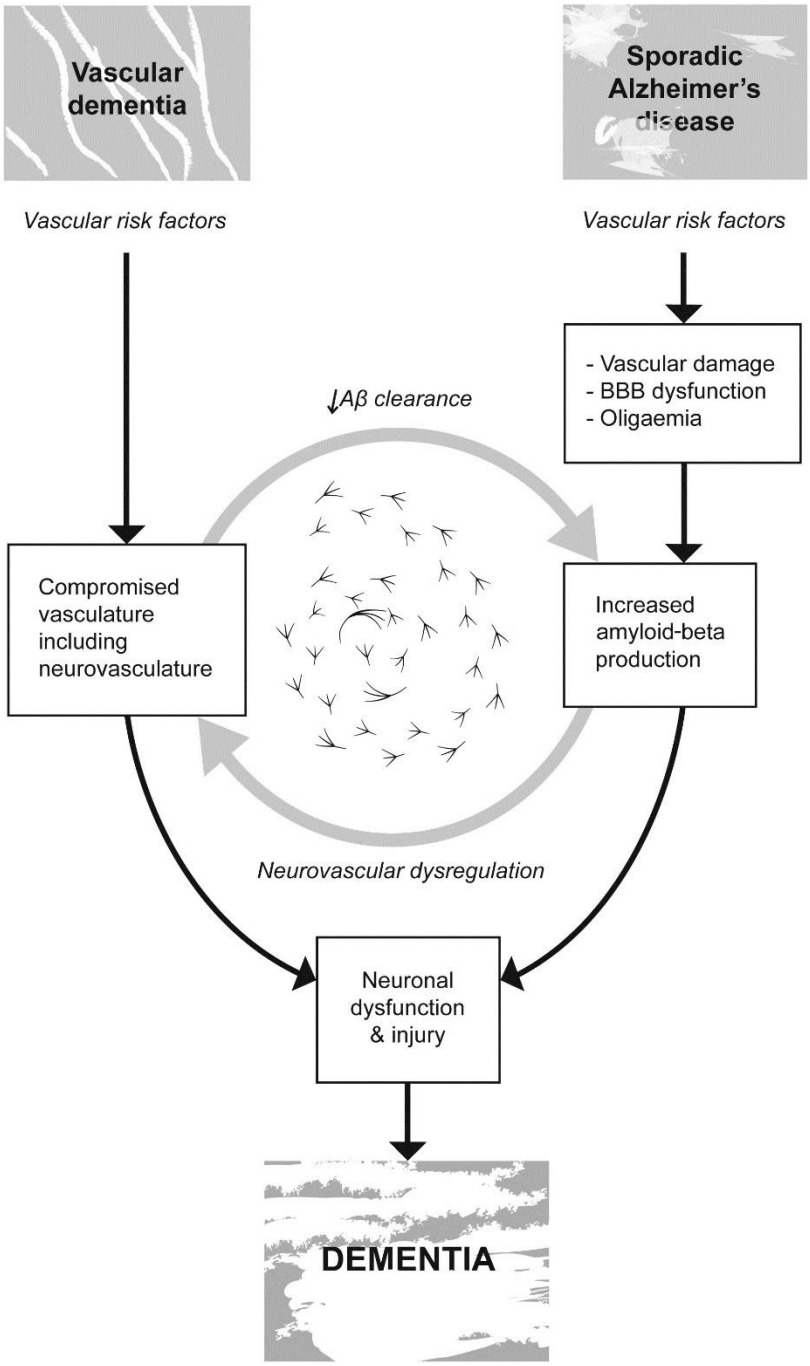


Figure 1.6. Vascular dementia (VaD) versus Alzheimer's disease (AD).

Sporadic AD is accompanied by both neurovascular dysregulation and the increased production and over accumulation of Aβ, whereas the presentation of dementia in VaD is attributed to dysfunctional vascular mechanisms alone.

1.7 Physical activity as a therapeutic intervention for MCI and AD

Exercise has been demonstrated as an effective therapeutic intervention for hypertension, atherosclerosis, MCI, and AD [52-54]. Specifically, aerobic exercise stimulates endothelium-dependent vasodilation through increased production of NO, and with regular compliance aerobic exercise inhibits age associated loss in endothelium-dependent vasodilation and restores levels in previously sedentary individuals [55]. Consequently, most studies have focused on aerobic exercise due to shear wall stress and the subsequent release of NO. Moreover, a growing body of evidence suggests that exercise training that targets cardiovascular fitness (VO_{2max}) may offer neuroprotective benefits and attenuate neuronal structural and functional changes that are associated with dementia and MCI [56-58]. Certainly, evidence from animal models has demonstrated that aerobic exercise can increase neurogenesis, angiogenesis, learning and memory in the rat [59,60] and inhibit the progression of AD related neuropathology in the mouse [61]. Current literature reports that exercise taken up in midlife by healthy adults increases cognitive functioning in various domains [62] and reduces the likelihood of developing dementia later in life [62]. Similarly, the HAAS results provide evidence that untreated midlife hypertension is associated with hippocampal atrophy and of developing AD in later life [63,64]. Furthermore, recent MRI studies have reported a link between brain atrophy and untreated hypertension [63] and brain atrophy and cardiovascular fitness in AD [57,58], and Erickson et al. [65] reported increased hippocampal volumes in the brains of healthy individuals who participated in exercise training compared to sedentary controls. A growing number of randomised controlled trials (RCTs) have focused on the impact of physical activity on the neurocognitive performance of individuals at risk of or living with dementia [66-70], these studies have been able to demonstrate that physical exercise may offer significant improvement across several neurocognitive domains including attention, executive function, and fluid intelligence, as well as significant changes in global

cognition and clinical dementia rating scales. Subsequently, this literature does offer mild support for exercise as an attenuating or stabilising intervention in relation to certain cognitive domains.

1.8 Physiological and neurophysiological benefits of exercise

1.8.1 Neurotrophins and synaptic integrity

Neurotrophins such as brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) provide nurturance to neurons and glia supporting their proliferation and differentiation [5]. Neurotrophins also support learning, memory, and behaviour. By the later stages of AD there is a severe deficit of neurotrophin receptors in the basal forebrain [5]. In MCI, decline in synaptic transmission in the hippocampal region becomes evident, and in mild/early stage AD a 25% reduction in synaptophysin, a presynaptic vesicle protein, is observed [71]. As the disease progresses synaptic loss becomes disproportionate relative to neuronal loss, synaptic demise corresponding to dementia severity [72,73].

BDNF plays an integral role in the nurturance, survival, and plasticity of neurons within the central nervous system (CNS) and modulates neuritic outgrowth and synaptic function [50,74]. BDNF levels are significantly reduced in the brains of individuals with AD. Because BDNF is transported in both directions across the BBB, measurement of serum levels of BDNF may be also be a relevant gauge of its neural levels [74]. BDNF is up regulated by physical activity [50] and has been significantly associated with cognitive test score outcomes [74]. Physical activity also stimulates the up regulation of VEGF, an angiogenic growth factor that generates new blood vessels and promotes increased collateral circulation [75].

1.8.2 Insulin-signalling pathways

In AD insulin signalling in the brain is disrupted. Neurons that are insulin resistant become energy-deficient, vulnerable to oxidising, and suffer impairments in synaptic-plasticity. Increased serum glucose levels damage hippocampal structures, deplete neural levels of insulin-degrading enzyme, and up-regulate tau kinase and glycogen synthase kinase 3β. Insulin-like growth factor 1 (IGF-1) promotes the growth and differentiation of cells and is widely expressed in the human brain [55]. Insufficient IGF-1 is suggested as a risk factor for AD [74]. IGF-1 is up regulated by physical activity, specifically in resistance training [74]. Furthermore, IGF-1 and BDNF are function synergistically with each other in the brain [74].

1.8.3 Catecholamines

Exercise is considered to be a stressor. Exercise induced stress increases metabolic load (i.e., sweating, heart rate, respiratory rate, and plasma levels of norepinephrine and epinephrine) and CNS catecholamine release (i.e., epinephrine, norepinephrine, and dopamine) [76]. In accordance with cognitive-energetic models, as exercise intensity increases, within the range of 50–80% $VO_{2max,}$ so too do cognitive arousal levels [35,42]. These models suggest an inverted-U effect of exercise on cognition, such that rest and low intensity exercise (low arousal) equates to poor cognitive performance, intermediate intensity (50–80% VO_{2max}; optimal arousal) equates to maximal performance, and high intensity (high arousal > 80% VO_{2max}) equates to poor cognitive performance [47,49,76,77]. Furthermore, the inverted-U hypothesis also suggests that intermediate exercise elicits increased sympathoadrenal system and hypothalamic-pituitary-adrenal axis activity which in turn increases brain concentrations of catecholamines, adrenocorticotrophin hormone (ACTH), and cortisol [49], all of which contribute to improved cognitive performance.

The catecholamine hypothesis, initially proposed by Cooper in 1973 [78], states that immediately prior to and during exercise the sympathoadrenal system is activated by the hypothalamus and the brain stem. This activation facilitates catecholamine release at the postganglionic cells of the neurons that require activation or inhibition. As the intensity of exercise increases from low to moderate, catecholamines are also released peripherally from the adrenal medulla [76]. Peripheral release of the catecholamines epinephrine and norepinephrine has a direct effect on the synthesis and release of norepinephrine in the brain. Catecholamines function as both neurotransmitters and hormones: dopamine is in part responsible for cognitive alertness; epinephrine is responsible for regulating heartbeat, blood vessels and air passage diameters, and metabolic shifts, and norepinephrine is most responsible for vigilant concentration. Subsequently, it is argued that increases in neural concentrations of these compounds, both during and following moderate intensity exercise, should facilitate cognitive arousal [76,79].

1.9 Exercise and blood pressure response

Recent literature investigating the effects of aerobic exercise on cognitive impairment; correlations among VRF, exercise, and dementia; and the proposed vascular and two-hit vascular hypotheses of dementia tend to intimate that changes in BP may be related to changes in cognition. Both national and international treatment guidelines for primary and secondary prevention of hypertension recommend non-pharmacological lifestyle modifications as the first line of therapy, including increasing levels of physical activity [80]. There is Class I, Level B evidence that 150 minutes of weekly physical activity offers an effective non-pharmacological therapeutic treatment that may be used to complement anti-hypertensive medication [81]. With the effects of exercise training variable depending on different exercise prescriptions, an optimal exercise training prescription remains unclear.

Dynamic aerobic endurance exercise involves large muscle groups in dynamic repetitive activities and this is often time consuming; moreover, aerobic exercise generally can require access to a gymnasium or to suitable equipment. For these reasons adherence to aerobic exercise is often sub-optimal. On the other hand, isometric exercise can be performed in-residence using a portable handgrip dynamometer. Isometric exercise involves a sustained muscle contraction against an immovable load or resistance with no, or minimal, change in length of the involved muscle group. Similar to aerobic exercise, isometric exercise also has the ability to elicit anti-hypertensive effects [52,82]. Current thinking varies with respect to the preferred type of physical activity for blood pressure; historically endurance training has been preferred. Isometric activity has previously been associated with exaggerated hypertensive responses; however, data from recent analyses suggests isometric exercise may elicit blood pressure reductions greater than those seen with dynamic aerobic and resistance exercise [52] and is safe for elderly cohorts to participate in [83]. Specifically, acute isometric hand grip training (IHG) has been shown to improve resting endothelium-dependant vasodilation [84].

1.10 Summary

Every 6 minutes in Australia someone is diagnosed with dementia. Dementia is the second leading cause of death in Australia and the greatest cause of disability in people aged 65 years or older. In the absence of any significant medical breakthroughs, and if the current rate of diagnosis continues, by 2050 more than 900,000 Australian people will be living with dementia. The direct health care costs associated with this prognosis are estimated to reach $83 billion. Currently, on a global scale, it is estimated that there are more than 46.8 billion people living with dementia at an estimated cost of $815 billion USD.

AD is an incurable neurodegenerative disease that ravages the brain and causes extensive sub-cortical and cortical damage. It is the most common form of dementia accounting for up

to 80% of all dementia cases. While age is a risk factor contributing to the development of the disease, it is not indispensable, other modifiable lifestyle factors are also hypothesised to contribute to the etiology of the disease. Subsequently, it is argued that early detection of other potential precursors of dementia such as VRF, MCI, and the attenuation of modifiable risk factors through physical activity as an intervention may reduce the prevalence of these neurodegenerative pathologies. AD is an irrevocable condition; consequently, there is an urgent need for therapeutic treatments that may prevent, attenuate, or slow down the progression of MCI to AD and early stage AD to more advanced stages. Furthermore, preventative actions and treatments are believed to most likely be effective in the early stages of AD and other dementing disorders.

Recent literature reports that exercise taken up in midlife by healthy adults increases cognitive functioning in various domains and reduces the likelihood of developing AD later in life. However, the literature is not conclusive, nor is the data consistent with regards to the magnitude of the benefits that exercise has on adults with a diagnosis of MCI, or AD. Thus, while the literature does offer mild support for exercise as an effective intervention to attenuate the effects of cognitive decline in older adults with dementia, comparative analysis of the literature is difficult.

Alzheimer's disease is characterised by the presence of beta amyloid plaques and neurofibrillary tangles, which, among other things, interferes with synaptic transmission between neurons, the proliferation of nerve growth, and neuroprotective hormones, and has recently been associated with vascular injury and cerebral hypoperfusion. The vascular hypothesis of AD acknowledges the intimate relationship between vascular dysfunction and neuronal dysfunction and highlights the importance of the circulatory system to brain functions. The hypothesis proposes that sporadic AD is a multifactorial disease fuelled by

VRF such as hypertension, atherosclerosis, cardiac disease, stroke, and diabetes that contribute to chronic brain hypoperfusion. These VRF prevent the efficient delivery of nutrients and micronutrients to the brain and compromise energy metabolism and neural activity. More recently, the two-hit vascular hypothesis also proposes a non-amyloidogenic pathway of AD which is driven by VRF that lead to damage at the BBB and oligaemia. This theory goes one step further than the vascular hypothesis in that it describes how vascular injury propagates the neuritc plaques and p-tau that are the hallmark pathologies of AD. It is likely that therapeutic treatments that target vascular health may assist in the prevention, attenuation, and progression of AD and MCI due to AD.

Biological markers known to contribute to the functioning of a healthy brain include BDNF, IGF-1, and NO. A decrease in the production and/or transmission of any of these factors may contribute to various aspects of neuronal dysfunction including cognitive decline and dementia. Presumably, these neurobiological processes do not operate as efficiently in people with AD and MCI. Exercise has been demonstrated to support the production and function of BDNF, VEGF, IGF-1, and NO, and serum levels of BDNF have been significantly associated with cognitive test score outcomes.

Exercise has been demonstrated to moderate both dementia-related and age-related atrophy of the medial temporal lobe, and brain atrophy has been linked to untreated hypertension. Recently there is evidence within the literature to suggest that cardiovascular and isometric training may prevent, reduce, or attenuate the effects of hypertension and atherosclerosis. Data from recent analyses suggests isometric exercise may elicit blood pressure reductions greater than those seen with dynamic aerobic and resistance exercise. Specifically, IHG training has been shown to improve resting endothelium-dependant vasodilation.

Cognitive deficits and compromised mobility and balance are significant inhibitors to participation in physical activity for the elderly, as are the logistical arrangements involved in attending a gymnasium or a similar situation. Subsequently, an activity such as isometric exercise that does not necessitate these demands yet is able to stimulate the numerous physiological benefits of more traditional aerobic and resistance styles of exercise might be a viable substitute for the elderly. Specifically, isometric exercise training (IET) may prevent, attenuate, or delay the onset of cognitive decline and the progression of MCI to incidence of late-onset AD.

There are no studies available in the current literature that report on the effects of IET on cognitive performance in elderly individuals with cognitive impairment or AD. Consequently, the aim of this thesis will be to investigate the efficacy of isometric exercise training in elderly individuals with cognitive impairment or AD. I will gauge the extent, timeframe, and decay of post intervention changes such as blood pressure, mean arterial pressure, pulse pressure, and cognitive test score outcomes. In this regard, the following questions are addressed:

1. To what extent does physical activity confer neurocognitive benefits on individuals with cognitive decline and/or dementia?
2. Is isometric exercise, utilising IHG training, at 10% maximum voluntary contraction (MVC) and 5% MVC above the BP lowering threshold in normotensive adult men and women?
3. Is IET a viable non-pharmacological therapy for preventing and/or attenuating the progression of MCI to incidence of sporadic AD and for preventing and/or attenuating the progression of early stage AD to more advanced stages?

4. Can IET elicit improvements in resting BP and cognitive performance in elderly individuals experiencing cognitive impairment or diagnosed with AD and would changes in cognitive performance be linked with anti-hypertensive effects?

References

1. Archer T. Physical exercise alleviates debilities of normal aging and Alzheimer's disease. *Acta Neurol Scand.* Apr 2011;123(4):221-238.

2. Archer T, Kostrzewa R, Beninger R, Palomo T. Staging Neurodegenerative Disorders: Structural, Regional, Biomarker, and Functional Progressions. *Neurotoxicity Research.* 2011/02/01 2011;19(2):211-234.

3. Alzheimer's Disease Health Center. Alzheimers disease and other forms of dementia. 2012; http://www.webmd.com/alzheimers/guide/alzheimers-dementia. Accessed 24.04.2013.

4. Alzheimers Association. What is Dementia. 2013; http://www.alz.org/what-is-dementia.asp. Accessed 25.02.2013.

5. Querfurth HW, LaFerla FM. Alzheimer's DiseaseMechanisms of Disease. *The New England Journal of Medicine.* 2010;362(4):329-344.

6. Braak E, Griffing K, Arai K, Bohl J, Bratzke H, Braak H. Neuropathology of Alzheimer's disease: what is new since A. Alzheimer? *European Archives of Psychiatry and Clinical Neuroscience.* 1999/12/01 1999;249(3):S14-S22.

7. Shim YS, Morris JC. Biomarkers predicting Alzheimer's disease in cognitively normal aging. *Journal of Clinical Neurology.* 2011;7(2):60-68.

8. Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiology of aging.* 1997;18:351-357.

9. Blennow K, Hampel H, Weiner M, Zetterberg H. Cerebrospinal fluid and plasma biomarkers in Alzheimer disease. *Nature Reviews Neurology.* 2010;6(3):131-144.

10. Price JL, Morris JC. Tangles and plaques in nondemented aging and" preclinical" Alzheimer's disease. *Annals of neurology.* 1999;45(3):358-368.

11. Etgen T, Sander D, Bickel H, Förstl H. Mild cognitive impairment and dementia: the importance of modifiable risk factors. *Deutsches Ärzteblatt International.* 2011;108(44):743.

12. Ferri CP, Prince M, Brayne C, Brodaty H, et al. Global prevalence of dementia: a Delphi consensus study. *The Lancet.* 2005;366(9503):2112-2117.

13. Statistics ABo. Causes of Death, Australia, 2013: Cat no. 3303.0. 2015.

14. Australian Institute of Health and Welfare. Dementia in Australia. 2012.

15. Economics A. Keeping Dementia front of mind: incidence and prevalence 2009-2050. *Alzhiemer's Australia.* 2009.

16. Prince M, Wimo A, Guerchet M, Ali G, Wu Y, Prina M. The Global Impact of Dementia: An analysis of prevalence, incidence, cost and trends. *World Alzheimer Report.* 2015.

17. Health AIo. Residential Aged Care in Australia 2010-11: A Statistical Overview. AIHW; 2012.

18. Kim Y, Schulz R. Family caregivers' strains: comparative analysis of cancer caregiving with dementia, diabetes, and frail elderly caregiving. *Journal of Aging and Health.* 2008.

19. Ritchie K, Artero S, Touchon J. Classification criteria for mild cognitive impairment: A population-based validation study. *Neurology.* 2001;56(37):37-42.

20. Alzheimers Association. Mild Cognitive Impairment (MCI). 2012; http://www.alz.org/dementia/mild-cognitive-impairment-mci.asp. Accessed 25.02.2013.

21. Duara R, Loewenstein DA, Greig-Custo MT, et al. Diagnosis and staging of mild cognitive impairment, using a modification of the clinical dementia rating scale: the mCDR. *Int J Geriatr Psychiatry.* 2010;25(3):282-289.

22. DeCarli C. Mild cognitive impairment: prevalence, prognosis, aetiology, and treatment. *The Lancet Neurology.* 2003;2(1):15-21.

23. Li J, Wang Y, Zhang M, et al. Vascular risk factors promote conversion from mild cognitive impairment to Alzheimer disease. *Neurology.* 2011;76(17):1485-1491.

24. Helzner EP, Luchsinger JA, Scarmeas N, et al. Contribution of vascular risk factors to the progression in Alzheimer disease. *Archives of neurology.* 2009;66(3):343.

25. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia.* 2011;7(3):270-279.

26. Petersen RC. Mild cognitive impairment as a diagnostic entity. *Journal of internal medicine.* 2004;256(3):183-194.

27. Braak H, Alafuzoff I, Arzberger T, Kretzschmar H, Del Tredici K. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta neuropathologica.* 2006;112(4):389-404.

28. Arnold SE, Hyman BT, Flory J, Damasio AR, Van Hoesen GW. The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease. *Cerebral Cortex.* 1991;1(1):103-116.

29. Arriagada PV, Growdon JH, Hedley-Whyte ET, Hyman BT. Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. *Neurology.* 1992;42(3):631-631.

30. Newell KL, Hyman BT, Growdon JH, Hedley-Whyte ET. Application of the National Institute on Aging (NIA)-Reagan Institute criteria for the neuropathological diagnosis of Alzheimer disease. *Journal of Neuropathology & Experimental Neurology.* 1999;58(11):1147-1155.

31. Braak H, Braak E. Staging of alzheimer's disease-related neurofibrillary changes. *Neurobiology of aging.* 1995;16(3):271-278.

32. Glenner GG, Wong CW. Alzheimer's disease and Down's syndrome: sharing of a unique cerebrovascular amyloid fibril protein. *Biochemical and biophysical research communications.* 1984;122(3):1131-1135.

33. Tanzi RE, Bertram L. Twenty Years of the Alzheimer's Disease Amyloid Hypothesis: A Genetic Perspective. *Cell.* 2005;120(4):545-555.

34. Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nature Reviews Neuroscience.* 2011;12(12):723-738.

35. de la Torre JC, Mussivand T. Can disturbed brain microcirculation cause Alzheimer's disease? *Neurological research.* 1993;15(3):146.

36. de la Torre JC. A turning point for Alzheimer's disease? *Biofactors.* 2012;38(2):78-83.

37. de la Torre JC. Vascular risk factor detection and control may prevent Alzheimer's disease. *Ageing research reviews.* 2010;9(3):218-225.

38. Alzheimer's Association. What is Alzheimer's. 2012; http://www.alz.org/alzheimers_disease_what_is_alzheimers.asp. Accessed 25.02.2013.

39. Middleton LE, Yaffe K. Targets for the prevention of dementia. *J Alzheimers Dis.* 2010;20(3):915-924.

40. Savva GM, Wharton SB, Ince PG, Forster G, Matthews FE, Brayne C. Age, Neuropathology, and Dementia. *The New England Journal of Medicine.* 2009;360(22):2302-2309.

41. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. *The Lancet Neurology.* 2005;4(8):487-499.

42. Graham N, Emery T, Hodges J. Distinctive cognitive profiles in Alzheimer's disease and subcortical vascular dementia. *Journal of Neurology, Neurosurgery & Psychiatry.* 2004;75(1):61-71.

43. Agüero-Torres H, Kivipelto M, von Strauss E. Rethinking the Dementia Diagnoses in a Population-Based Study: What Is Alzheimer's Disease and What Is Vascular Dementia? *Dementia and geriatric cognitive disorders.* 2006;22(3):244-249.

44. Laukka E, Fratiglioni L, Bäckman L. The influence of vascular disease on cognitive performance in the preclinical and early phases of Alzheimer's disease. *Dementia and geriatric cognitive disorders.* 2010;29(6):498-503.

45. Viswanathan A, Rocca WA, Tzourio C. Vascular risk factors and dementia How to move forward? *Neurology.* 2009;72(4):368-374.

46. Choi H-J. Blood Pressure Variability and Its Management in Hypertensive Patients. *Korean journal of family medicine.* 2012;33(6):330-335.

47. Korf ES, White LR, Scheltens P, Launer LJ. Midlife Blood Pressure and the Risk of Hippocampal Atrophy The Honolulu Asia Aging Study. *Hypertension.* 2004;44(1):29-34.

48. Solfrizzi V, Panza F, Colacicco A, et al. Vascular risk factors, incidence of MCI, and rates of progression to dementia. *Neurology.* 2004;63(10):1882-1891.

49. Silver AE, Vita JA. Shear Stress–Mediated Arterial Remodeling in Atherosclerosis Too Much of a Good Thing? *Circulation.* 2006;113(24):2787-2789.

50. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. 1980.

51. Steinert JR, Chernova T, Forsythe ID. Nitric oxide signaling in brain function, dysfunction, and dementia. *The Neuroscientist.* 2010;16(4):435-452.

52. Cornelissen V, Smart N. Exercise Training for Blood Pressure: A Systematic Review and Meta-analysis. *Journal of the American Heart Association.* 2013;2(1).

53. Cardoso Jr CG, Gomides RS, Queiroz A, et al. Acute and chronic effects of aerobic and resistance exercise on ambulatory blood pressure. *Clinics.* 2010;65(3):317-325.

54. van Uffelen JG, Paw MJCA, Hopman-Rock M, van Mechelen W. The effects of exercise on cognition in older adults with and without cognitive decline: a systematic review. *Clinical Journal of Sport Medicine.* 2008;18(6):486-500.

55. DeSouza CA, Shapiro LF, Clevenger CM, et al. Regular aerobic exercise prevents and restores age-related declines in endothelium-dependent vasodilation in healthy men. *Circulation.* 2000;102(12):1351-1357.

56. Bugg JM, Head D. Exercise moderates age-related atrophy of the medial temporal lobe. *Neurobiology of aging.* 2011;32(3):506-514.

57. Burns JM, Cronk BB, Anderson HS, et al. Cardiorespiratory fitness and brain atrophy in early Alzheimer disease. *Neurology.* 2008;71(3):210-216.

58. Honea R, Thomas GP, Harsha A, et al. Cardiorespiratory fitness and preserved medial temporal lobe volume in Alzheimer's disease. *Alzheimer disease and associated disorders.* 2009;23(3):188.

59. Cotman CW, Berchtold NC. Exercise: a behavioral intervention to enhance brain health and plasticity. *Trends in neurosciences.* 2002;25(6):295-301.

60. Mattson MP, Chan SL, Duan W. Modification of brain aging and neurodegenerative disorders by genes, diet, and behavior. *Science Signaling.* 2002;82(3):637.

61. Adlard PA, Perreau VM, Pop V, Cotman CW. Voluntary exercise decreases amyloid load in a transgenic model of Alzheimer's disease. *Journal of Neuroscience.* 2005(25):4217-4221.

62. Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. *Archives of neurology.* 2001;58(3):498.

63. Launer LJ, Masaki K, Petrovitch H, Foley D, Havlik RJ. The association between midlife blood pressure levels and late-life cognitive function. *JAMA: the journal of the American Medical Association.* 1995;274(23):1846-1851.

64. Launer LJ, Ross GW, Petrovitch H, et al. Midlife blood pressure and dementia: the Honolulu–Asia aging study ☆. *Neurobiology of aging.* 2000;21(1):49-55.

65. Erickson KI, Voss MW, Prakash RS, et al. Exercise training increases size of hippocampus and improves memory. *Proceedings of the National Academy of Sciences.* 2011;108(7):3017-3022.

66. Brown AK, Liu-Ambrose T, Tate R, Lord SR. The effect of group-based exercise on cognitive performance and mood in seniors residing in intermediate care and self-care

retirement facilities: a randomised controlled trial. *Br J Sports Med.* 2009;43(8):608-614.

67. Cheng ST, PK C, YQ S, et al. Mental and Physical Activities Delay Cognitive Decline in Older Persons With Dementia. *Am J Geriatr Psychiatry.* 2012;5:5.

68. Kemoun G, Thibaud M, Roumagne N, et al. Effects of a physical training programme on cognitive function and walking efficiency in elderly persons with dementia. *Dement Geriatr Cogn Disord.* 2010;29(2):109-114.

69. Lam LC, Chau RC, Wong BM, et al. Interim follow-up of a randomized controlled trial comparing Chinese style mind body (Tai Chi) and stretching exercises on cognitive function in subjects at risk of progressive cognitive decline. *Int J Geriatr Psychiatry.* Jul 2011;26(7):733-740.

70. Lautenschlager NT, L CK, L F, et al. Effect of physical activity on cognitive function in older adults at risk of Alzheimer Disease: a randomized trial. *JAMA.* 2008;300(9):1027-1037.

71. Masliah E, Mallory M, Alford M, et al. Altered expression of synaptic proteins occurs early during progression of Alzheimer's disease. *Neurology.* 2001;56(1):127-129.

72. DeKosky ST, Scheff SW. Synapse loss in frontal cortex biopsies in Alzheimer's disease: correlation with cognitive severity. *Annals of neurology.* 1990;27(5):457-464.

73. Masliah E, Crews L, Hansen L. Synaptic remodeling during aging and in Alzheimer's disease. *Journal of Alzheimer's Disease.* 2006;9:91-99.

74. Ahlskog JE, Geda YE, Graff-Radford NR, Petersen RC. Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. Paper presented at: Mayo Clinic Proceedings2011.

75. Font MA, Arboix A, Krupinski J. Angiogenesis, neurogenesis and neuroplasticity in ischemic stroke. *Current cardiology reviews.* 2010;6(3):238.

76. McMorris T, Hale BJ. Differential effects of differing intensities of acute exercise on speed and accuracy of cognition: A meta-analytical investigation. *Brain and cognition.* 2012;80(3):338-351.

77. Brisswalter J, Collardeau M, René A. Effects of acute physical exercise characteristics on cognitive performance. *Sports Medicine.* 2002;32(9):555-566.

78. Cooper C. Anatomical and physiological mechanisms of arousal, with special reference to the effects of exercise. *Ergonomics.* 1973;16(5):601-609.

79. Tomporowski PD. Effects of acute bouts of exercise on cognition. *Acta psychologica.* 2003;112(3):297-324.

80. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension.* Dec 2003;42(6):1206-1252.

81. Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the American Heart Association. *J Am Coll Cardiol.* Mar 22 2011;57(12):1404-1423.

82. Carlson DJ, Dieberg G, Hess NC, Millar PJ, Smart NA. Isometric exercise training for blood pressure management: a systematic review and meta-analysis. Paper presented at: Mayo Clinic Proceedings2014.

83. Olher RdRV, Bocalini DS, Bacurau RF, et al. Isometric handgrip does not elicit cardiovascular overload or post-exercise hypotension in hypertensive older women. *Clinical interventions in aging.* 2013;8:649.

84. McGowan CL, Levy AS, Millar PJ, et al. Acute vascular responses to isometric handgrip exercise and effects of training in persons medicated for hypertension. *American Journal of Physiology-Heart and Circulatory Physiology.* 2006;291(4):H1797-H1802.

Chapter 2 : Methods

2.1 Methods used to conduct meta-analysis in Chapter 3

2.1.1 Search strategy

Potential studies were identified by conducting a systematic search of PubMed from 1966–June 1, 2014 (www.ncbi.nlm.nih.gov/pubmed; the search strategy is included in Appendix, Figure B1). The Cumulative Index to Nursing and Allied Health Literature and the Cochrane Central Register of Controlled Trials were also searched (1966–2014). The search strategy included the key concepts of Alzheimer's disease (AD), dementia, mild cognitive impairment (MCI), exercise training, and physical activity as an intervention. These were combined with a sensitive search strategy to identify randomized controlled trials. We also scrutinized the reference lists from the papers found for new references. All identified papers were assessed independently by two reviewers (NS and NH).

2.1.2 Inclusions

Randomized controlled trials of physical activity intervention in people with MCI or dementia were included. There were no language restrictions.

2.1.3 Exclusions

Animal studies, studies involving healthy individuals, studies that did not have the desired outcome measures, studies that included participants who were non-demented or without cognitive impairment in any allocation group, review papers, and non-randomized controlled trials were excluded. Several authors were contacted to provide missing data or to clarify whether the data was duplicated in multiple publications by the same author or research group; four authors failed to provide the requested information. Incomplete data or data from an already included study were excluded. Studies using interventions other than physical activity were also excluded, e.g., music, handicrafts.

2.1.4 Studies included in the review

Our initial search identified 269 manuscripts, and examination of the latest editions of relevant journals yielded a further 12 manuscripts. Out of the total 281 studies, six were excluded at first inspection as duplicates, 188 were removed after reading the titles or abstracts, and 52 studies were not trials of exercise therapy in cognitively impaired or demented adults. Of the remaining 35 studies, four were not randomized controlled trials, four studies used healthy controls, and 13 studies failed to report the outcome data in a format that allowed meta-analysis (see excluded studies in the Appendix, Table B1). When the authors were contacted, they did not provide the information requested, leaving 14 studies for our analysis (see included studies Appendix, Table B2 and consort statement, Appendix, Figure B2). A reference of both the included and excluded studies can also be found in Appendix B.

2.1.5 Data analysis

The data relating to cognitively impaired patients undertaking physical activity versus sedentary controls were reviewed and archived in a database. All of the data from cognitive performance tools were pooled. Only the analyses that demonstrated a statistically significant post-intervention change and included more than one study are reported in the results section. Egger plots of the significant analyses can be found in the Appendix, Figures B3-B10.

2.1.6 Statistical analysis

Meta-analyses were completed for the continuous data by calculating the change in the means and standard deviations of the outcome measures because we did not want to assume that all allocation groups were matched at baseline. Changes in the post-intervention means were calculated by subtracting the baseline from the post-intervention values. Changes in the

standard deviations of the post-intervention outcomes were calculated using RevMan 5.0 (Nordic Cochrane Centre Denmark). The data were required to have: (i) a 95% confidence interval [CI] for the pre-post intervention change for each group, or when this was unavailable, (ii) actual *P*-values for the pre-post intervention change for each group, or if only the level of statistical significance was available, (iii) we used default *P*-values, e.g., $P < 0.05$ became $P = 0.049$, $P < 0.01$ became $P = 0.0099$, and P = not significant became $P = 0.05$. A random effects inverse variance was used with the effects measure of the mean difference. Heterogeneity was quantified using Cochrane's Q test (I^2). Egger plots were made to assess the risk of publication bias (see Appendix, Figures B3-B10). The study quality was assessed using a modified PEDro score (out of a maximum score of 9; see Appendix, Table B3) because blinding was difficult in the intervention studies. We used a 5% level of significance and 95% CI; all figures were produced using RevMan 5.

2.2 Methods used to conduct randomised trial in Chapter 4

2.2.1 Participants

Twenty two participants, 13 males and 9 females, aged 38.8 ± 11 years, with resting blood pressure (BP) within the normal range (>90/>60mmHg to <139/<90 mmHg) volunteered to participate in the study (participant information sheet Appendix C and invitation to participate Appendix D). All participants were staff or students of the University of New England. Two participants (one male and one female) were unable to complete the study; both due to family circumstances. Participants were assessed as eligible if they were normotensive, had no significant visual or motor impairments, could follow verbal instructions and were between the ages of 25 and 65 years. At a screening session prior to commencement of the isometric exercise program all potential volunteers were asked to complete a participant history and medical questionnaire (Appendix E), an adult exercise

screening questionnaire (Appendix F), and a written consent (Appendix G). At this time it was determined that participants were able to exercise and were not taking any medication that could affect the haemodynamic variables being investigated or their ability to perform isometric hand grip (IHG) exercise. Baseline BP measurements were taken on 3 consecutive days, at the same time each day, prior to the commencement of training.

To minimise the influence of external variables on BP measurements, participants were asked to refrain from vigorous exercise and alcohol for 24 hours prior to each scheduled continuous BP measurement, to abstain from caffeine for 12 hours prior and fast for 4 hours prior. Prior to the commencement of BP measurements and IHG exercise participants were familiarised with the all equipment and IHG and BP measurement procedures. All study protocols were approved by the research ethics committee of the University of New England, HREC Approval Number HE14-047.

2.2.2 Study design

Based upon the mean difference for change in systolic BP (SBP) in our meta-analyses [1], we calculated that 10 participants in each group were required to detect a 5% significant change with 80% power. Participants were randomly allocated to either IHG training at 10% maximal voluntary contraction (MVC; n = 10) or IHG training at 5% MVC (n = 10). Blind randomisation of participants was done using Microsoft Excel 2007 random number generator. Following group allocation all participants were instructed on the correct usage of the IHG equipment. Subsequent to group assignment all participants underwent baseline cardiovascular measures (systolic, diastolic and mean arterial BP, heart rate) which were repeated each week for the duration of the training program.

2.2.3 Arterial BP and heart rate

Arterial BP and heart rate were continuously monitored using the Finometer (FMS, Amsterdam, Netherlands) Model-2 blood pressure monitor. The Finometer is considered to provide BP information which is robust unless potent vasoactive agents are administered [2]. A wrap around finger cuff equip with, air bladder, light source (LED) and light detector (photo diode) was placed around the middle finger of the dominant hand. Care was taken when selecting and fitting an appropriate size cuff for each participant. The cuffed digit was maintained near heart level and the hydrostatic height correction unit of the Finometer compensated for any further hydrostatic pressure differences. Prior to recording cardiovascular measures the Finometer measurement of the finger arterial pressure was calibrated until the physical repetition rate recorded 40 beats or more. The Finometer provided a beat to beat estimate of the arterial waveform.

2.2.4 IHG training protocol

Participants in both groups completed four sets of 2 minute IHG contractions 3 days per week for 6 weeks with the aid of a programmed dynamometer (DHD-3 Digital Hand Dynamometer, Saehan Corp, South Korea). Isometric contractions were performed using the non-dominant hand at either 10% or 5% MVC separated by a 1 minute rest period. A direct-reading light box was attached directly to the dynamometer to provide visual feedback to assist participants in maintaining the desired contraction force. The light box was calibrated to either 5% or 10% MVC for every participant every session, furthermore, the dynomometer display was monitored by an investigator each time. In terms of force exerted, our participants were able to exert a maximal handgrip force of between 30-50 Nm, so at 10% MVC this equated to 3.0-5.0 Nm and at 5% MVC this was 1.5-2.5Nm.

To avoid Valsalva manoeuvres participants were instructed to breathe at a normal rhythm and depth. Participants were seated in an erect position so that the shoulder was adducted and neutrally rotated, the elbow was flexed at a 90° angle and the forearm and wrist were in a neutral position. The dynamometer was arranged in the participants' hand to ensure that it fitted comfortably, where necessary, the handle of the dynamometer was adjusted to the desired fit. Participants were instructed to apply grip force gently and smoothly and were advised by the researcher to hold their contraction once they had reached the desired IHG intensity. Participants trained every other weekday (Monday, Wednesday and Friday) with rest days in between. MVC was determined at the beginning of each training session (via imbedded electronic linear load cells contained within each handgrip); participants were asked to perform three MVCs with their non- dominant hand. The three measurements were then averaged to arrive at the MVC. On the third day of training each week, and prior to commencement of IHG training, resting BP measurements were recorded; continuous BP measurements were also recorded throughout the duration of these training sessions. Before resting BP measures were taken participants were asked to sit quietly for at least 10 minutes. All resting BP measurements were conducted within 2 hours of the initial baseline testing time of day. All sessions were supervised in the exercise physiology laboratory at the University of New England, Armidale, Australia.

2.2.5 Data handling and statistical analysis

The Finometer device computed all heamodynamic variables online and stored the data in result files on a hard disk. Calibration of all pressure transducers was maintained throughout the study. Waveform filtering and level correction protocols corrected arterial haemodynamic measures. BeatScope 1.1a software (FMS, Amsterdam, Netherlands) was used to integrate participants' gender, age, body mass and weight; this information was further integrated to

compute beat-to-beat SBP and diastolic BP (DBP) values. Finometer non-invasive arterial pressure was averaged over 120, 60, 30, and 15 seconds to account for the effects of BP variability due to different sampling durations. All processed data were transferred to Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) spreadsheets.

Prior to statistical analysis all data were assessed for compliance with parametric test assumptions, where assumptions were violated transformations were applied [3]. Specifically, an outlying case was detected for a participant's post SBP from the 10% group. To reduce the impact of the univariate outlier the deviant result was reduced to reflect a measurement one unit larger than the next most extreme score. Statistical analysis was performed using Microsoft Excel and SPSS Statistics (IBM Corporation, Armonk, NY, USA) software, version 22. Paired t-tests were conducted to establish change in BP values between groups at baseline and post-intervention, in addition Cohen's d statistics were calculated to classify effect size. A two-way ANOVA with baseline BP values as covariates (to assess whether changes in resting BP following IHG training were influenced by the initial baseline BP values) was performed to detect group effects over time. The magnitude of change in BP has been associated with initial resting values [4]. Similarly in a separate analysis, age was added as a co-variate. An alpha level of < 0.05 was determined as representing statistical significance, and the Bonferroni post-hoc procedure was used to further explore any significant differences that were detected.

2.3 Methods used to conduct case study in Chapter 5

2.3.1 Participants

Following approval by the University's Human Research Ethics Committee (Approval Number HE14-047) participants were recruited at an information session held at a residential

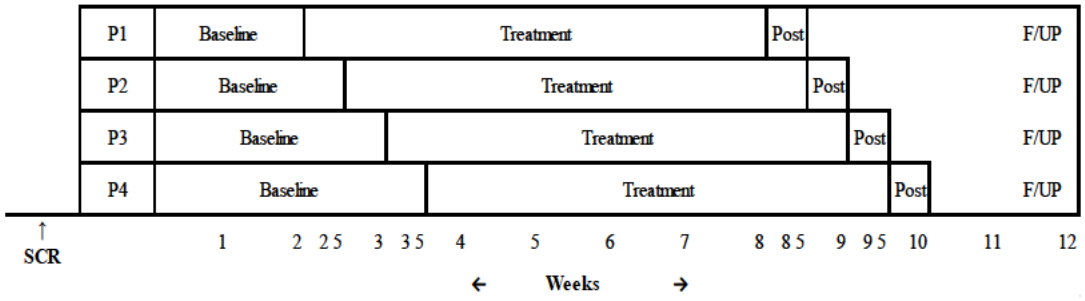
facility for elderly adults (Recruitment sheets and participant information sheets are presented in Appendix H–J). Ten potential volunteers were identified.

At a screening session prior to commencement of the isometric exercise program all potential volunteers (N = 10) were asked to complete a participant history questionnaire which also included a medical questionnaire, an adult exercise screening questionnaire, a written consent (Appendix K). The MMSE (Appendix L) and GDS (Appendix M) were also administered. At this time participant eligibility was assessed and (n = 4) were identified as meeting the following inclusion and exclusion criteria: aged between 55 and 85 years; returned a MMSE score >16; returned a GDS score of between 0 to 9; reported experiencing difficulties in cognition and/or memory or had received a diagnosis of either MCI or early stage AD; were non-smokers; had no significant psychiatric or substance abuse history; were able to complete cognitive tasks (no significant verbal, visual, or motor impairment); and, were able to respond to visual and verbal commands.

Four participants, two males and two females, with ages ranging from 67 to 85 years, (*Mage* = 77.8 years; *SD* = 7.9), met the inclusion criteria and agreed to participate in the study. All participants were medicated for hypertension. All participants resided in a city in rural Australia. Two participants resided at a community residential facility for older adults and two participants resided with family. At the commencement of the study Participant 4 had received a diagnosis of Alzheimer's disease. During the study phase Participant 3 received a diagnosis of posterior cortical atrophy (a form of dementia). For personal reasons, two participants completed the study early: one after a treatment phase of 3 weeks and the other after a treatment phase of 5 weeks.

2.3.2 Study design

A *single case, multiple baseline, across-subjects experimental design* was utilised to investigate haemodynamic and cognitive responses in four participants experiencing cognitive impairment or diagnosed with AD. An overview of the study design is presented below in Figure 2.1. Baseline measurements were administered in a temporal sequence over a 2 to 3 week time-period which enabled the participants to function as their own control. Each intervention consisted of four sets of 2 minute IHG contractions 3 days per week for 6 weeks. All Participants completed IHG training at 20% MVC.



SCR = Initial screening prior to intervention
P1 - P4 = Participants 1 to 4
Baseline = RBANS at time 1 (first day of baseline) and time 2 (last day of baseline) and daily BP measurements
Treatment = Four bouts of IET performed 3 times per week at 20% MVC and twice weekly BP measurements
Post = Post-test 1 day after final treatment (RBANS time 3 and BP measurements)
F/UP = Follow up at week 12 for all participants (RBANS time 4 and BP measurements)

Figure 2.1. An overview of the study design.

2.3.3 Arterial BP

Arterial SBP and DBP was monitored using the Omron Automatic Blood Pressure Monitor with Fit Cuff (Omron Healthcare Co., Ltd, Kyoto, Japan) Model-IA1B. A wrap around cuff equip with air bladder was placed around the bicep and over the brachial artery of the dominant arm. Care was taken when selecting and fitting an appropriate size cuff for each participant. The Omron Automatic Blood Pressure Monitor measured systolic and diastolic

BP. Three BP measurements were taken each time that BP was assessed; readings were separated by a two minute rest period. The average of these three readings was recorded and utilised for the purposes of data analysis.

To minimise the influence of external variables on BP measurements, participants were asked to refrain from vigorous exercise and alcohol for 24 hours prior to each scheduled BP measurement; to abstain from caffeine for 12 hours prior; and fast for 4 hours prior. Before resting BP measures were taken participants were asked to sit quietly for at least 10 minutes. BP measurements were taken at the same time each day. Prior to the commencement of BP measurements and IET participants were familiarised with all equipment and IET and BP measurement procedures.

2.3.4 RBANS assessment

The RBANS were administered by provisional psychologists enrolled in the Clinical Psychology program at the University of New England, Armidale (RBANS form A is presented in Appendix N). The RBANS were administered on four separate occasions throughout the study at the time points outlined in the *study design* above. Importantly, the RBANS test battery is suitably sensitive to screen for MCI up to moderately severe dementia. The RBANS measures cognitive function in the domains of immediate and delayed memory, attention, language, and visuospatial/constructional abilities. This test battery provides for up to four equivalent tests that can be administered at four different time points for repeat evaluations while controlling for content practice effects. The RBANS consists of 12 subtests which yield 5 Index scores (see below) and a Total scale score with a mean of 100 and a standard deviation of 15 index points. All subtests were administered and scored as prescribed in the RBANS manual [5]. The battery indexes are:

1) *Immediate memory.* Identifies an examinee's aptitude to recall information immediately after it is given. The subtests that contribute to this index are List Learning and Story Memory.
2) *Visuospatial/constructional.* Identifies an examinee's aptitude to perceive spatial relations and to construct a spatially accurate copy of drawing. The subtests that contribute to this index are Copy and Line Orientation.
3) *Language.* Identifies an examinee's aptitude to respond verbally to either naming or recalling learned material. The subtests that contribute to this index are Picture Naming and Semantic Fluency.
4) *Attention.* Identifies an examinee's aptitude to remember and manipulate both visually and orally presented information in short-term memory storage. The subtests that contribute to this index are Digit Span and Coding.
5) *Delayed memory.* Identifies an examinee's anterograde memory capacity. The subtests that contribute to this index are List Recall, List Recognition, Story Memory, and Figure Recall.

A Total Scale score is calculated by adding together the five index scores.

2.3.5 IET training protocol

Participants completed four sets of 2 minute IHG contractions 3 days per week for 6 weeks with the aid of a programmed dynamometer (DHD-3 Digital Hand Dynamometer, Saehan Corp, South Korea). Isometric contractions were performed using the dominant hand at 20% MVC separated by a 2 minute rest period. A direct-reading light box was attached directly to the dynamometer to provide visual feedback to assist participants in maintaining the desired contraction force. The light box was calibrated to 20% MVC for every participant every

session, furthermore, the dynomometer display was monitored by an investigator each time to ensure that 20% MVC was mantained for the duration of the 2 minute contraction period.

To avoid Valsalva manoeuvres participants were instructed to breathe at a normal rhythm and depth. Participants were seated in an erect position so that the shoulder was adducted and neutrally rotated, the elbow was flexed at a 90° angle and the forearm and wrist were in a neutral position. The dynamometer was arranged in the participants' hand to ensure that it fitted comfortably, where necessary, the handle of the dynamometer was adjusted to the desired fit. Participants were instructed to apply grip force gently and smoothly and were advised by the researcher to hold their contraction once they had reached the desired IHG intensity. Participants trained every other weekday (Monday, Wednesday and Friday) with rest days in between. MVC was determined at the beginning of each training session (via imbedded electronic linear load cells contained within each handgrip); participants were asked to perform three MVCs with their dominant hand. The three measurements were then averaged to arrive at the MVC. Twice each week, and prior to commencement of IHG training, resting systolic and diastolic BP measurements were recorded. All sessions were supervised in a common room area of the aged care facility in rural Australia.

2.3.6 Data handling and analysis

The data for each participant was assessed individually for changes in RBANS scores, systolic and diastolic BP, PP and MAP. BP data and RBANS data was recorded on Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) spreadsheets and converted into graphical representation for observational analysis. RBANS subtest Indexes and Total scale scores were cross referenced and interpreted utilising standardised tables for clinical interpretation [5], these are displayed in Table 2.1. Non-parametric statistical analytics, improved rate difference (IRD) analysis, was used to assess changes in both SBP and DBP.

IRD scores are calculated as the improvement rate observed in the experimental phase less the improvement rate observed in the baseline phase. The formula for calculating IRD is:

$$IRD = IR_T - IR_B$$

Where:

$$IR_T = \frac{N\ improved\ data\ treatment\ phase}{Total\ data\ points\ treatment\ phase}$$

$$IR_B = \frac{N\ improved\ data\ points\ baseline\ phase}{Total\ data\ points\ baseline\ phase}$$

The maximum IRD score is 100% (1.00) indicating that all of the scores in the treatment phase exceed all of the scores in the base-line phase in an improved direction. An IRD of 50% (.50) indicates that half of the scores are overlapping and represents a chance level of change and signifies that no improvement was evident. A negative score indicates deterioration below baseline.

Table 2.1. Qualitative and clinical descriptions of RBANS index scores

Index score	Percentile bands	Classification	Clinical descriptor
130 and above	≥ 98th	Very superior	
120-129	91st - 97th	Superior	
110-119	75th - 90th	High Average	(Above average)
90-109	25th - 74th	Average	
80-89	10th - 24th	Low Average	(Mildly Impaired)
70-79	3rd - 9th	Borderline	(Moderately Impaired)
69 and below	≤ 2nd	Extremely low	(Severely Impaired)

References

1 Carlson DJ, Dieberg G, Hess NC, Millar PJ, Smart NA. Isometric Exercise Training for Blood Pressure Management: A Systematic Review and Meta-analysis. *Mayo Clinic Proceedings.* MAR 2014 2014;89(3):327-334.

2 (McAuley, Silke et al. 1997)

3 (Tabachnick and Fidell 2007b)

4 Millar PJ, Bray SR, McGowan CL, MacDonald MJ, McCartney N. Effects of isometric handgrip training among people medicated for hypertension: a multilevel analysis. *Blood Pressure Monitoring.* 2007;12(5):307-314.

5 Randolph C. *RBANS update Repeatable Battery for the Assessment of Neuropsychological Status manual.* Bloomington, MN: Pearson; 1998.

Chapter 3 : The Effect of Exercise Intervention on Cognitive Performance in Persons at Risk of, or with, Dementia: A Systematic Review and Meta-Analysis

N. C. L. Hess, G. Dieberg, J. R. McFarlane and N. A. Smart

Published online in Healthy Aging Research, July 30, 2014

Citation: Hess NCL, Dieberg G, McFarlane JR, Smart NA (2014) The effect of exercise intervention on cognitive performance in persons at risk of, or with, dementia: A systematic review and meta-analysis. Healthy Aging Research 3:3. doi:10.12715/har.2014.3.3

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The effect of exercise intervention on cognitive performance in persons at risk of, or with, dementia: A systematic review and meta-analysis

Nicole C.L. Hess[1], Gudrun Dieberg[1], James R. McFarlane[1], Neil A. Smart[1*]

1 School of Science and Technology, University of New England, Armidale, Australia

Abstract

Background: The aim of this study was to examine the benefits of exercise on the neurocognitive performance of individuals with dementia.

Methods: We conducted a systematic search of PubMed, the Cumulative Index to Nursing and Allied Health Literature, and the Cochrane Central Register of Controlled Trials (1966–2014) using the concepts of dementia, cognitive impairment, cognitive function, and exercise.

Results: Fourteen randomized controlled trials were included, providing data from 1056 individuals. We found that exercise provided significant improvements in the following assessments: mini mental state examination, mean difference (MD) 1.17 (95% confidence interval [CI] 0.75–1.59, $P < 0.00001$); Alzheimer's Disease Assessment Scale, MD −1.41 (95% CI −2.48–−0.34, $P = 0.01$); Clinical Dementia Rating scale, MD −0.37 (95% CI −0.57–−0.16, $P = 0.0004$); similarities subscale of Wechsler Adult Intelligence Scale Revised, MD 2.21 (95% CI 0.75–3.67, $P = 0.003$); arithmetic subscale of Wechsler Adult Intelligence Scale Revised, MD 1.11 (95% CI 0.03–2.20, $P = 0.04$); Amsterdam Dementia Screening Test 6 picture recognition, MD −2.30 (95% CI −3.59–−1.01, $P = 0.0005$); and clock drawing test, MD 0.75 (95% CI 0.45–1.05, $P < 0.00001$).

Conclusions: Physical activity may improve neurocognitive function in people with cognitive impairments.

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Received: May 14, 2014; **Accepted:** June 27, 2014; **Published:** July 30, 2014

Competing interests: The authors have declared that no competing interests exist.

Sources of funding: None to report

*Email: nsmart2@une.edu.au

Introduction

Ranging across a spectrum from mild cognitive impairment (MCI) to Alzheimer's disease (AD), one of the greatest health threats facing the elderly today is cognitive decline [1]. Whilst dementia is not considered part of the normal aging process, age does appear to be the principle risk factor, with the majority of people aged 65 years or older at the time of AD diagnosis [2,3]. The incidence of AD doubles every five years thereafter [2]. After the age of 85 years, the likelihood of being diagnosed with AD is more than one in three [2], and most cases of dementia are diagnosed in this age category [4]. The social and economic costs associated with dementia in the western world are forecast to reach epidemic proportions [1].

Severe, selective cortical atrophy in regions of the brain such as the temporal, medial temporal, limbic, frontal, and prefrontal cortices is one of the hallmarks of neurodegenerative and age-related dementia [5,6].

The functional and cognitive attributes affected by the deterioration of these brain structures include learning, memory, attention, motivation, executive function, motor function, global cognition, and

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activities during daily living [5,7]. MCI, which is often a prelude to dementia [8,9], is also associated with disproportionate atrophy in the medial temporal and temporal cortices [6,7]. The severity and extent of dementia-related atrophy increase as a function of time, destroying cognitive and functional abilities at each stage. This damage is irreversible and devastating to both the individual sufferers and their families or carers. Currently, there is no cure for dementia; therefore, it is paramount that researchers identify behavioral interventions that can prevent, attenuate, or impede the progression or genesis of this condition.

While not fully understood, several mechanisms have been identified that underlie the neurocognitive benefits of physical activity. These include the promotion of neurogenesis, angiogenesis, synaptogenesis, neurotrophin production [10], and the mitigation of vascular risk factors that promote increased cerebral perfusion. The three processes of neurogenesis, angiogenesis, and synaptogenesis are also integral in neurorepair processes [11].

Physical activity stimulates the upregulation of several neurotrophic agents: brain-derived neurotrophic factor, which plays an integral role in the nurturance, survival, and plasticity of neurons within the central nervous system and modulates neuritic outgrowth and synaptic function [12,13]; insulin-like growth factor, which promotes the growth and differentiation of cells and is widely expressed in the human brain [14]; and vascular endothelial growth factor, an angiogenic growth factor that generates new blood vessels and promotes increased collateral circulation [11].

Physical activity that targets cardiovascular fitness (peak VO_2) may offer neuroprotective benefits and attenuate the neuronal structural and functional changes that are associated with MCI and dementia [15-17]. Evidence from animal models has demonstrated that aerobic exercise can increase neurogenesis, angiogenesis, learning, and memory in rats [18,19] and inhibit the progression of Alzheimer's-related neuropathology in mice [20]. The current literature reports that exercise, taken up in midlife by healthy adults, increases cognitive functioning in various domains and reduces the likelihood of developing dementia later in life [21]. Recently, a growing number of randomized controlled trials have focused on the impact of physical activity on the neurocognitive performance of individuals at risk of, and living with, dementia. The literature offers mild support for exercise as an attenuating or stabilizing intervention for certain cognitive domains [22].

Unfortunately, it is difficult to draw meaningful comparisons about the efficacy of physical activity from the current literature because inconsistencies exist across the studies, in terms of the intervention, neurocognitive outcome measure, statistical reporting method, and disease severity and associated levels of care. For example, a 2008 systematic review from van Uffelen et al. investigated the effects of physical activity on neurocognitive outcomes in individuals diagnosed with MCI or AD, but it only included studies up until early 2008 [23]. A 2011 systematic review on the effects of exercise on cognitive decline was conducted, but the participants were non-demented people [24]. In 2013, Breher et al. conducted a systematic review on exercise training effects on cognition, but data pooling was not performed [25]. The 2013 updated Cochrane review by Forbes et al. assessed changes in cognition, activities of daily living, behavior, depression, and mortality [26]. However, the cognition data were generated and pooled from several different tests of cognition, and a standard mean difference (% change) was used to adjust for the different scoring scales [26].

The lack of recent in-depth publications in this area necessitates a clinical update. Therefore, we conducted a systematic review and meta-analysis that included all published randomized controlled trials up to June 1, 2014. The primary aim was to quantify the expected neurocognitive benefits of physical activity on individuals with cognitive decline and/or dementia. We have taken the unique approach of separately analyzing the different tests of cognitive function.

Methods

Search strategy

Potential studies were identified by conducting a systematic search of PubMed from 1966–2014 (www.ncbi.nlm.nih.gov/pubmed; the search strategy is included in Suppl. Data). The Cumulative Index to Nursing and Allied Health Literature and the Cochrane Central Register of Controlled Trials were also searched (1966–2014). The search strategy included the key concepts of AD, dementia, MCI, exercise training, and physical activity as an intervention. These were combined with a sensitive

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search strategy to identify randomized controlled trials. We also scrutinized the reference lists from the papers found for new references. All identified papers were assessed independently by two reviewers (NS and NH). The search of published papers was conducted up until June 1, 2014.

Inclusions

Randomized controlled trials of physical activity intervention in people with MCI or dementia were included. There were no language restrictions.

Exclusions

Animal studies, studies involving healthy individuals, studies that did not have the desired outcome measures, studies that included participants who were non-demented or without cognitive impairment in any allocation group, review papers, and non-randomized controlled trials were excluded. Several authors were contacted to provide missing data or to clarify whether the data was duplicated in multiple publications by the same author or research group; four authors failed to provide the requested information. Incomplete data or data from an already included study were excluded. Studies using interventions other than physical activity were also excluded, e.g., music, handicrafts.

Studies included in the review

Our initial search identified 269 manuscripts, and examination of the latest editions of relevant journals yielded a further 12 manuscripts. Out of the total 281 studies, six were excluded at first inspection as duplicates, 188 were removed after reading the titles or abstracts, and 52 studies were not trials of exercise therapy in cognitively impaired or demented adults. Of the remaining 35 studies, four were not randomized controlled trials, four studies used healthy controls, and 13 studies failed to report the outcome data in a format that allowed meta-analysis. When the authors were contacted, they did not provide the information requested, leaving 14 studies for our analysis (see the consort statement in Suppl. Data).

Data analysis

The data relating to cognitively impaired patients undertaking physical activity versus sedentary controls were reviewed and archived in a database. All of the data from cognitive performance tools were pooled. Only the analyses that demonstrated a statistically significant post-intervention change and included more than one study are reported in the results section. Egger plots of the significant analyses can be found in Suppl. Fig. 1-8.

Statistical analysis

Meta-analyses were completed for the continuous data by calculating the change in the means and standard deviations of the outcome measures because we did not want to assume that all allocation groups were matched at baseline. Changes in the post-intervention means were calculated by subtracting the baseline from the post-intervention values. Changes in the standard deviations of the post-intervention outcomes were calculated using RevMan 5.0 (Nordic Cochrane Centre Denmark). The data were required to have: (i) a 95% confidence interval [CI] for the pre-post intervention change for each group, or when this was unavailable, (ii) actual P-values for the pre-post intervention change for each group, or if only the level of statistical significance was available, (iii) we used default P-values, e.g., $P < 0.05$ became $P = 0.049$, $P < 0.01$ became $P = 0.0099$, and P = not significant became $P = 0.05$. A random effects inverse variance was used with the effects measure of the mean difference. Heterogeneity was quantified using Cochrane's Q test (I^2). Egger plots were made to assess the risk of publication bias (see Suppl. Data). The study quality was assessed using a modified PEDro score (out of a maximum score of 9) because blinding was difficult in the intervention studies. We used a 5% level of significance and 95% CI; all figures were produced using RevMan 5.

Results

Our analyses included data from 14 studies, totaling 1056 participants. The included studies provided data on 548 elderly men and women, with varying severities of cognitive impairment or AD, who participated in physical activity and 508 elderly men and women control participants, with varying severities of cognitive impairment or AD. One study reported on participants with severe AD [27], and two studies reported on participants with a range of severe-to-mild AD [28,29]. Three reports included

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participants with moderate-to-mild dementia [30-32], three studies reported on individuals with amnestic MCI and mild dementia [33-35], and one study reported on participants with a range of moderate-to-mild cognitive impairment and mild dementia [36]. One study reported on individuals with a range of moderate-to-mild cognitive impairment [37], another study reported on participants with MCI and mild dementia [38], and two reported on individuals with MCI only [39,40].

The study durations ranged from 6 weeks to 12 months, and the type of physical activity program varied between studies. The physical activities included walking, varied intensity aerobic training, strength training, flexibility training, postural balance training, and Tai Chi. In most studies, these activities were thoroughly monitored using either qualified instructors, exercise therapists, or physiotherapists; however, one trial also encouraged home-based participation, and another was an exclusively home-based exercise intervention. The physical training sessions were conducted 2–4 times per week, and each lasted from 30–60 minutes per session. The control groups varied in nature across all of the studies: six were of a sedentary nature, two included social visits, two included recreational activities such as handicrafts and cards, and one group participated in stretching and toning exercises. Details of the included studies can found in Suppl. Table 1. A list of excluded studies [32,41-60] can be also found in Suppl. Table 2. Using a modified PEDro scale (out of 9) to assess the quality of the studies, one study scored 5, five studies scored 6, five studies scored 7, and three studies scored 8 (Suppl. Table 3).

Mini mental state examination (MMSE)

Our analysis revealed that physical activity was associated with significant improvements in MMSE scores compared to the control groups; the mean difference (MD) was 1.17 (95% CI 0.75–1.59, P < 0.00001; Fig. 1). A sensitivity analysis (removing the Lam and Suzuki studies) reduced the heterogeneity while retaining the statistical significance, MD 2.28 (95% CI 1.68–2.88, P < 0.00001; Supp. Sub-Analysis 1).

Cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog)

We found that physical activity was associated with significant improvements in ADAS-cog performance compared to the control groups; MD −1.41 (95% CI −2.48–−0.34, P = 0.01; Fig. 2).

Clinical Dementia Rating scale (CDR) - sum of boxes

The data from the CDR showed that physical activity was associated with significantly improved scores compared to the sedentary control groups; MD −0.37 (95% CI −0.57–−0.16, P = 0.0004; Fig. 3). Of the two studies analyzed, one study reported a significant improvement in CDR scores in the intervention group compared to a significant decline in scores in the control group, while the other study reported a marginal improvement in CDR scores in the intervention group compared to a marginal decline in scores in the control group.

Wechsler Adult Intelligence scale revised (WAIS-R) - similarities subscale

Physical activity was associated with a significant improvement in performance on the similarities subscale of the WAIS-R compared to a marginal decline in the control group. The absolute change in score between the intervention and control groups was significant; MD 2.21 (95% CI 0.75–3.67, P = 0.003; Fig. 4).

Wechsler Adult Intelligence scale revised (WAIS-R) - arithmetic subscale

On the arithmetic subscale of the WAIS-R, physical activity was associated with a significant improvement in performance compared to a marginal decline in the control group. The absolute change in score between the groups was significant; MD 1.11 (95% CI 0.03–2.20, P = 0.04; Fig. 5).

Amsterdam Dementia Screening Test (ADS 6) - picture recognition

ADS 6 (picture recognition) was significantly improved with physical activity versus the control groups; MD −2.30 (95% CI −3.59–−1.01, P = 0.0005; Fig. 6).

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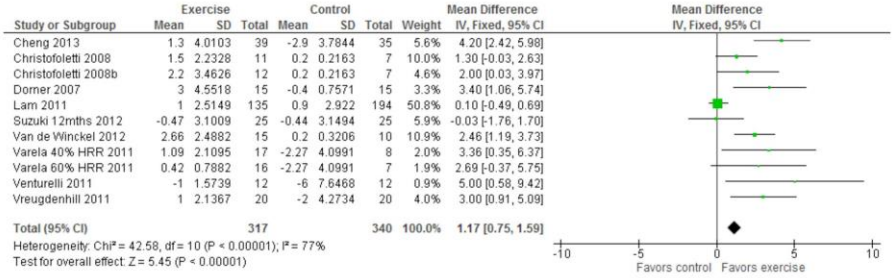

Figure 1. Change in MMSE: physical activity versus control

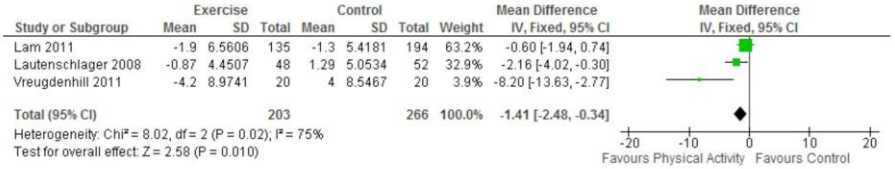

Figure 2. Change in ADAS-Cog: physical activity versus control

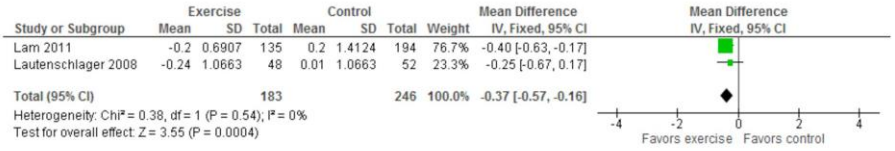

Figure 3. Change in CDR-sum of boxes: physical activity versus control

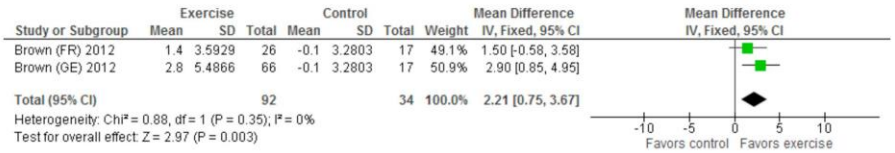

Figure 4. Change in WAIS-R (similarities): physical activity versus control

FR = flexibility and relaxation training, GE = general exercise

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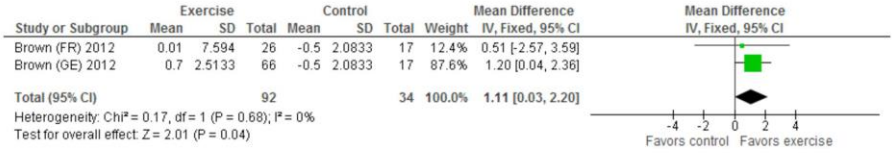

Figure 5. Change in WAIS-R (arithmetic): physical activity versus control

FR = flexibility and relaxation training, GE = general exercise

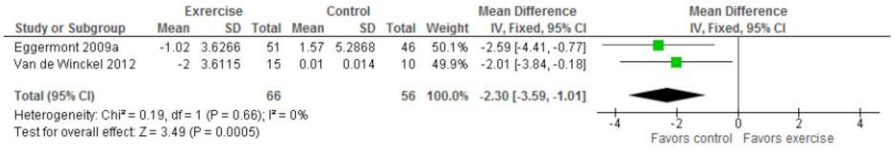

Figure 6. Change in ADS 6 (picture recognition): physical activity versus control

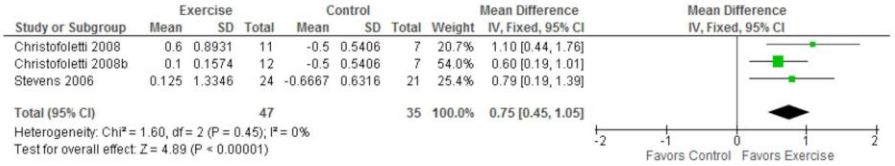

Figure 7. Change in clock drawing test: physical activity versus control

Clock drawing test (CDT)

While exercise did not significantly improve cognitive performance in relation to clock-drawing, a significant decrease in clock-drawing ability was observed in the control subjects compared to the exercise group; MD 0.75 (95% CI 0.45–1.05, P < 0.00001; Fig. 7).

ADS 6 - drawing alternating sequences

Only one study used the drawing of alternating sequences as a readout. We found that there was a significant improvement in performance in the physical activity versus the control group; MD 1.99 (95% CI 0.16–3.82, P = 0.03).

Rapid Evaluation of Cognitive Function- French version (ERFC)

There was a significant improvement in the physical activity versus the control group in the one study that used the ERFC as its evaluation tool; MD 8.67 (95% CI 4.56–12.78, P < 0.0001).

The following cognitive testing measurements did not report any significant post-intervention differences between the individuals who undertook physical activity and the control subjects: visual span forwards, visual span backwards, verbal fluency (category), verbal fluency (letter), Chinese trail making B, word list delayed recall, digit symbol coding, digit span forwards, digit span backwards, logical memory of

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immediate recall (WMS-LM I), logical memory of delayed recall (WMS-LM II), stroop colour word test (SCWT-colour), orientation in time/space, copying figures, ERFC, and free recall subscales.

Study quality

The median study quality score was 7 (Suppl. Table 3).

Egger plots

There was a minimal suggestion of publication bias, which is shown on the Egger Plots in Suppl. Fig. 1-8).

Discussion

To the best of our knowledge, this study is the first meta-analysis that specifically focused on cognitive-related outcomes in elderly individuals diagnosed with MCI, amnestic MCI, and/or dementia or AD. The findings are pertinent because cognitive performance is arguably the most important outcome measure in people with a cognitive impairment. Previous analyses have reviewed the effects of exercise training across a range of functional- and health-related outcomes for mixed populations of healthy-to-demented individuals. Our pooled data analysis showed significant improvements in nine neurocognitive measurement scores in the participants who completed physical activity versus the control groups. With the exception of the MMSE (Fig. 1), our analyses were justified because the heterogeneity between studies was low. We conducted a sensitivity analysis on the MMSE and removed the studies by Lam [34] and Suzuki [33], which appeared to be a major source of heterogeneity for this scale. This strengthened the effect size for this measurement. A significant improvement in the global measures was particularly notable; most of the subscales and narrow outcome measures did not show any significant differences. However, the subscale-type outcomes failed to reveal any measures where the control group performed better than the participants that underwent physical activity: either the non-significant trends favored the exercise group or the outcomes were similar. Our work demonstrates that physical activity has an aggregate benefit, supporting a growing body of literature that posits the therapeutic benefits of physical activity on cognitive performance outcomes [22-24,61-63].

Cognitive improvements were observed across several neurocognitive domains, including attention (ADS-6 drawing alternative sequences), executive function (CDT and ADS-6 verbal fluency), and fluid intelligence (WAIS-R similarities and arithmetic). We also found improvements in global cognition (MMSE, ADAS-cog, and ERFC) and clinical dementia ratings (CDR). Across all of the studies, the measurements of global cognition were the most robust in terms of detecting significant changes in cognitive performance. For example, of the nine studies that used a global cognitive measurement tool, seven reported significant results, irrespective of the severity of the cognitive impairment of the participants and the physical activity performed. It may be that global tests of cognition are inherently the most sensitive to changes in cognitive performance because they take into account numerous cognitive domains.

Analyses using the WAIS-R (similarities and arithmetic), ADS-6 category fluency, and clock drawing tests all demonstrated sufficient sensitivity to detect changes in executive function between the physical activity and control groups. All three tools showed physical activity improved executive function. While memory performance was reported in four studies, none of these studies observed significant absolute differences between the intervention and control groups. Memory is the cognitive domain most significantly impaired in MCI and in early stages of dementia, whereas executive functions tend to falter in the later stages of AD [6,64].

Recent MRI studies have reported an association between medial temporal deterioration and cardiovascular fitness [17] and an association between increased cardiovascular fitness and reduced brain atrophy in AD [16]. The spectrum of physical training interventions adopted in these trials included Tai Chi, flexibility, relaxation, balancing techniques, and varying intensities of aerobic exercise and strength training. Consequently, not all of the physical activities reported are considered aerobic; despite this, there was still evidence of improvement in certain domains (executive function) of cognitive function. Unfortunately, the notable variation in the modalities of physical intervention prevented speculation regarding which exercise modality was optimal.

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Limitations

The relatively small pooled sample size of this analysis may have reduced our ability to detect significant effects. Data pooling from a number of related studies is one method to counteract the pitfalls of small sample sizes; however, this method is most effective when comparable interventions and outcome measures are used across most, if not all, studies. The Cochrane I2 values in our analyses suggest that, except for the MMSE analysis (Fig. 1), all of the studies were appropriate for data pooling. Indeed, removal of the largest studies by Lam et al. and Suzuki et al. reduced the heterogeneity to 0% (Suppl. Sub-Analysis 1). In the current analysis, there was considerable variation between the studies in a number of areas: type and version of neurocognitive testing tool, mode of physical intervention, time period of the intervention, data reporting method, definition of the control group (e.g., sedentary, handicrafts, stretch, or tone), and severity of the cognitive impairment and dementia among the participants. Individuals with MCI may be more inclined to engage in physical activity and at a higher level (i.e., less apathy, which is common in severe dementia). Moreover, the benefit of the intervention may differ depending on the degree of neuronal loss (i.e., individuals with advanced dementia may be too ill to benefit). Finally, there may have been a Hawthorne effect, where the improved clinical trial outcome was simply due to interaction with the participants. More attention and interaction may have influenced their motivation to perform on the tests and influenced the scoring of the global assessments.

Suggestions for future research

While aerobic exercise has been heralded as delivering neuroprotective benefits and attenuating the neuronal, structural, and functional changes associated with dementia and MCI, the results of our analysis suggest that other modes of physical activity may also have the capacity to deliver similar benefits. Because of the considerable variation in physical activity programs, it was not possible to draw any specific conclusions about which physical activity program was optimal. Therefore, future research should use a standardized approach to investigating and comparing the efficacy of different exercise modalities on cognitive performance.

Conclusions

Our analysis lends further support to the suggestion that physical activity may be an effective therapeutic intervention tool for individuals diagnosed with cognitive impairment and dementia.

References

1. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, et al. Global prevalence of dementia: a Delphi consensus study. Lancet. 2005;366:2112-17.
2. Querfurth HW, LaFerla FM. Alzheimer's disease. N Engl J Med. 2010;362:329-44.
3. Middleton LE, Yaffe K. Targets for the prevention of dementia. J Alzheimers Dis. 2010;20:915-24.
4. Savva GM, Wharton SB, Ince PG, Forster G, Matthews FE, Brayne C. Age, neuropathology, and dementia. N Engl J Med. 2009;360:2302-9.
5. Archer T. Physical exercise alleviates debilities of normal aging and Alzheimer's disease. Acta Neurol Scand. 2011;123:221-38.
6. Braak H, Alafuzoff I, Arzberger T, Kretzschmar H, Del Tredici K. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. Acta Neuropathol. 2006;112:389-404.
7. Archer T, Kostrzewa R, Beninger R, Palomo T. Staging Neurodegenerative Disorders: Structural, Regional, Biomarker, and Functional Progressions. Neurotox Res. 2011;19:211-34.
8. Etgen T, Sander D, Bickel H, Forstl H. Mild cognitive impairment and dementia: the importance of modifiable risk factors. Dtsch Arztebl Int. 2011;108:743-50.
9. DeCarli C. Mild cognitive impairment: prevalence, prognosis, aetiology, and treatment. Lancet Neurol. 2003;2:15-21.
10. Greenwood PM, Parasuraman R. Neuronal and cognitive plasticity: a neurocognitive framework for ameliorating cognitive aging. Front Aging Neurosci. 2010;2:150.
11. Font MA, Arboix A, Krupinski J. Angiogenesis, neurogenesis and neuroplasticity in ischemic stroke. Curr Cardiol Rev. 2010;6:238.
12. Ahlskog JE, Geda YE, Graff-Radford NR, Petersen RC. Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. Paper presented at: Mayo Clinic Proceedings 2011;86:876-84.
13. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature. 1980;288:373-6.
14. DeSouza CA, Shapiro LF, Clevenger CM, Dinenno FA, Monahan KD, Tanaka H, et al. Regular aerobic exercise prevents and restores age-related declines in endothelium-dependent vasodilation in healthy men. Circulation. 2000;102:1351-7.

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HEALTHY AGING RESEARCH

15. Bugg JM, Head D. Exercise moderates age-related atrophy of the medial temporal lobe. Neurobiol Aging. 2011;32:506-14.
16. Burns JM, Cronk BB, Anderson HS, Donnelly JE, Thomas GP, Harsha A, et al. Cardiorespiratory fitness and brain atrophy in early Alzheimer disease. Neurology. 2008;71:210-6.
17. Honea R, Thomas GP, Harsha A, Anderson HS, Donnelly JE, Brooks WM, et al. Cardiorespiratory fitness and preserved medial temporal lobe volume in Alzheimer's disease. Alzheimer Dis Assoc Disord. 2009;23:188.
18. Cotman CW, Berchtold NC. Exercise: a behavioral intervention to enhance brain health and plasticity. Trends Neurosci. 2002;25:295-301.
19. Mattson MP, Chan SL, Duan W. Modification of brain aging and neurodegenerative disorders by genes, diet, and behavior. Physiol Rev. 2002;82:637-72.
20. Adlard PA, Perreau VM, Pop V, Cotman CW. Voluntary exercise decreases amyloid load in a transgenic model of Alzheimer's disease. J Neurosci. 2005;25:4217-21.
21. Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. Arch Neurol. 2001;58:498-504.
22. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol Sci. 2003;14:125-30.
23. van Uffelen JG, Chin APMJ, Hopman-Rock M, van Mechelen W. The effects of exercise on cognition in older adults with and without cognitive decline: a systematic review. Clin J Sport Med. 2008;18:486-500.
24. Sofi F, Valecchi D, Bacci D, Abbate R, Gensini GF, Casini A, et al. Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. J Intern Med. 2011;269:107-17.
25. Bherer L, Erickson KI, Liu-Ambrose T. A review of the effects of physical activity and exercise on cognitive and brain functions in older adults. J Aging Res. 2013;2013:657508.
26. Forbes D, Thiessen EJ, Blake CM, Forbes SC, Forbes S. Exercise programs for people with dementia. Cochrane Database Syst Rev. 2013;12:CD006489.
27. Venturelli M, Scarsini R, Schena F. Six-month walking program changes cognitive and ADL performance in patients with Alzheimer. Am J Alzheimers Dis Other Demen. 2011;26:381-8.
28. Kemoun G, Thibaud M, Roumagne N, Carette P, Albinet C, Toussaint L, et al. Effects of a physical training programme on cognitive function and walking efficiency in elderly persons with dementia. Dement Geriatr Cogn Disord. 2010;29:109-14.
29. van de Winckel A, Feys H, De Weerdt W, Dom R. Cognitive and behavioural effects of music-based exercises in patients with dementia. Clin Rehabil. 2004;18:253-60.
30. Stevens J, Killeen M. A randomised controlled trial testing the impact of exercise on cognitive symptoms and disability of residents with dementia. Contemp Nurse. 2006;21:32-40.
31. Christofoletti G, Oliani MM, Gobbi S, Stella F, Bucken Gobbi LT, Renato Canineu P. A controlled clinical trial on the effects of motor intervention on balance and cognition in institutionalized elderly patients with dementia. Clin Rehabil. 2008;22:618-26.
32. Eggermont LH, Swaab DF, Hol EM, Scherder EJ. Walking the line: a randomised trial on the effects of a short term walking programme on cognition in dementia. J Neurol Neurosurg Psychiatry. 2009;80:802-4.
33. Suzuki T, Hiroyuki S, Makizako H, Doi T, Yoshida D, Tsutsumimoto K, et al. Effects of multicomponent exercise on cognitive function in older adults with amnestic mild cognitive impairment: a randomized controlled trial. BMC Neurology. 2012;12:128.
34. Lam LC, Chau RC, Wong BM, Fung AW, Lui VW, Tam CC, et al. Interim follow-up of a randomized controlled trial comparing Chinese style mind body (Tai Chi) and stretching exercises on cognitive function in subjects at risk of progressive cognitive decline. Int J Geriatr Psychiatry. 2011;26:733-40.
35. Vreugdenhil A, Cannell J, Davies A, Razay G. A community-based exercise programme to improve functional ability in people with Alzheimer's disease: a randomized controlled trial. Scand J Caring Sci. 2012;26:12-9.
36. Cheng ST, Chow PK, Song YQ, Yu EC, Chan AC, Lee TM, et al. Mental and physical activities delay cognitive decline in older persons with dementia. Am J Geriatr Psychiatry. 2014;22:63-74.
37. Dorner T, Kranz A, Zettl-Wiedner K, Ludwig C, Rieder A, Gisinger C. The effect of structured strength and balance training on cognitive function in frail, cognitive impaired elderly long-term care residents. Aging Clin Exp Res. 2007;19:400-5.
38. Lautenschlager NT, Cox KL, Flicker L, Foster JK, van Bockxmeer FM, Xiao J, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. JAMA. 2008;300:1027-37.
39. Brown AK, Liu-Ambrose T, Tate R, Lord SR. The effect of group-based exercise on cognitive performance and mood in seniors residing in intermediate care and self-care retirement facilities: a randomised controlled trial. Br J Sports Med. 2009;43:608-14.
40. Varela S, Ayan C, Cancela JM, Martin V. Effects of two different intensities of aerobic exercise on elderly people with mild cognitive impairment: a randomized pilot study. Clin Rehabil. 2012;26:442-50.
41. Baker LD, Frank LL, Foster-Schubert K, Green PS, Wilkinson CW, McTiernan A, et al. Effects of aerobic exercise on mild cognitive impairment: a controlled trial. Arch Neurol. 2010;67:71-9.
42. Liu-Ambrose T, Nagamatsu LS, Voss MW, Khan KM, Handy TC. Resistance training and functional plasticity of the aging brain: a 12-month randomized controlled trial. Neurobiol Aging. 2012;33:1690-8.

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43. McMurdo ME, Rennie LM. Improvements in quadriceps strength with regular seated exercise in the institutionalized elderly. Arch Phys Med Rehabil. 1994;75:600-3.
44. McMurdo ME, Millar AM, Daly F. A randomized controlled trial of fall prevention strategies in old peoples' homes. Gerontology. 2000;46:83-7.
45. Nagamatsu LS, Handy TC, Hsu CL, Voss M, Liu-Ambrose T. Resistance training promotes cognitive and functional brain plasticity in seniors with probable mild cognitive impairment. Arch Intern Med. 2012;172:666-8.
46. Scherder EJ, Van Paasschen J, Deijen JB, Van Der Knokke S, Orlebeke JF, Burgers I, et al. Physical activity and executive functions in the elderly with mild cognitive impairment. Aging Ment Health. 2005;9:272-80.
47. Williamson JD, Espeland M, Kritchevsky SB, Newman AB, King AC, Pahor M, et al. Changes in cognitive function in a randomized trial of physical activity: results of the lifestyle interventions and independence for elders pilot study. J Gerontol A Biol Sci Med Sci. 2009;64:688-94.
48. van Uffelen JG, Chinapaw MJ, van Mechelen W, Hopman-Rock M. Walking or vitamin B for cognition in older adults with mild cognitive impairment? A randomised controlled trial. Br J Sports Med. 2008;42:344-51.
49. Yaguez L, Shaw KN, Morris R, Matthews D. The effects on cognitive functions of a movement-based intervention in patients with Alzheimer's type dementia: a pilot study. Int J Geriatr Psychiatry. 2011;26:173-81.
50. Yerokhin V, Anderson-Hanley C, Hogan MJ, Dunnam M, Huber D, Osborne S, et al. Neuropsychological and neurophysiological effects of strengthening exercise for early dementia: a pilot study. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2012;19:380-401.
51. Conradsson M, Littbrand H, Lindelof N, Gustafson Y, Rosendahl E. Effects of a high-intensity functional exercise programme on depressive symptoms and psychological well-being among older people living in residential care facilities: a cluster-randomized controlled trial. Aging Ment Health. 2010;14:565-76.
52. Davis JC, Bryan S, Marra CA, Sharma D, Chan A, Beattie BL, et al. An economic evaluation of resistance training and aerobic training versus balance and toning exercises in older adults with mild cognitive impairment. PLoS One. 2013;8:e63031.
53. Fallah N, Hsu CL, Bolandzadeh N, Davis J, Beattie BL, Graf P, et al. A multistate model of cognitive dynamics in relation to resistance training: the contribution of baseline function. Ann Epidemiol. 2013;23:463-8.
54. Frances T SJ, Butler FR. The effects of regular exercise on muscle strength and functional abilities of late stage Alzheimer's residents. Am J Alzheimer's Dis. 1997;12:122-7.
55. Holliman DC OU, Forney JP. Developing an interactive physical activity group in a geriatric psychiatry facility. Act Adapt Aging. 2001;26:57-69.
56. Hwang HH CY. The effects of the dance therapy program through rhythmic exercise on cognitive memory performance of the elderly with dementia. Proceedings of the 21st Pan-Asian Congress of Sports and Physical Education. 2010:412-7.
57. Rolland Y, Pillard F, Klapouszczak A, Reynish E, Thomas D, Andrieu S, et al. Exercise program for nursing home residents with Alzheimer's disease: a 1-year randomized, controlled trial. J Am Geriatr Soc. 2007;55:158-65.
58. Santana-Sosa E, Barriopedro MI, Lopez-Mojares LM, Perez M, Lucia A. Exercise training is beneficial for Alzheimer's patients. Int J Sports Med. 2008;29:845-50.
59. Steinberg M, Leoutsakos JM, Podewils LJ, Lyketsos CG. Evaluation of a home-based exercise program in the treatment of Alzheimer's disease: the Maximizing Independence in Dementia (MIND) study. Int J Geriatr Psychiatry. 2009;24:680-5.
60. Williams CL, Tappen RM. Exercise training for depressed older adults with Alzheimer's disease. Aging Ment Health. 2008;12:72-80.
61. Heyn P, Abreu BC, Ottenbacher KJ. The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis. Arch Phys Med Rehabil. 2004;85:1694-704.
62. Aarsland D, Sardahaee FS, Anderssen S, Ballard C. Is physical activity a potential preventive factor for vascular dementia? A systematic review. Aging Ment Health. 2010;14:386-95.
63. Smith PJ, Blumenthal JA, Hoffman BM, Cooper H, Strauman TA, Welsh-Bohmer K, et al. Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. Psychosom Med. 2010;72:239-52.
64. Braak E, Griffing K, Arai K, Bohl J, Bratzke H, Braak H. Neuropathology of Alzheimer's disease: what is new since A. Alzheimer? Eur Arch Psychiatry Clin Neurosci. 1999;249,S3:14-22.

Higher Degree Research Thesis by Publication
University of New England

STATEMENT OF AUTHORS' CONTRIBUTION

(To appear at the end of each thesis chapter submitted as an article/paper)

We, the Research Master/PhD candidate and the candidate's Principal Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated in the *Statement of Originality*.

	Author's Name (please print clearly)	**contribution**
Candidate	Nicole Hess	Literature review, data extraction, conducting meta-analysis, writing manuscript
Other Authors	Neil Smart	Demonstrated how to conduct the meta-analysis and use the statistical software, provided editorial comments and assisted in addressing reviewers comments.
	Gudrun Dieberg	Provided editorial comments
	Jim McFarlane	Provided editorial comments
		.

Name of Student/Candidate: Nicole Hess

Name/title of Principal Supervisor: Neil Smart

[redacted]

18.09.2016
Date

[redacted]

Principal Supervisor

19.09.2016
Date

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University of New England

STATEMENT OF ORIGINALITY

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We, the Research Master/PhD candidate and the candidate's Principal Supervisor, certify that the following text, figures and diagrams are the candidate's original work.

Type of work	Page numbers
All text, tables and diagrams	Chapter 3 pp 51–60

Name of Student/Candidate: Nicole Hess

Name/title of Principal Supervisor: Neil Smart

[redacted]

18.09.2016
Date

[redacted]
Principal Supervisor

19.09.2016
Date

Chapter 4 : Clinically Meaningful Blood Pressure Reductions With Low Intensity Isometric Handgrip Exercise. A Randomized Trial

N. C. L. Hess, D. J. Carlson, J. D. Inder, E. Jesulola, J. R. MCFarlane and N. A. Smart

Published online in Physiological Research, April 12, 2016

Citation: Hess NC, Carlson D, Inder J, Jesulola E, McFarlane J, Smart N. Clinically Meaningful Blood Pressure Reductions with Low Intensity Isometric Handgrip Exercise. A Randomized Trial. *Physiological research* 2016;65.

Candidate Signature

Principal Supervisor Signature

Physiol. Res. 65: 461-468, 2016

Clinically Meaningful Blood Pressure Reductions With Low Intensity Isometric Handgrip Exercise. A Randomized Trial

N. C. L. HESS[1], D. J. CARLSON[1], J. D. INDER[1], E. JESULOLA[1], J. R. MCFARLANE[1], N. A. SMART[1]

[1]School of Science and Technology, University of New England, Armidale, Australia

Received July 2, 2015
Accepted January 8, 2016
On-line April 12, 2016

Summary

There exists no examination of what is the minimum anti-hypertensive threshold intensity for isometric exercise training. Twenty two normotensive participants were randomly assigned to training intensities at either 5 % or 10 % of their maximal contraction. Twenty participants completed the study. Clinical meaningful, but not statistically significant, reductions in systolic blood pressure were observed in both 5 % and 10 % groups −4.04 mm Hg (95 % CI −8.67 to +0.59, p=0.08) and −5.62 mm Hg (95 % CI −11.5 to +0.29, p=0.06) respectively after 6 weeks training. No diastolic blood pressure reductions were observed in either 5 % −0.97 mm Hg (95 % CI −2.56 to +0.62, p=0.20) or 10 % MVC +1.8 mm Hg (95 % CI −1.29 to +4.89, p=0.22) groups respectively after training. In those unable to complete isometric exercise at the traditional 30 % intensity, our results suggest there is no difference between 5 and 10 % groups and based on the principle of regression to the mean, this could mean both interventions induce a similar placebo-effect.

Key words

Blood pressure • Isometric exercise • Hypertension

Corresponding author

N. Smart, School of Science and Technology, University of New England, Armidale, NSW 2350, Australia. E-mail: nsmart2@une.edu.au

Introduction

Hypertension is considered to be the greatest modifiable risk factor pertaining to CVD (Hajjar and Kotchen 2003). Health professionals recommend lifestyle modifications such as exercise for the prevention and treatment of hypertension in both normotensive and hypertensive individuals (James *et al.* 2014), traditionally, aerobic exercise training that targets cardiovascular fitness has been the first line exercise prescription for managing hypertension.

Isometric exercise training (IET) involves a single sustained muscle contraction against an immovable load or resistance with no, or minimal, change in length of the involved muscle group. Whilst the physiological mechanisms elicited by IET are not entirely clear there is a growing body of evidence that supports the role of IET to accommodate significant reductions in resting systolic and diastolic blood pressures in both hypertensive and normotensive men and women (Millar *et al.* 2008, Wiles *et al.* 2010, Devereux *et al.* 2011, Badrov *et al.* 2013a,b). Results of a recent meta-analyses reported that compared to dynamic aerobic endurance training, dynamic resistance training, and training comprising both dynamic endurance and resistance work, IET elicited the greatest reductions in resting SBP (Cornelissen and Smart 2013, Carlson *et al.* 2014). The effect size is similar to that of monotherapy with beta-blockade (Wong and Wright 2014).

The isometric training stimulus, responsible for the reductions in resting blood pressure, probably relates to a combination of intensity (% MVC), muscle mass (IHG vs. double-leg) and program length (number of weeks). Moreover similar blood pressure responses to isometric arm and leg exercise are observed (Williams 1991), however it is intuitive to assume that the smaller active muscle mass in arm compared to leg isometric

PHYSIOLOGICAL RESEARCH • ISSN 0862-8408 (print) • ISSN 1802-9973 (online)

Fax +420 241 062 164, e-mail: physres@biomed.cas.cz, www.biomed.cas.cz/physiolres

exercise may induce a greater blood pressure response. Whilst the effects of different IET intensities have been investigated across a number of hemodynamic measures such as systolic, diastolic and mean-arterial blood pressures, heart rate and total peripheral resistance, there are currently only three randomized controlled trials (RCT) that have directly compared the effects of different IET intensities on resting BP (Wiles *et al.* 2010, Baross *et al.* 2012). Baross *et al.* (2012) and Gill *et al.* (2015) compared the effects of isometric bilateral leg extensions (four sets of 2 min contractions) at a lower maximal voluntary contraction (MVC) (~8 %) and a higher (~14 % MVC) intensity. Reductions in resting BP and concomitant vascular adaptations were observed in the high intensity group; whereas, no BP reductions or vascular adaptations were evident in the lower group suggesting the threshold for anti-hypertensive effect lies between 8-14 %, but Wiles *et al.* (2010) also compared the effects of isometric bilateral leg extensions on BP (four sets of 2 min contractions) at a lower (~10 % MVC) and a higher (~20 % MVC) intensity. At 4 weeks into the study no significant differences in resting BP were observed in either group, however, at the studies end (8 weeks) significant reductions in resting blood pressure were reported in each group. More recently, Gill *et al.* (2015) compared the effects of low (~23 % MVC) and moderate (~34 % MVC) IET over a 3 week period and reported a reduction in SBP in the moderate intensity group only. In our recent meta-analysis of IET to manage BP (Carlson *et al.* 2014) two studies utilized an intensity of 10 % MVC as a lower intensity comparison. One of these studies (Wiles *et al.* 2010) used leg exercise and another (Wiley *et al.* 1992) used handgrip exercise. The data from Wiles *et al.* leaves open the possibility that there may be some anti-hypertensive effect from 10 % MVC (Wiles *et al.* 2010). Those who have participated in IET studies understand the physical and mental demands of sustaining four sets of isometric exercise at 30 % MVC for 2 min. Moreover the frail or elderly, who may initially struggle with IET at 30 % MVC, are more likely to be hypertensive and therefore derive most benefit from IET. The primary reason we are conducting this study is to establish if there exists an anti-hypertensive effect when conducting MVC at intensities of 10 % or as low as 5 %. Our hypothesis is that we can show an anti-hypertensive effect with IET at 10 % MVC, but not 5 % MVC, in normotensive people, as we particularly wished to avoid conducting this initial study in populations exposed to potent vasoactive agents. If we can show an anti-hypertensive effect in normotensive participants, then intuitively these effects are also likely in older hypertensive patients. In addition, in the interests of scientific validity it would be valuable to truly establish if 10 % MVC or even 5 % MVC elicit placebo or anti-hypertensive effects. Our secondary aim was to examine if sampling blood pressure for longer periods eliminated the 'white coat hypertension' effect.

The purpose of the present study is to compare the effect of two isometric handgrip training programs performed at different intensities.

Materials and Methods

Participants

Twenty two participants, 13 males and 9 females, aged 38.8±11 years, with resting BP within the normal range (>90/>60 mm Hg to <139/<90 mm Hg) volunteered to participate in the study. All participants were staff or students of the University of New England. Two participants (one male and one female) were unable to complete the study; both due to family circumstances. Participants were assessed as eligible if they were normotensive, had no significant visual or motor impairments, could follow verbal instructions and were between the ages of 25 and 65 years. At a screening session prior to commencement of the isometric exercise program all potential volunteers were asked to complete a participant history and medical questionnaire, an adult exercise screening questionnaire, and a written consent. At this time it was determined that participants were able to exercise and were not taking any medication that could affect the hemodynamic variables being investigated or their ability to perform IHG exercise. Baseline BP measurements were taken on 3 consecutive days, at the same time each day, prior to the commencement of training. Baseline participant characteristics are displayed in Table 1.

To minimize the influence of external variables on BP measurements, participants were asked to refrain from vigorous exercise and alcohol for 24 h prior to each scheduled continuous blood pressure measurement, to abstain from caffeine for 12 h prior and fast for 4 h prior. Prior to the commencement of BP measurements and IHG exercise participants were familiarized with the all equipment and IHG and BP measurement procedures. All study protocols were approved by the research ethics committee of the University of New England, HREC Approval Number HE14-047.

Study design

Based upon the mean difference for change in SBP in our meta-analyses (Carlson *et al.* 2014) we calculated that 10 participants in each group were required to detect a 5 % significant change with 80 % power. Participants were randomly allocated to either IHG training at 10 % MVC (n=10) or IHG training at 5 % MVC (n=10). Blind randomisation of participants was done using Microsoft Excel 2007 random number generator. Following group allocation all participants were instructed on the correct usage of the IHG equipment. Subsequent to group assignment all participants underwent baseline cardiovascular measures (systolic, diastolic and mean arterial blood pressure, heart rate) which were repeated each week for the duration of the training program.

Arterial BP and heart rate

Arterial BP and heart rate were continuously monitored using the Finometer (FMS, Amsterdam, Netherlands) Model-2 blood pressure monitor. The Finometer is considered to provide blood pressure information which is robust unless potent vasoactive agents are administered (McAuley *et al.* 1997). A wrap around finger cuff equip with, air bladder, light source (LED) and light detector (photo diode) was placed around the middle finger of the dominant hand. Care was taken when selecting and fitting an appropriate size cuff for each participant. The cuffed digit was maintained near heart level and the hydrostatic height correction unit of the Finometer compensated for any further hydrostatic pressure differences. Prior to recording cardiovascular measures the Finometer measurement of the finger arterial pressure was calibrated until the physical repetition rate recorded 40 beats or more. The Finometer provided a beat to beat estimate of the arterial waveform.

IHG training protocol

Participants in both groups completed four sets of 2 min IHG contractions 3 days per week for 6 weeks with the aid of a programmed dynamometer (DHD-3 Digital Hand Dynamometer, Saehan Corp, South Korea). Isometric contractions were performed using the non-dominant hand at either 10 % or 5 % MVC separated by a 1 min rest period. A direct-reading light box was attached directly to the dynamometer to provide visual feedback to assist participants in maintaining the desired contraction force. The light box was calibrated to either 5 % or 10 % MVC for every participant every session, furthermore, the dynomometer display was monitored by an investigator each time. In terms of force exerted, our participants were able to exert a maximal handgrip force of between 30-50 Nm, so at 10 % MVC this equated to 3.0-5.0 Nm and at 5 % MVC this was 1.5-2.5 Nm.

To avoid Valsalva manoeuvres participants were instructed to breathe at a normal rhythm and depth. Participants were seated in an erect position so that the shoulder was adducted and neutrally rotated, the elbow was flexed at a 90° angle and the forearm and wrist were in a neutral position. The dynamometer was arranged in the participants' hand to ensure that it fitted comfortably, where necessary, the handle of the dynamometer was adjusted to the desired fit. Participants were instructed to apply grip force gently and smoothly and were advised by the researcher to hold their contraction once they had reached the desired IHG intensity. Participants trained every other weekday (Monday, Wednesday and Friday) with rest days in between. MVC was determined at the beginning of each training session (*via* imbedded electronic linear load cells contained within each handgrip); participants were asked to perform three MVCs with their non- dominant hand. The three measurements were then averaged to arrive at the MVC. On the third day of training each week, and prior to commencement of IHG training, resting BP measurements were recorded; continuous BP measurements were also recorded throughout the duration of these training sessions. Before resting BP measures were taken participants were asked to sit quietly for at least 10 min. All resting BP measurements were conducted within 2 h of the initial baseline testing time of day. All sessions were supervised in the exercise physiology laboratory at the University of New England, Armidale, Australia.

Data handling and statistical analysis

The Finometer device computed all hemodynamic variables online and stored the data in result files on a hard disk. Calibration of all pressure transducers was maintained throughout the study. Waveform filtering and level correction protocols corrected arterial hemodynamic measures. BeatScope 1.1a software (FMS, Amsterdam, Netherlands) was used to integrate participants' gender, age, body mass and weight; this information was further integrated to compute beat-to-beat SBP and DBP values. Finometer non-invasive arterial pressure was averaged over 120, 60, 30, and 15 s to account for the effects of BP variability due to different sampling durations. All processed data were transferred to Microsoft Excel (Microsoft

Corporation, Redmond, WA, USA) spread sheets.

Prior to statistical analysis all data were assessed for compliance with parametric test assumptions, where assumptions were violated transformations were applied (Tabachnick and Fidell 2013). Specifically a lower than expected outlying case was detected for a participant's post systolic blood pressure from the 10 % group. To reduce the impact of the univariate outlier the deviant result was reduced to reflect a measurement one unit larger than the next most extreme score. Statistical analysis was performed using Microsoft Excel and SPSS Statistics (IBM Corporation, Armonk, NY, USA) software, version 22. We used independent sample t-tests to compare baseline BP and post intervention BP between groups and paired sample t-tests were performed to determine within groups variations from baseline to post intervention blood pressure, in addition Cohen's *d* statistics were calculated to classify effect size. Two-way ANOVA with co-variates was performed to determine between group differences over time.

The magnitude of change in BP has been associated with initial resting values (Millar *et al.* 2007) to assess whether changes in resting BP following IHG training were influenced by the initial baseline BP values. Similarly in a separate analysis, age was added as a co-variate. An alpha level of <0.05 was determined as representing statistical significance, and the Bonferroni *post-hoc* procedure was used to further explore any significant differences that were detected.

Results

The adherence to IHG was 100 % in the 20 participants who completed the 6 week study. Groups were matched at baseline for age (range 27-61 years), gender, body mass, SBP (range 105-134 mm Hg), DBP (range 64-84 mm Hg) and BMI (range 23-46) (Table 1).

As we collected 120 s of resting BP data we chose this as the default for our primary aim which was to see if BP was reduced. In Table 2 we have also reported 60, 30 and 15 s rolling sample data in order to address our secondary aim of examining effect of sample duration on BP change.

Systolic blood pressure

Reductions in baseline versus post-intervention SBP were not significantly different in the 5 % MVC group, –4.04 mm Hg (95 % CI –8.67 to +0.59, p=0.08), Cohen's *d* for this test was 0.56 which can be described as a medium to large effect size. There was no significant baseline versus post-intervention reductions in the 10 % MVC group, –5.62 mm Hg (95 % CI –11.5 to +0.29, p=0.06), Cohen's *d* for this test was 0.78 which can be described as large. Post-intervention SBP was similar between the 5 % MVC and 10 % MVC groups 116.3±6 mm Hg vs. 114.8±2.6 mm Hg respectively $F(1,17)$=0.45, p=0.51. No interaction effects were observed.

Diastolic blood pressure

Changes in baseline versus post-intervention DBP were not significantly different in the 5 % MVC group, –0.97 mm Hg (95 % CI –2.56 to +0.62, p=0.20), d=0.18. Similarly, there were no significant baseline versus post-intervention difference in the 10 % MVC group, +1.8 mm Hg (95 % CI –1.29 to +4.89, p=0.22), d=0.26 which can be described as small. Post-intervention DBP was similar between the 5 % MVC and 10 % MVC groups 68.5±4 mm Hg vs. 69.4±7 mm Hg respectively $F(1,17)$=0.72, p=0.41. No interaction effects were observed.

Heart rate

There were no significant changes in heart rate during the 6 week study. Heart rate did not increase during IHG exercise >10 beats.min^{-1} in any participant during any session.

Effect of sampling duration

ANOVA showed that using 120 s produced significantly higher SBP and DBP than using 15, 30 or 60 s sampling durations (Table 2).

Table 1. Resting baseline data.

	5 % (n=10)	**10 % (n=10)**
Age (years)	38.8 ± 10.5	38.7 ± 12.6
Male (n)	6	6
Female (n)	4	4
Height (m)	1.72 ± 0.1	1.75 ± 0.1
Weight (kg)	83.3 ± 21.4	85.3 ± 26.9
BMI	28.4 ± 7.7	27.7 ± 7.4
RSBP (mm Hg)	120.3 ± 8.1	120.5 ± 11.8
RDBP (mm Hg)	69.5 ± 6.4	67.6 ± 6.4

All values are reported as means. BMI – body mass index, RSBP – resting systolic blood pressure, RDBP – resting diastolic blood pressure. All p>0.05.

Table 2. Mean difference scores for continuous blood pressure measurement.

	Blood pressure at 120 s			
	Pre SBP	**Post SBP**	**Pre DBP**	**Post DBP**
Blood pressure				
60 s	0.57 ± 0.75	0.02 ± 1.81	0.39 ± 0.54	–0.09 ± 1.25
30 s	0.91 ± 1.76	–0.09 ± 3.46	0.48 ± 0.95	0.03 ± 2.88
15 s	1.44 ± 2.35	0.01 ± 4.0	1.07 ± 1.44	0.17 ± 4.21

t statistic: * $p<0.05$, ** $p<0.01$. Data are means ± SD.

Age as a covariate

An ANOVA indicated that 20 % of the variance in post training SBP was explained by the participant ages, $F(1,17)=4.30$, $p=0.05$, partial $\eta^2=0.202$. Furthermore, 20 % of the variance in post training DBP was also explained by participant ages, $F(1,17)=4.31$, $p=0.05$, partial $\eta^2=0.202$.

Discussion

Our work examines the effects of the lowest isometric training intensities that have been explored. Our primary finding was that IHG training performed at either 5 % MVC or 10 % MVC elicited no statistically significant reduction on either SBP or DBP after 6 weeks of training in normotensive adult men and women. However, our results did show a reduction in SBP in both the 5 % and 10 % groups and this was supported by medium to large effect sizes suggesting that IHG training at both intensities has an anti-hypertensive effect. In the current study, after 6 weeks of IHG training, reductions in SBP were similar to the antihypertensive effects observed in monotherapy of 5-7 mm Hg (Wong and Wright 2014). Reductions in SBP and DBP of ≥2 mm Hg can significantly reduce the incidence of CVD in both hypertensive and normotensive individuals, subsequently small reductions of this magnitude are considered clinically meaningful (Collaboration 2003, Wong and Wright 2014). We identified one other published RCT that did not detect statistically significant reductions in resting BP yet were able to report clinically meaningful reductions in ambulatory SBP and night-time SBP (~3-4 mm Hg) (Stiller-Moldovan *et al.* 2012). Our secondary finding was that there was minimal effect of different sampling durations for rolling averages (assessed over 120, 60, 30 and 15 s) on pre- or post-blood pressure values.

Our primary finding was no statistically significant effect on either SBP or DBP after 6 weeks of training in normotensive adults. If one assumes for arguments' sake that there exists a 2/3 relative intensity of isometric handgrip (IHG) exercise to Double Leg (DL) isometric exercise, then the comparison of our data (non-significant changes after 6 weeks of IHG at 10 % MVC) might actually be showing similar results as Wiles *et al.* (2010) who used 10 % MVC DL for 8 weeks. Thus, Wiles *et al.* (2010) used a slightly higher intensity (comparing 'like-for-like' IHG to DL, but in a longer program). This interpretation is further confirmed by the 4-weeks to 6-weeks comparison between the data of Wiles *et al.* (2010) and the current data (both being non-significant). However, it should be noted that Wiles *et al.* (2010) did report significant reductions in resting BP at ~10 % MVC after 8 weeks, but not after 4 weeks of training.

Contrary to the findings of Wiles *et al.* (2010), Howden *et al.* (2002) observed statistically significant reductions in SBP after 3 weeks of isometric leg exercise at ~20 % MVC and after 4 weeks of isometric arm training at ~30 % MVC. Furthermore, Gill *et al.* (2015) hypothesized that reductions in resting BP from IET would be intensity dependent, they compared the effects of low (~23 % MVC) and moderate (~34 % MVC) IET over a 3 week period and reported a reduction in SBP in the moderate intensity group only. Baross *et al.* (2012) found that ~14 % MVC, but not ~8 % MVC elicited BP reductions after 8 weeks of isometric bilateral leg extension exercise. Collectively, these studies highlight a relationship between IET intensity, time (study duration) and reductions in resting BP. They suggest that the magnitude and rate at which resting BP is reduced increases as exercise intensity increases and that where present these reductions will continue to increase over time, with 8-10 weeks being the longest durations investigated so far. Subsequently, in terms of the current study, it could be the case that at intensity levels as low as

5 % and 10 % MVC that 6 weeks of IHG training is not a sufficiently long enough training period to elicit statistically significant results, but may elicit clinically significant results. Whilst the relationship between IET intensity, time and BP reductions are not fully understood, together, our findings and those of others suggest an anti-hypertensive threshold that may be well below 10 % MVC.

The precise mechanism(s) of the anti-hypertensive effect(s) of isometric exercise remain unclear; however, it appears likely that the true stimulus is probably a result of the competing drives of reduced blood flow (from external compression of the blood vessels and sympathetic vasoconstriction) in the face of a vasodilator stimulus from metabolite accumulation. The variation in individual adaptation rates to IET are probably due to the individual variations in plasma noradrenaline levels, which exist prior to training (Esler 2011). Indeed, plasma noradrenaline levels have been shown to be linked to training-induced reductions in resting blood pressure (especially in hypertensives, who seemingly have higher levels of plasma noradrenaline) (Cornelissen and Fagard 2005).

Previous work has suggested that blood flow is fully occluded at approximately 55-75 % of MVC, but those able to exert more handgrip force will have higher occlusion thresholds (Barnes 1980). Intuitively even at lower percentage of MVC with arm or leg isometric exercise, partial occlusion of blood flow is likely. The reactive hyperemia may therefore be due to partial or full occlusion of the brachial artery during 2 min IHG efforts. Previous work has postulated that in response to ischemia induced by IHG activity a number of metabolites are produced; these include prostaglandins, beta-endorphins and HIF-alpha (Wong *et al.* 2015, Stiller-Moldovan *et al.* 2012, Wong and Wright 2014). It may be that the presence or absence of reactive hyperemia is determined by the MVC intensity during isometric exercise. Moreover, the results of our work and of others such as Wiles *et al.* (2010) and Baross *et al.* (2012) suggest that MVC intensities as little as 5-14 % may induce sufficient, albeit partial, occlusion to blood flow to induce ischemia and the subsequent metabolite production that may be contributing to BP reductions. Nonetheless, IET response rates are highly variable between individual participants whereby some respond to IET (in highly varying degrees) and others do not (McGowan *et al.* 2007, Stiller-Moldovan *et al.* 2012). Whilst the reasons for this are not fully understood there are a number of variables that are likely to affect the magnitude of reduction in resting BP. For instance, the greatest isometric exercise reductions in resting BP have been observed in pre-hypertensive and hypertensive individuals (Wiley *et al.* 1992, Taylor *et al.* 2003) and magnitude of change in BP has been associated with initial resting BP values such that greater reductions are observed in individuals with higher pre-IET BP (Millar *et al.* 2007). In the current study participant age was also identified as a significant predictor of resting BP reduction in response to IET, this finding was not surprising as age is related to arterial stiffness and hypertension.

Our secondary aim was to assess whether different sampling durations for rolling averages affected BP values for continuous BP measurements. Due to the transient nature of blood pressure the recommended gold standard procedure for measuring blood pressure is *via* 24 h ambulatory monitoring, however, ambulatory means of BP measurement were unavailable to this study. In an attempt to attenuate the natural fluctuations of BP we used a continuous BP measurement and also measured baseline resting BP on three separate occasions for a 2 min period each time. We found that in all cases 120 s sampling data was significantly higher than for the other sampling durations. We believe that the longer 120 s sampling duration provides a more robust default for our primary analysis.

The lack of a non-exercising or 'sham IRT' control group was a limitation in this study.

Conclusion

This is the first threshold (MVC %) examination for antihypertensive responses to IET at intensities traditionally used as a control or placebo. In those people unable to complete IET at the traditional intensity of 30 % MVC, our results suggest that IET intensities of both 5 % and 10 % MVC may offer clinically relevant anti-hypertensive effects, despite the absence of statistically significant reductions in resting BP. As this is the first study of its kind, the study duration and the sample size may have been insufficient to demonstrate a statistically significant reduction in resting BP at these low intensities. Further research involving a larger participant cohort, conducted over a longer period of time is required to determine a minimum therapeutic threshold for antihypertensive response, this determination would aid in the design of future RCT's to determine if sham groups are truly that. Moreover, ascertaining the

minimum IET intensity for BP reduction may also be important in terms of designing exercise programs for the frail and elderly. Elderly people may struggle to complete IHG exercise at 30 %MVC, and why would we ask them to in light of our clinically significant findings.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

The authors thank Dr Gudrun Dieberg for her assistance with study design.

References

BADROV MB, BARTOL CL, DIBARTOLOMEO MA, MILLAR PJ, MCNEVIN NH, MCGOWAN CL: Effects of isometric handgrip training dose on resting blood pressure and resistance vessel endothelial function in normotensive women. *Eur J Appl Physiol* **113**: 2091-2100, 2013a.

BADROV MB, HORTON S, MILLAR PJ, MCGOWAN CL: Cardiovascular stress reactivity tasks successfully predict the hypotensive response of isometric handgrip training in hypertensives. *Psychophysiology* **50**: 407-414, 2013b.

BARNES WS: The relationship between maximum isometric strength and intramuscular circulatory occlusion. *Ergonomics* **23**: 351-357, 1980.

BAROSS AW, WILES JD, SWAINE IL: Effects of the intensity of leg isometric training on the vasculature of trained and untrained limbs and resting blood pressure in middle-aged men. *Int J Vasc Med* **2012**: 964697, 2012.

CARLSON DJ, DIEBERG G, HESS NC, MILLAR PJ, SMART NA: Isometric exercise training for blood pressure management: a systematic review and meta-analysis. *Mayo Clin Proc* **89**: 327-334, 2014.

COLLABORATION BPLTT: Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet* **362**: 1527-1535, 2003.

CORNELISSEN VA, FAGARD RH: Effects of endurance training on blood pressure, blood pressure-regulating mechanisms, and cardiovascular risk factors. *Hypertension* **46**: 667-675, 2005.

CORNELISSEN VA, SMART NA: Exercise training for blood pressure: a systematic review and meta-analysis. *J Am Heart Assoc* **2**: e004473, 2013.

DEVEREUX GR, WILES JD, SWAINE I: Markers of isometric training intensity and reductions in resting blood pressure. *J Sports Sci* **29**: 715-724, 2011.

ESLER M: The sympathetic nervous system through the ages: from Thomas Willis to resistant hypertension. *Exp Physiol* **96**: 611-622, 2011.

GILL KF, ARTHUR ST, SWAINE I, DEVEREUX GR, HUET YM, WIKSTROM E, CORDOVA ML, HOWDEN R: Intensity-dependent reductions in resting blood pressure following short-term isometric exercise training. *J Sports Sci* **33**: 616-621, 2015.

HAJJAR I, KOTCHEN TA: Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988-2000. *JAMA* **290**: 199-206, 2003.

HOWDEN R, LIGHTFOOT JT, BROWN SJ, SWAINE IL: The effects of isometric exercise training on resting blood pressure and orthostatic tolerance in humans. *Exp Physiol* **87**: 507-515, 2002.

JAMES PA, OPARIL S, CARTER BL, CUSHMAN WC, DENNISON-HIMMELFARB C, HANDLER J, LACKLAND DT, LEFEVRE ML, MACKENZIE TD, OGEDEGBE O, SMITH SC JR, SVETKEY LP, TALER SJ, TOWNSEND RR, WRIGHT JT JR, NARVA AS, ORTIZ E: 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* **311**: 507-520, 2014.

MCAULEY D, SILKE B, FARRELL S: Reliability of blood pressure determination with the Finapres with altered physiological states or pharmacodynamic conditions. *Clin Auton Res* **7**: 179-184, 1997.

MCGOWAN C, LEVY A, MCCARTNEY N, MACDONALD M: Isometric handgrip training does not improve flow-mediated dilation in subjects with normal blood pressure. *Clin Sci* **112**: 403-409, 2007.

MILLAR PJ, BRAY SR, MCGOWAN CL, MACDONALD MJ, MCCARTNEY N: Effects of isometric handgrip training among people medicated for hypertension: a multilevel analysis. *Blood Press Monit* **12**: 307-314, 2007.

MILLAR PJ, BRAY SR, MACDONALD MJ, MCCARTNEY N: The hypotensive effects of isometric handgrip training using an inexpensive spring handgrip training device. *J Cardiopulm Rehabil Prev* **28**: 203-207, 2008.

STILLER-MOLDOVAN C, KENNO K, MCGOWAN CL: Effects of isometric handgrip training on blood pressure (resting and 24 h ambulatory) and heart rate variability in medicated hypertensive patients. *Blood Press Monit* **17**: 55-61, 2012.

TABACHNICK BG, FIDELL LS: *Using Multivariate Statistics*. Pearson & Allyn and Bacon, Boston, 6th Edn., 2013.

TAYLOR AC, MCCARTNEY N, KAMATH MV, WILEY RL: Isometric training lowers resting blood pressure and modulates autonomic control. *Med Sci Sports Exerc* **35**: 251-256, 2003.

WILES JD, COLEMAN DA, SWAINE IL: The effects of performing isometric training at two exercise intensities in healthy young males. *Eur J Appl Physiol* **108**: 419-428, 2010.

WILEY RL, DUNN CL, COX RH, HUEPPCHEN NA, SCOTT MS: Isometric exercise training lowers resting blood pressure. *Med Sci Sports Exerc* **24**: 749-754, 1992.

WILLIAMS CA: Effect of muscle mass on the pressor response in man during isometric contractions. *J Physiol* **435**: 573-584, 1991.

WONG GW, WRIGHT JM: Blood pressure lowering efficacy of nonselective beta-blockers for primary hypertension. *Cochrane Database Syst Rev* **2**: CD007452, 2014.

WONG GW, LAUGEROTTE A, WRIGHT JM: Blood pressure lowering efficacy of dual alpha and beta blockers for primary hypertension. *Cochrane Database Syst Rev* **8**: CD007449, 2015.

Higher Degree Research Thesis by Publication
University of New England

STATEMENT OF AUTHORS' CONTRIBUTION

(To appear at the end of each thesis chapter submitted as an article/paper)

We, the Research Master/PhD candidate and the candidate's Principal Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated in the *Statement of Originality*.

	Author's Name (please print clearly)	**contribution**
Candidate	Nicole Hess	Responsible for study design data, recruitment of participants, study coordination, collection and cleaning of data, statistical analysis, writing of paper.
Other Authors	Neil Smart	Assisted with study design, provided editorial comments and assisted in addressing reviewers comments.
	Debra Carlson	Assisted with study coordination, and the collection and cleaning data.
	Jodie Inder	Assisted with the data collection.
	Emmanuel Jesulola	Provided Phlebotomy services (blood collection) and assisted with data collection.
	Jim McFarlane	Provided editorial comments, provided lab space and lab facilities, and reviewed data integrity.

Name of Student/Candidate: Nicole Hess

Name/title of Principal Supervisor: Neil Smart

[redacted]

18.09.2016
Date

[redacted]

Principal Supervisor

19.09.2016
Date

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University of New England

STATEMENT OF ORIGINALITY

(To appear at the end of each thesis chapter submitted as an article/paper)

We, the Research Master/PhD candidate and the candidate's Principal Supervisor, certify that the following text, figures and diagrams are the candidate's original work.

Type of work	Page numbers
All text, tables and diagrams	Chapter 4 pp 64–71

Name of Student/Candidate: Nicole Hess

Name/title of Principal Supervisor: Neil Smart

[redacted]

18.09.2016
Date

[redacted]

Principal Supervisor

19.09.2016
Date

Chapter 5 : Managing Vascular Risk Factors at the Mild Cognitive Impairment Stage of Alzheimer's Disease Utilising Isometric Exercise Training

N. C. L. Hess and N. A. Smart

Submitted to Frontiers in Aging Neuroscience, April 4, 2016
Currently in the review process

Candidate Signature

Principal Supervisor Signature

Abstract

Alzheimer's disease (AD) is the most common form of dementia diagnosed amongst the elderly. Mild cognitive impairment (MCI) is a condition often indicative of the earliest symptomology of AD with 10-15% of MCI patients progressing to a diagnosis of AD. Individuals with a history of vascular risk factors (VRF) are considered high risk candidates for developing cognitive impairment in later life. Evidence suggests that vascular injury resulting from untreated VRF promotes progression from MCI to AD and exacerbates the severity of dementia in AD, and neuroimaging studies have found that the neurodegenerative processes associated with AD are heavily driven by VRF that promote cerebral hypoperfusion. Subsequently, common links between vascular disorders such as hypertension and neurodegenerative disorders such as AD include compromised vasculature, cerebral hypoperfusion and chronic low grade inflammation (a hallmark of both hypertension and AD). Exercise has been demonstrated to be an effective intervention for blood pressure management, chronic low grade inflammation, and improvements in cognition. Data from recent analyses suggests that isometric exercise training (IET) may improve vascular integrity and elicit blood pressure reductions greater than those seen with dynamic aerobic and resistance exercise. IET may also play an effective role in the management of VRF at the MCI stage of AD and may prove to be a significant strategy in the prevention, attenuation or delay of progression to AD. A plausible hypothesis is that the reactive hyperaemia stimulated by IET initiates a cascade of vascular, neurotrophic and neuro-endocrine events that lead to improvements in cognitive function.

Key words: Alzheimers disease; Mild cognitive impairment; Vascular risk factors; Hypertension; Blood pressure; Reactive hyperaemia; Isometric exercise training

5.1 Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative dementing disorder responsible for severe cortical atrophy in selective regions of the brain such as the temporal, medial-temporal, limbic, frontal and prefrontal cortices [1-3], see Figure 5.1. The decay of these neural structures is deleterious to a number of cognitive and functional domains including learning, memory, attention, motivation, executive function, motor function, global cognition [1,4]. Mild cognitive impairment (MCI), often considered to be the earliest symptomatic manifestation of AD [5,6] is also accompanied by significant, non-normative atrophy of the medial temporal and temporal cortices [1,3]. Currently, there is no cure or effective treatment for AD and despite decades of investigation the pathogenesis of sporadic (late-onset) AD remains both elusive and controversial. Knowledge of the disease pathogenesis would likely aid in the development of an effective treatment.

The amyloid cascade hypothesis initially suggested by Glenner and Wong [7] still remains somewhat of an axiom. This hypothesis purports genetic causation and proposes that the amyloid beta (Aβ) peptide initiates a cascade of events that manifest in amyloid plaque deposition and the hyperphosphorlation of tau protein, forming neurofibrillary tangles. The end result of these events is neuronal injury and loss, and ultimately, the development of AD. This theory has been criticised for its inability to explain the etiology of these hallmark pathologies and also for its inability to deliver an effective treatment [8]. Current pharmacotherapy does not act on these indicators and has minimal effect on the symptomatic presentations of the disease [8-11]. Consequently, investigators continue to examine alternative hypotheses to explain AD pathogenesis. Over the past two decades vascular hypotheses of AD have received considerable attention [12,13]; these theories focus on a non-amyloidogenic pathway of AD that is driven by vascular risk factors (VRF) such as hypertension,

atherosclerosis, hyperlipidemia, and cerebrovascular disease which may ultimately lead to cerebral hypoperfusion and as a consequence result in neuronal dysfunction leading to cognitive decline and AD. There is convincing research to support a vascular hypothesis of AD; the severity of dementia in AD patients has been found to be exacerbated by the presence of cerebral ischemic lesions [14], neuroimaging studies have identified that damaged and dysfunctional cerebral microcirculation is one of the earliest predictors of AD [15], hypertension is reported to cause injury to the vascular system [16] and is associated with cerebral vascular pathology, hypoperfusion and cognitive decline [17].

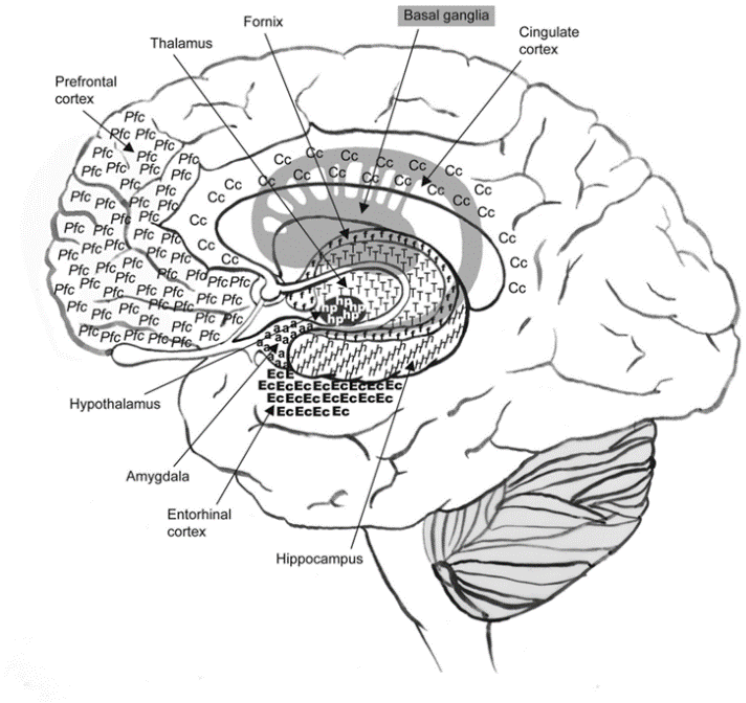


Figure 5.1. Sagittal view of the brain.

Alzheimer's disease is responsible for severe cortical atrophy in selective regions of the brain such as the frontal and prefrontal cortex, and the temporal, medial-temporal and limbic areas. Neural structures associated with these regions include the thalamus, basal ganglia, cingulate cortex, fornix, hypothalamus, amygdala, hippocampus and entorhinal cortex. One of the earliest indicators of Alzheimer's disease, identified by imaging studies, is the presence of cerebral hypoperfusion in temporoparietal regions such as the entorhinal and hippocampal areas.

Exercise has long been recommended and demonstrated as an effective therapeutic intervention for hypertension [18,19], MCI and AD and has been associated with marginal improvements in cognitive performance outcomes [20-27]. Most studies have focused on aerobic exercise due to shear wall stress and the subsequent release of nitric oxide (NO) [28,29], however, an increasing body of evidence supports the role of isometric exercise training (IET) to affect significant reductions in resting systolic and diastolic blood pressures in both hypertensive and normotensive men and women [30-35]. Unlike aerobic exercise, the potential for IET to assist with improvements in cognitive performance have not yet been investigated; though the feasibility of inducing limb ischemia to support and repair distant organs such as the heart and the brain has been successfully demonstrated through the application of techniques such as remote ischemic conditioning (RIC) [36] and physiological ischemic training (PIT) [37]. The physiological mechanisms elicited by IET are not fully understood and are still under investigation; however, it may be the case that resulting from repeated exposure to ischemia, hypoxia, and reactive hyperaemia, IET elicits increases in angiogenesis, neuro-endocrine function, and metabolites such as beta endorphins and prostaglandins. Subsequently, it may be the case that in conjunction with its anti-hypertensive effects, isometric exercise may also offer the potential to elicit improvements in cognitive performance.

The following article reviews, 1) the purported linkages between VRF and cognitive impairment, 2) the shared pathological events prevalent in hypertension and AD, and 3) considers the potential benefits and efficacy of utilising IET as a non-pharmacological therapy for preventing and/or attenuating the progression of MCI to incidence of sporadic AD.

5.2 Alzheimers disease and vascular dementia

Alzheimer's disease and vascular dementia (VaD) are the two most common forms of dementia diagnosed amongst older adults with AD being most common [38]. The severity and extent of AD-related neurodegenerative atrophy grows as a function of time selectively and predictably destroying memory functions, cognitive performance and functional abilities at each stage. Whereas, in VaD the presentation of dementia is attributed to dysfunctional vascular mechanisms [39] and is not accompanied by the hallmark neurodegenerative processes prevalent in AD**.** Throughout the progression of VaD memory remains intact with attentional and executive functioning disproportionately impaired [39,40]. Traditionally these two diseases have been studied separately, however, increasingly, over the past two decades investigators have been able to link the contribution of VRF such as hypertension, atherosclerosis, hyperlipidemia and cerebrovascular disease to cognitive disorders such as MCI and sporadic AD [41-44]. Vascular damage associated with aging, hypertension and other vascular risk factors is thought to inhibit both the delivery of nutrients to the brain and the clearance of toxic metabolites. The ensuing homeostatic disruption of altered cerebral vasculature is purported to promote cellular disruption, cell death and cognitive impairment [45], see Figure 5.2.

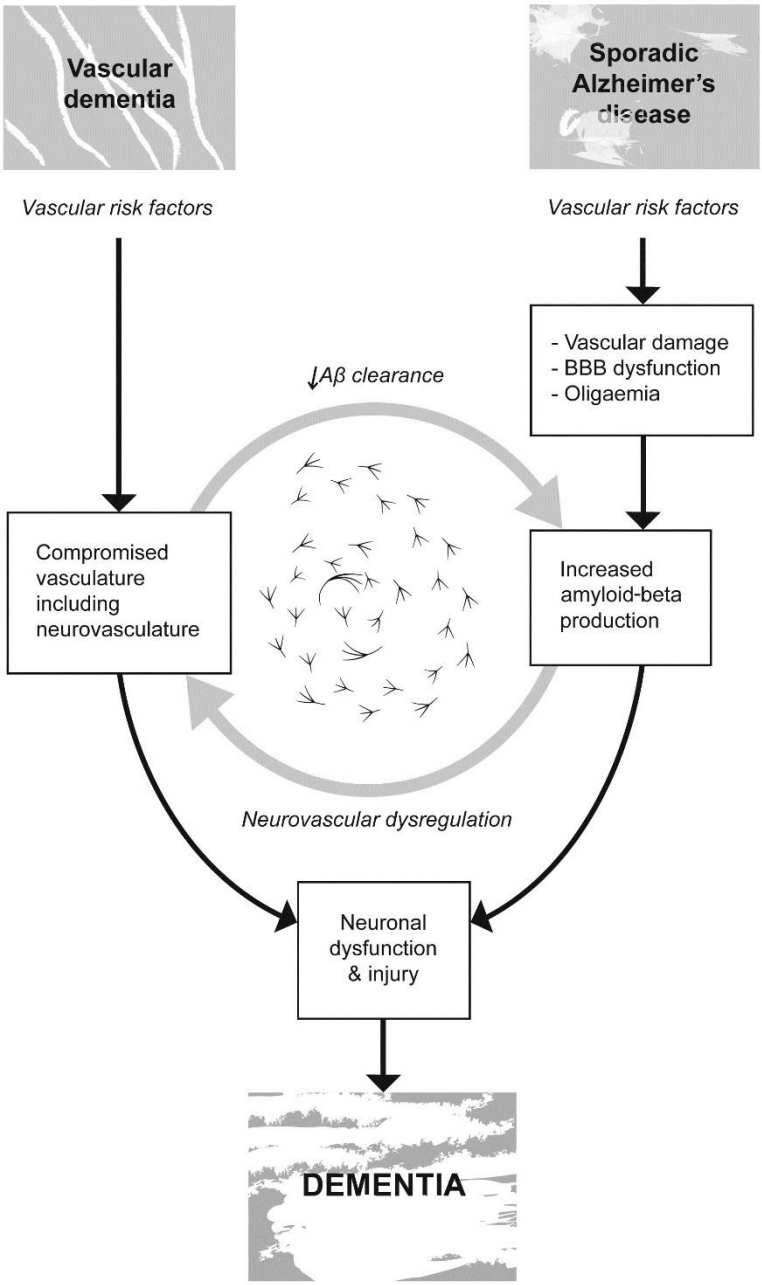


Figure 5.2. Vascular risk factors in vascular dementia (VaD) and Alzheimer's disease (AD).

Vascular risk factors such as hypertension, atherosclerosis, hyperlipidemia and cerebrovascular disease are linked to cognitive disorders such as VaD and sporadic AD. Vascular damage associated with aging, hypertension and other vascular risk factors is thought to; inhibit both the delivery of nutrients to the brain and the clearance of toxic metabolites, compromise the integrity of the blood brain barrier promoting the accumulation and propagation of the hallmark proteogenic pathologies associated with AD. VaD is not accompanied by these same hallmark neurodegenerative processes. In both VaD and AD, the homeostatic disruption of altered cerebral vasculature is believed to promote cellular disruption, cell death and cognitive impairment ultimately resulting in dementia.

5.3 The vascular hypothesis of Alzheimers disease

The vascular hypothesis of AD proposes that cerebral hypoperfusion is the causal factor in disease development [12]. The hypothesis recognises an intimate link between vascular dysfunction and neuronal dysfunction and highlights the importance of the circulatory system to brain functions. The hypothesis proposes that sporadic AD is a multifactorial disease fuelled by VRF such as hypertension, atherosclerosis, cardiac disease, stroke, and diabetes, which contribute to chronic brain hypoperfusion/oligaemia—reduced cerebral blood flow CBF). Obstructed CBF prevents the efficient delivery of nutrients such as oxygen, glucose, and micronutrients to the brain and compromises energy metabolism and neural activity. Similar to the vascular hypothesis, the two-hit hypothesis also proposes that a non-amyloidogenic pathway driven by VRF and reduced cerebral perfusion might be contributing to the development of late on-set AD [13].

The two-hit theory proposes that cerebral hypoperfusion and an over accumulation of the Aβ peptide triggers the hyperphosphorylation of p-tau which manifests in neurofibrillary tangles, neuronal degeneration and eventually AD [13]. This theory suggests that VRF play a pivotal role in the pathogenesis of the disease. Hit one proposes that vascular damage compromises the integrity of the blood brain barrier (BBB) and facilitates a reduction in CBF. Vascular injury inhibits the clearance of Aβ at the BBB; this in turn mediates increased production of Aβ and results in the over accumulation of neurotoxic levels of this peptide. Both the aggregation of toxic levels of Aβ, and cerebral hypoperfusion promote early neuronal dysfunction. Hit two proposes that continuing increases in Aβ accumulation exacerbates neuronal dysfunction, is a catalyst for neurodegeneration and AD, and promotes self-propagation of the disease.

5.4 Vascular pathology and cognitive decline in AD

Pathological changes to the cerebral microvasculature precede and/or accompany vascular disorders such as hypertension, neurovascular disorders such as AD, and cognitive decline [17]. Individuals with a history of VRF and vascular disease are considered high risk candidates for developing cognitive impairment in later life [41,46,47]. Evidence suggests that vascular injury exacerbates the severity of dementia in AD and that the neurodegenerative process is heavily driven by vascular factors [48-52]. Additionally, vascular lesions and VRF have been reported to increase the rate of cognitive decline and accelerate the disease progression [53].

Imaging studies have identified cerebral hypoperfusion in selective neural regions as one of the earliest indicators of AD, specifically in the temporoparietal regions such as the entorhinal, transentorhinal and hippocampal areas (areas linked to memory function, and the first regions to be afflicted with AD neuropathology), see Figure 1. [11,15,54]. In these studies, individuals displaying hypoperfusion and complaining of memory problems or diagnosed with MCI went on to develop AD [11,15], whereas, those individuals who showed normal CBF did not convert to AD during the observation period. Other studies have identified that cerebral hypoperfusion accompanies hippocampal atrophy [54,55].

Neuroimaging research suggests that the clinical symptoms associated with late-onset AD result from neurodegeneration not amyloid deposition and that cognitive decline is directly related to the neurodegenerative process of the disease pathology and not amyloidosis [56-58]. These studies also suggest that there is no association between the rate of neurodegeneration and the rate of amyloid deposition. Consequently, if the neurodegenerative processes of AD are intensified by vascular factors then timely interventions that address these risk factors and reinstate the delivery of a nutrient rich oxygenated blood supply to the brain may ameliorate or attenuate the neurodegenerative process and disease trajectory.

5.5 Hypertension

Hypertension is associated with cerebrovascular pathology, hypoperfusion [17], and cognitive decline [59]. Magnetic resonance imaging (MRI) studies have demonstrated a link between brain atrophy and untreated hypertension [60] and results from the 'The Honolulu Asia Aging Study' (HAAS) [46] show that hippocampal atrophy can be linked to untreated hypertension in midlife, and that a positive correlation exists among systolic blood pressure (SBP), diastolic blood pressure (DBP), and burden of neural AD pathology. Hypertension causes injury to the vascular system and is associated with an elevated burden of neural white matter lesions [16]. Hypertension promotes vascular inflammation, vascular damage, and activated astrocytes and microglia; these events stimulate dysfunctional arterial dilation, the generation of pro-inflammatory stimuli and enhanced levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS) [45]. Consequently, CBF is significantly reduced and mitochondrial damage becomes pervasive. Ultimately, these physiological cascades manifest in a neuronal energy crisis, neuronal damage, apoptosis, neuro-degeneration, inflammation and finally, AD [45].

The deleterious structural and functional alterations in cerebral circulation that are associated with hypertension are potentially reversible [61], presumably, improving CBF may also lead to improvements in cognitive performance. Li et al. (2011) [62] observed that the treatment of VRF such as hypertension reduced the risk of late-onset AD and the progression from MCI to AD; Deschaintre et al. (2009) [63] also reported that the treatment of VRF resulted in slower cognitive decline in individuals with AD. Similarly, antihypertensive treatment utilising pharmacotherapy has been shown to offer protection against dementia in elderly individuals with hypertension [64] and to increase the velocity of CBF and improve the distensibility of the

carotid artery, supporting a correlation between blood pressure reduction and increased CBF [61].

5.6 Pro-inflammatory markers, systemic inflammation and cytokine responses to AD and hypertension.

Chronic low grade systemic inflammation is a condition characterised by the persistent activation of the bodies intrinsic immune system and is perpetuated by the release of pro-inflammatory cytokines from immune-related cells [65]. Chronic low grade systemic inflammation is believed to contribute to the development and clinical trajectory of conditions such as hypertension and AD [65]. Subsequently, besides the hallmark neuropathology associated with AD chronic low-grade inflammation is also considered a hallmark of AD that may be influencing the neurodegenerative progression of the disease [65,66]. Similarly, chronic low-grade inflammation is recognised as a hallmark of hypertension and is attributed, in part, to the etiology of vascular disease [67,68].

Elevated inflammatory biomarkers that share a clinical association with AD and hypertension include; interleukin (IL) -1β and -6, acute phase C reactant protein (CRP), and tumor necrosis factor (TNF-α) [65,67,68]. Specifically, TNF-α can induce apoptic cell death and inflammation [65], and is positively correlated with blood pressure levels [68]. Dysregulated TNF-α production is implicated in a variety of human diseases including AD [65] with high levels of this cytokine associated with dementia [69]. IL-6 has been characterised as both a pro- and anti-inflammatory cytokine [70], on one hand IL-6 expression is stimulated by the production of TNF-α and IL-1 (both pro-inflammatory cytokines), on the other hand it is also responsible for supressing the production of these two inflammatory markers [71]. Furthermore IL-6 is involved in upregulating the expression of anti-inflammatory cytokines IL-10 and IL-1ra [72].

5.7 Exercise as a modifiable risk factor

Exercise is recommended as a therapeutic intervention for hypertension, atherosclerosis [18,19], MCI, and AD [20-27,73] and an inverse relationship exists between levels of physical activity and levels of chronic low grade inflammation [68]. Specifically, aerobic exercise incites endothelium-dependent vasodilation via the upregulation of NO production, and with regular adherence, inhibits age associated loss in endothelium-dependent vasodilation and restores levels in previously sedentary individuals [74]. Thus, most studies have focused on aerobic exercise due to shear wall stress and the subsequent release of NO. Moreover, prevalent in the broader literature is evidence suggesting that exercise training targeting cardiovascular fitness (VO_{2max}) may provide neuroprotective benefits and moderate the structural and functional neuronal changes associated with conditions such as MCI and dementia [75-77]. Evidence derived from animal models indicates that aerobic exercise has the ability to facilitate improvements in angiogenesis, neurogenesis, and learning and memory in rats [78,79], and in the mouse model, aerobic exercise has been shown to inhibit the evolution of Alzheimer's-associated neuropathology [80]. Current literature suggests that exercise taken up in midlife by healthy adults facilitates improvements in various domains of cognitive functioning and decreases the chances of developing dementia in later life [81]. Recent MRI studies have reported a link between brain atrophy and cardiovascular fitness in Alzheimer's disease [76,77], and Erickson et al. (2011) [82] reported increased hippocampal volumes in the brains of healthy individuals who participated in exercise training compared to sedentary controls. A growing number of training studies have investigated the effect of physical activity on the neurocognitive performance outcomes of people at risk of, and living with dementia [83-87], subsequently, this literature does offer some support for exercise as a mitigating or stabilising intervention in relation to some cognitive domains.

Exercise provides an anti-inflammatory environment within the body, post exercise circulating cytokines remaining in the plasma are IL-6, IL-10 and IL-1ra [71]. Exercise increases IL-6 transcription rates [28] and during exercise the IL-6 protein is expressed in contracting muscle fibers [57,88], markedly increasing circulating levels [58,89]. Even moderate exercise has been demonstrated to induce marked increases in IL-6 in both the young and elderly. These increases in IL-6 plasma levels are exponential relative to exercise intensity, duration, endurance and recruited muscle mass [69,71].

5.8 Remote limb ischemia to affect distant organs

Inducing limb ischemia and hypoxia to support and improve the healthy functioning of distant organs such as the heart and brain has been successfully demonstrated through techniques such as remote ischemic conditioning (RIC) [36] and physiological ischemic training (PIT) [37].

Remote ischemic conditioning

Originally ischemic conditioning (IC) was developed as a cardio protective application [90] for patients with cardiovascular arterial disease (CAD) and myocardial ischemia. By stimulating ischemic and hypoxic events via the direct occlusion of a coronary artery, the impact and size of future myocardial infarction was reduced significantly [91]. Initially IC was an invasive procedure administered by directly occluding coronary arteries for short periods of time, enough to induce small doses of the injurious agents ischemia and hypoxia [90]. Subsequently, non-invasive applications of IC have been investigated and the benefits of RIC have been illuminated; that is, inducing ischemia in a healthy limb stimulates endogenous protective pathways [92] that are transferable from one organ to another distant organ [93-95]. RIC involves

the repetitive inflation and deflation of a BP cuff placed around a limb at pressures above SBP [96].

Similar to the heart, the brain can also be conditioned with ischemia and hypoxia [97]. Recently, RIC has been demonstrated to stimulate endogenous neuroprotective pathways [98] and increase CBF [96]. Mouse models of vascular cognitive impairment (VCI) [99] have demonstrated that when compared to the control cohort, RIC administered daily for 2 weeks resulted in less inflammation, less amyloid beta deposition, reduced white and grey matter damage, increased CBF and improved cognition. Furthermore, RIC has also been implicated in enhancing neuroplasticity, Cherry-Allen et al. (2015) [100] reported significant improvements in motor learning that were not associated with the ischemic trained limb. Although the hypothesised improvements in cognitive learning were not forthcoming in this study, the researchers postulated that this was most likely due to the difficult nature and the narrow assessment framework of the cognitive assessment task that was utilised and not necessarily indicative that cognitive improvements did not occur. Consequently, to elucidate the cognitive benefits of remotely induced ischemia and hypoxia the authors recommended that future research in this domain utilise cognitive assessment tasks that assess broad ranges of neural regions and networks.

Whilst the mechanisms involved in the remote signalling and stimulation of endogenous pathways to facilitate protective responses and structural changes in distant organs are not fully understood, evidence obtained through animal models and clinical trials supports a number of mechanisms involving; blood borne factors [96,101-103] induced by peripheral nerves [104,105], epigenetic modulations of the genome [106-108], and immune and anti-inflammatory responses [109]. Consequently, it is the interaction of blood borne and neuronal factors that are postulated to both initiate and transmit these signals to the brain.

Physiological ischemic training

Inspired by RIC, the feasibility of PIT to stimulate remote ischemia has also been investigated. PIT is a technique whereby skeletal muscle is subjected to intense contraction via isometric contraction or tourniquet in order to stimulate physiological ischemia [37]. In animal models, PIT applied 8 times daily for 4 weeks to a normal healthy limb has been shown to upregulate vascular endothelial growth factor (VEGF) and facilitate angiogenesis improving blood flow and capillary supply in a remote pathological ischemic limb [110,111]. In clinical trials, PIT using isometric handgrip exercise performed at 50% maximal voluntary contraction (MVC) by patients with coronary artery disease and a coronary artery occlusion significantly increased collateral blood flow in the myocardium [112]. The proposed mechanisms responsible for the effects of PIT include; upregulation in circulating vascular endothelial growth factor (VEGF) and VEGF mRNA, angiogenesis [113], the differential expression of proteins involved in cell migration and energy metabolism [114] and increased systemic endothelial progenitor cells (EPCs) [115]. Unlike RIC, the efficacy of PIT to neural applications has not yet been investigated.

Subsequently, the feasibility of limb ischemia to support and repair distant organs such as the heart and the brain has been demonstrated through the application of techniques such as remote ischemic conditioning (RIC) [36] and more recently, physiological ischemic training (PIT) [37]. Most encouraging is the potential neuroprotective implications that ischemic training may offer those with MCI, AD and VaD. Whilst the protocols between these two techniques differ from each other and the extent of the commonality of shared signalling and protective mechanisms is still the subject of investigation, it is likely that there is a cross over whereby some of these mechanisms are shared. Encouragingly RIC administered to patients aged 80-95 years old with intracranial atherosclerosis stenosis was found to be both safe and effective

in stroke prevention and treatment [116]. Moreover, the principles that support the efficacy of RIC and PIT also support the feasibility of a hypothesis that IET performed by elderly individuals might promote healthy neural functioning and boost cognitive performance.

5.9 Isometric exercise training

Traditionally, aerobic endurance training has been the preferred type of physical activity recommended for blood pressure management, however, current thinking does vary with respect to this. IET involves a single sustained muscle contraction against an immovable load or resistance with no, or minimal, change in length of the involved muscle group. An increasing body of evidence suggests that IET promotes significant reductions in resting systolic and diastolic blood pressures in hypertensive and normotensive men and women [30-35]. Previously, isometric exercise has been associated with exaggerated hypertensive responses, however, data from recent analyses suggests that isometric resistance exercise may elicit blood pressure reductions greater than those seen with dynamic aerobic and resistance exercise [18] and has been safely implemented among a cohort of hypertensive elderly women, 70-82yrs old [117]. Specifically, acute isometric hand grip training (IHG) has been shown to improve resting endothelium-dependant vasodilation [118]. Recent meta-analyses have reported IET to elicit greater reductions in resting SBP than those observed in dynamic resistance training, dynamic aerobic exercise training, and training consisting of both dynamic resistance and aerobic activity [18,119]. The magnitude of effect is comparable to that of monotherapy with beta-blockade [120].

The precise mechanism(s) of the anti-hypertensive effect(s) of isometric exercise remain unclear, however, it appears likely that the initial stimulus is repeated exposure to transient increases in blood flow that result after short periods of ischemia, reactive hyperaemia. Edwards et al. (2007) [68] suggest that reduced peripheral vascular resistance facilitated via

neurohormonal and structural adaptations might also explain the antihypertensive effects of exercise. The reactive hyperaemia elicited during a two minute bout of isometric handgrip (IHG) training may occur due to either partial or full occlusion of the brachial artery. Previous research suggests that full occlusion of blood flow occurs at approximately 55-75% of MVC with higher occlusion thresholds evident in individuals who were able to exert a greater handgrip force [121]. The production of a number of metabolites such as beta endorphins, prostaglandins and hypoxia-inducible factor – 1 α (HIF 1 α) are postulated to result from ischemia induced by full or partial restriction of the brachial artery during IHG exercises [120,122,123]. These metabolites play a number of roles including, supporting the immune system, managing inflammation [89,124], vasodilation and vasoconstriction [125], stimulating angiogenesis, and tissue repair and regeneration [126]. It may be that the intensity of the hand grip contraction employed during IHG exercise determines the existence or absence of reactive hyperaemia; intuitively, even at intensities less than 55% of MVC partial occlusion of blood flow is likely. Indeed, previous work with isometric exercise suggests that intensities as little as 10–14% of MVC may be sufficient to elicit partial occlusion to blood flow, inducing ischemia and the resulting metabolic production that might be contributing to BP reductions [30,33,127]. Utilising lower intensity IHG exercise for BP reduction may prove beneficial in the design of exercise programs for the frail and elderly, elderly people may struggle to complete IHG exercise at 30% MVC yet may still benefit from an isometric exercise program at 10% MVC. Considering the anti-hypertensive effects elicited by isomeric exercise and the purported mechanisms responsible for this, it is also plausible that IET may play an effective role in the management of hypertension at the MCI stage of AD and in conjunction prove to be a significant strategy in the prevention, attenuation or delay of progression to AD. Further research is probably warranted in this area.

5.10 Summary

The contribution of cerebral hypoperfusion to the development of MCI and AD is receiving increasing attention. Evidence points to a strong proportional relationship amongst decline in CBF due to hypoperfusion, aggregation and proliferation of amyloid plaques and hyper-phosphorylated tau protein, neuronal injury and a decline in cognition. In sporadic AD cognitive decline is directly related to the neurodegenerative process of the disease pathology, not amyloidosis, and the neurodegenerative process is heavily driven by VRF. Hypertension is responsible for promoting cerebral ischemia, neurovascular dysfunction and cognitive decline, consequently, it would make sense that ameliorating and attenuating the effects of hypertension and increasing cerebral perfusion might also slow down the neurodegenerative processes related to MCI and dementia in AD. Indeed, there is growing evidence that BP reduction in elderly hypertensive adults can reduce the incidence of dementia and cognitive decline highlighting the need for early therapeutic interventions that stimulate anti-hypertensive effects and promote growth and reparation to the vasculature.

Evidence suggesting that IET may be more efficacious at reducing SBP and DBP than aerobic exercise and resistance training provokes questions relating to the possible role that IET might play in facilitating reparations to the vasculature, increasing CBF, reducing chronic low grade inflammation and possibly improving cognitive performance. Adding strength to this line of enquiry are recent reports that remote limb ischemia can improve aspects of neural functioning. The physiological basis that underpins the potential benefits of IET in individuals with MCI is that IET provides the stimulus to reduce resting blood pressure and changes in blood flow and volume are linked with transient changes in cognition. It could be that the repeated increases in CBF and the associated nutrient and oxygen delivery that result from the sustained isometric exercise trigger (primary or

secondary) the subsequent cascade of structural, biochemical and functional adaptations that increase brain plasticity, function, and cognition. Supporting this proposition is evidence that exercise induces increases in neurotrophins (such as BDNF, IGF-1), angiogenesis, neuro-endocrine function, and causes vascular wall changes (such as endothelial Nitric Oxide) [74,128-130]. A plausible hypothesis is that IET initiates a cascade of vascular, neurotrophic and neuro-endocrine events that lead to an improvement of cognitive function.

Acknowledgements

Anna Terentieva for artwork

References

1. Archer T, Kostrzewa R, Beninger R, Palomo T. Staging Neurodegenerative Disorders: Structural, Regional, Biomarker, and Functional Progressions. *Neurotoxicity Research.* 2011/02/01 2011;19(2):211-234.

2. Querfurth HW, LaFerla FM. Alzheimer's DiseaseMechanisms of Disease. *The New England Journal of Medicine.* 2010;362(4):329-344.

3. Braak H, Alafuzoff I, Arzberger T, Kretzschmar H, Del Tredici K. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta neuropathologica.* 2006;112(4):389-404.

4. Archer T. Physical exercise alleviates debilities of normal aging and Alzheimer's disease. *Acta Neurol Scand.* Apr 2011;123(4):221-238.

5. Etgen T, Sander D, Bickel H, Förstl H. Mild cognitive impairment and dementia: the importance of modifiable risk factors. *Deutsches Ärzteblatt International.* 2011;108(44):743.

6. DeCarli C. Mild cognitive impairment: prevalence, prognosis, aetiology, and treatment. *The Lancet Neurology.* 2003;2(1):15-21.

7. Glenner GG, Wong CW. Alzheimer's disease and Down's syndrome: sharing of a unique cerebrovascular amyloid fibril protein. *Biochemical and biophysical research communications.* 1984;122(3):1131-1135.

8. de la Torre JC. Alzheimer disease as a vascular disorder nosological evidence. *Stroke.* 2002;33(4):1152-1162.

9. Birks J. Cholinesterase inhibitors for Alzheimer’s disease (Review). 2012.

10. Campbell NL, Dexter P, Perkins AJ, et al. Medication adherence and tolerability of Alzheimer’s disease medications: study protocol for a randomized controlled trial. *Trials.* 2013;14(1):125.

11. de la Torre JC. Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics. *The Lancet Neurology.* 2004;3(3):184-190.

12. de la Torre JC, Mussivand T. Can disturbed brain microcirculation cause Alzheimer's disease? *Neurological research.* 1993;15(3):146.

13. Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nature Reviews Neuroscience.* 2011;12(12):723-738.

14. Iadecola C. The overlap between neurodegenerative and vascular factors in the pathogenesis of dementia. *Acta neuropathologica.* 2010;120(3):287-296.

15. Hirao K, Ohnishi T, Hirata Y, et al. The prediction of rapid conversion to Alzheimer's disease in mild cognitive impairment using regional cerebral blood flow SPECT. *Neuroimage.* 2005;28(4):1014-1021.

16. Brickman AM, Reitz C, Luchsinger JA, et al. Long-term blood pressure fluctuation and cerebrovascular disease in an elderly cohort. *Archives of neurology.* 2010;67(5):564-569.

17. Brown W, Thore C. Review: cerebral microvascular pathology in ageing and neurodegeneration. *Neuropathology and applied neurobiology.* 2011;37(1):56-74.

18. Cornelissen V, Smart N. Exercise Training for Blood Pressure: A Systematic Review and Meta-analysis. *Journal of the American Heart Association.* 2013;2(1).

19. Cardoso Jr CG, Gomides RS, Queiroz A, et al. Acute and chronic effects of aerobic and resistance exercise on ambulatory blood pressure. *Clinics.* 2010;65(3):317-325.

20. Smith PJ, Blumenthal JA, Hoffman BM, et al. Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. *Psychosom Med.* Apr 2010;72(3):239-252.

21. Aarsland D, Sardahaee FS, Anderssen S, Ballard C, group tAsSSR. Is physical activity a potential preventive factor for vascular dementia? A systematic review. *Aging & mental health.* 2010;14(4):386-395.

22. Heyn P, Abreu BC, Ottenbacher KJ. The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis. *Archives of physical medicine and rehabilitation.* 2004;85(10):1694-1704.

23. Sofi F, Valecchi D, Bacci D, et al. Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. *Journal of internal medicine.* 2011;269(1):107-117.

24. van Uffelen JG, Paw MJCA, Hopman-Rock M, van Mechelen W. The effects of exercise on cognition in older adults with and without cognitive decline: a systematic review. *Clinical Journal of Sport Medicine.* 2008;18(6):486-500.

25. Baker LD, Frank LL, Foster-Schubert K, et al. Effects of aerobic exercise on mild cognitive impairment: a controlled trial. *Archives of neurology.* 2010;67(1):71.

26. Colcombe S, Kramer AF. Fitness Effects on the Cognitive Function of Older Adults A Meta-Analytic Study. *Psychological science.* 2003;14(2):125-130.

27. Hess NC, Dieberg G, McFarlane JR, Smart NA. The effect of exercise intervention on cognitive performance in persons at risk of, or with, dementia: A systematic review and meta-analysis. *Healthy Aging Research.* 2014;3(3):1-10.

28. Keller C, Steensberg A, Pilegaard H, et al. Transcriptional activation of the IL-6 gene in human contracting skeletal muscle: influence of muscle glycogen content. *The FASEB Journal.* 2001;15(14):2748-2750.

29. Venturelli M, Scarsini R, Schena F. Six-month walking program changes cognitive and ADL performance in patients with Alzheimer. *American journal of Alzheimer's disease and other dementias.* 2011;26(5):381-388.

30. Baross AW, Wiles JD, Swaine IL. Effects of the intensity of leg isometric training on the vasculature of trained and untrained limbs and resting blood pressure in middle-aged men. *International journal of vascular medicine.* 2012;2012.

31. Millar P, Levy A, McGowan C, McCartney N, MacDonald M. Isometric handgrip training lowers blood pressure and increases heart rate complexity in medicated hypertensive patients. *Scandinavian journal of medicine & science in sports.* 2013;23(5):620-626.

32. Devereux GR, Wiles JD, Swaine IL. Reductions in resting blood pressure after 4 weeks of isometric exercise training. *European journal of applied physiology.* 2010;109(4):601-606.

33. Wiles JD, Coleman DA, Swaine IL. The effects of performing isometric training at two exercise intensities in healthy young males. *European journal of applied physiology.* 2010;108(3):419-428.

34. Badrov MB, Bartol CL, Dibartolomeo MA, Millar PJ, McNevin NH, McGowan CL. Effects of isometric handgrip training dose on resting blood pressure and resistance vessel endothelial function in normotensive women. *Eur J Appl Physiol.* Aug 2013;113(8):2091-2100.

35. Badrov MB, Horton S, Millar PJ, McGowan CL. Cardiovascular stress reactivity tasks successfully predict the hypotensive response of isometric handgrip training in hypertensives. *Psychophysiology.* Apr 2013;50(4):407-414.

36. Hess DC, Blauenfeldt RA, Andersen G, et al. Remote ischaemic conditioning [mdash] a new paradigm of self-protection in the brain. *Nature Reviews Neurology.* 2015;11(12):698-710.

37. Ni J, Lu H, Lu X, et al. The evolving concept of physiological ischemia training vs. ischemia preconditioning. *Journal of biomedical research.* 2015;29(6):445.

38. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. *The Lancet Neurology.* 2005;4(8):487-499.

39. Graham N, Emery T, Hodges J. Distinctive cognitive profiles in Alzheimer's disease and subcortical vascular dementia. *Journal of Neurology, Neurosurgery & Psychiatry.* 2004;75(1):61-71.

40. Agüero-Torres H, Kivipelto M, von Strauss E. Rethinking the Dementia Diagnoses in a Population-Based Study: What Is Alzheimer's Disease and What Is Vascular Dementia? *Dementia and geriatric cognitive disorders.* 2006;22(3):244-249.

41. Laukka E, Fratiglioni L, Bäckman L. The influence of vascular disease on cognitive performance in the preclinical and early phases of Alzheimer's disease. *Dementia and geriatric cognitive disorders.* 2010;29(6):498-503.

42. Viswanathan A, Rocca WA, Tzourio C. Vascular risk factors and dementia How to move forward? *Neurology.* 2009;72(4):368-374.

43. de la Torre JC. Vascular risk factor detection and control may prevent Alzheimer's disease. *Ageing research reviews.* 2010;9(3):218-225.

44. Choi H-J. Blood Pressure Variability and Its Management in Hypertensive Patients. *Korean journal of family medicine.* 2012;33(6):330-335.

45. Iadecola C, Park L, Capone C. Threats to the mind aging, amyloid, and hypertension. *Stroke.* 2009;40(3 suppl 1):S40-S44.

46. Korf ES, White LR, Scheltens P, Launer LJ. Midlife Blood Pressure and the Risk of Hippocampal Atrophy The Honolulu Asia Aging Study. *Hypertension.* 2004;44(1):29-34.

47. Solfrizzi V, Panza F, Colacicco A, et al. Vascular risk factors, incidence of MCI, and rates of progression to dementia. *Neurology.* 2004;63(10):1882-1891.

48. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. *New England Journal of Medicine.* 2003;348(13):1215-1222.

49. Song I-U, Kim J-S, Kim Y-I, Eah K-Y, Lee K-S. Clinical significance of silent cerebral infarctions in patients with Alzheimer disease. *Cognitive and behavioral neurology.* 2007;20(2):93-98.

50. Heyman A, Fillenbaum G, Welsh-Bohmer K, et al. Cerebral infarcts in patients with autopsy-proven Alzheimer's disease CERAD, part XVIII. *Neurology.* 1998;51(1):159-162.

51. Schneider JA, Arvanitakis Z, Leurgans SE, Bennett DA. The neuropathology of probable Alzheimer disease and mild cognitive impairment. *Annals of neurology.* 2009;66(2):200-208.

52. White L. Brain lesions at autopsy in older Japanese-American men as related to cognitive impairment and dementia in the final years of life: a summary report from the Honolulu-Asia aging study. *Journal of Alzheimer's disease: JAD.* 2008;18(3):713-725.

53. Helzner EP, Luchsinger JA, Scarmeas N, et al. Contribution of vascular risk factors to the progression in Alzheimer disease. *Archives of neurology.* 2009;66(3):343.

54. Ruitenberg A, den Heijer T, Bakker SL, et al. Cerebral hypoperfusion and clinical onset of dementia: the Rotterdam Study. *Annals of neurology.* 2005;57(6):789-794.

55. Jack, Petersen RC, Xu YC, et al. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. *Neurology.* 1999;52(7):1397-1397.

56. Jack C, Lowe VJ, Weigand SD, et al. Serial PIB and MRI in normal, mild cognitive impairment and Alzheimer's disease: implications for sequence of pathological events in Alzheimer's disease. *Brain.* 2009:awp062.

57. Hiscock N, Chan MS, Bisucci T, Darby IA, Febbraio MA. Skeletal myocytes are a source of interleukin-6 mRNA expression and protein release during contraction: evidence of fiber type specificity. *The FASEB Journal.* 2004;18(9):992-994.

58. Pedersen B, Steensberg A, Fischer C, et al. Searching for the exercise factor: is IL-6 a candidate? *Journal of Muscle Research & Cell Motility.* 2003;24(2-3):113-119.

59. Reitz C, Tang M-X, Manly J, Mayeux R, Luchsinger JA. Hypertension and the risk of mild cognitive impairment. *Archives of neurology.* 2007;64(12):1734-1740.

60. Launer LJ, Masaki K, Petrovitch H, Foley D, Havlik RJ. The association between midlife blood pressure levels and late-life cognitive function. *JAMA: the journal of the American Medical Association.* 1995;274(23):1846-1851.

61. Lipsitz LA, Gagnon M, Vyas M, et al. Antihypertensive therapy increases cerebral blood flow and carotid distensibility in hypertensive elderly subjects. *Hypertension.* 2005;45(2):216-221.

62. Li J, Wang Y, Zhang M, et al. Vascular risk factors promote conversion from mild cognitive impairment to Alzheimer disease. *Neurology*. 2011;76(17):1485-1491.

63. Deschaintre Y, Richard F, Leys D, Pasquier F. Treatment of vascular risk factors is associated with slower decline in Alzheimer disease. *Neurology* 2009;73(9):674-680.

64. Forette F, Seux M-L, Staessen JA, et al. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. *Archives of internal medicine.* 2002;162(18):2046-2052.

65. Swardfager W, Lanctôt K, Rothenburg L, Wong A, Cappell J, Herrmann N. A meta-analysis of cytokines in Alzheimer's disease. *Biological psychiatry.* 2010;68(10):930-941.

66. Wyss-Coray T. Inflammation in Alzheimer disease: driving force, bystander or beneficial response? *Nature medicine.* 2006;12(9):1005-1015.

67. Boos CJ, Lip GY. Is hypertension an inflammatory process? *Current pharmaceutical design.* 2006;12(13):1623-1635.

68. Edwards KM, Ziegler MG, Mills PJ. The potential anti-inflammatory benefits of improving physical fitness in hypertension. *Journal of hypertension.* 2007;25(8):1533-1542.

69. Bruunsgaard H, Andersen-Ranberg K, Jeune B, Pedersen AN, Skinhøj P, Pedersen BK. A high plasma concentration of TNF-α is associated with dementia in centenarians. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 1999;54(7):M357-M364.

70. Tilg H, Dinarello CA, Mier JW. IL-6 and APPs: anti-inflammatory and immunosuppressive mediators. *Immunology today.* 1997;18(9):428-432.

71. Petersen AMW, Pedersen BK. The anti-inflammatory effect of exercise. *Journal of applied physiology.* 2005;98(4):1154-1162.

72. Steensberg A, Fischer CP, Keller C, Møller K, Pedersen BK. IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans. *American Journal of Physiology-Endocrinology And Metabolism.* 2003;285(2):E433-E437.

73. Groot C, Hooghiemstra A, Raijmakers P, et al. The effect of physical activity on cognitive function in patients with dementia: A meta-analysis of randomized control trials. *Ageing research reviews.* 2016;25:13-23.

74. DeSouza CA, Shapiro LF, Clevenger CM, et al. Regular aerobic exercise prevents and restores age-related declines in endothelium-dependent vasodilation in healthy men. *Circulation.* 2000;102(12):1351-1357.

75. Bugg JM, Head D. Exercise moderates age-related atrophy of the medial temporal lobe. *Neurobiology of aging.* 2011;32(3):506-514.

76. Burns JM, Cronk BB, Anderson HS, et al. Cardiorespiratory fitness and brain atrophy in early Alzheimer disease. *Neurology.* 2008;71(3):210-216.

77. Honea R, Thomas GP, Harsha A, et al. Cardiorespiratory fitness and preserved medial temporal lobe volume in Alzheimer's disease. *Alzheimer disease and associated disorders.* 2009;23(3):188.

78. Cotman CW, Berchtold NC. Exercise: a behavioral intervention to enhance brain health and plasticity. *Trends in neurosciences.* 2002;25(6):295-301.

79. Mattson MP, Chan SL, Duan W. Modification of brain aging and neurodegenerative disorders by genes, diet, and behavior. *Science Signaling.* 2002;82(3):637.

80. Adlard PA, Perreau VM, Pop V, Cotman CW. Voluntary exercise decreases amyloid load in a transgenic model of Alzheimer's disease. *Journal of Neuroscience.* 2005(25):4217-4221.

81. Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. *Archives of neurology.* 2001;58(3):498.

82. Erickson KI, Voss MW, Prakash RS, et al. Exercise training increases size of hippocampus and improves memory. *Proceedings of the National Academy of Sciences.* 2011;108(7):3017-3022.

83. Brown AK, Liu-Ambrose T, Tate R, Lord SR. The effect of group-based exercise on cognitive performance and mood in seniors residing in intermediate care and self-care retirement facilities: a randomised controlled trial. *Br J Sports Med.* 2009;43(8):608-614.

84. Cheng ST, PK C, YQ S, et al. Mental and Physical Activities Delay Cognitive Decline in Older Persons With Dementia. *Am J Geriatr Psychiatry.* 2012;5:5.

85. Kemoun G, Thibaud M, Roumagne N, et al. Effects of a physical training programme on cognitive function and walking efficiency in elderly persons with dementia. *Dement Geriatr Cogn Disord.* 2010;29(2):109-114.

86. Lam LC, Chau RC, Wong BM, et al. Interim follow-up of a randomized controlled trial comparing Chinese style mind body (Tai Chi) and stretching exercises on cognitive function in subjects at risk of progressive cognitive decline. *Int J Geriatr Psychiatry.* Jul 2011;26(7):733-740.

87. Lautenschlager NT, L CK, L F, et al. Effect of physical activity on cognitive function in older adults at risk of Alzheimer Disease: a randomized trial. *JAMA.* 2008;300(9):1027-1037.

88. Penkowa M, Keller C, Keller P, Jauffred S, Pedersen BK. Immunohistochemical detection of interleukin-6 in human skeletal muscle fibers following exercise. *The FASEB Journal.* 2003;17(14):2166-2168.

89. Pedersen BK, Hoffman-Goetz L. Exercise and the immune system: regulation, integration, and adaptation. *Physiological reviews.* 2000;80(3):1055-1081.

90. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation.* 1986;74(5):1124-1136.

91. Przyklenk K, Bauer B, Ovize M, Kloner RA, Whittaker P. Regional ischemic'preconditioning'protects remote virgin myocardium from subsequent sustained coronary occlusion. *Circulation.* 1993;87(3):893-899.

92. Iadecola C, Anrather J. Stroke research at a crossroad: asking the brain for directions. *Nature neuroscience.* 2011;14(11):1363-1368.

93. Bøtker HE, Kharbanda R, Schmidt MR, et al. Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial. *The Lancet.* 2010;375(9716):727-734.

94. Sloth AD, Schmidt MR, Munk K, et al. Improved long-term clinical outcomes in patients with ST-elevation myocardial infarction undergoing remote ischaemic conditioning as an adjunct to primary percutaneous coronary intervention. *European heart journal.* 2014;35(3):168-175.

95. Davies WR, Brown AJ, Watson W, et al. Remote Ischemic Preconditioning Improves Outcome at 6 Years After Elective Percutaneous Coronary Intervention The CRISP Stent Trial Long-term Follow-up. *Circulation: Cardiovascular Interventions.* 2013;6(3):246-251.

96. Hess DC, Hoda MN, Khan MB. Humoral mediators of remote ischemic conditioning: important role of eNOS/NO/nitrite. *Brain Edema XVI*: Springer; 2016:45-48.

97. Kitagawa K, Matsumoto M, Tagaya M, et al. 'Ischemic tolerance'phenomenon found in the brain. *Brain research.* 1990;528(1):21-24.

98. Hougaard KD, Hjort N, Zeidler D, et al. Remote Ischemic Perconditioning as an Adjunct Therapy to Thrombolysis in Patients With Acute Ischemic Stroke A Randomized Trial. *Stroke.* 2014;45(1):159-167.

99. Bink DI, Ritz K, Aronica E, van der Weerd L, Daemen MJ. Mouse models to study the effect of cardiovascular risk factors on brain structure and cognition. *Journal of Cerebral Blood Flow & Metabolism.* 2013;33(11):1666-1684.

100. Cherry-Allen KM, Gidday JM, Lee J-M, Hershey T, Lang CE. Remote limb ischemic conditioning enhances motor learning in healthy humans. *Journal of neurophysiology.* 2015;113(10):3708-3719.

101. Koch S. Preconditioning the human brain: practical considerations for proving cerebral protection. *Translational stroke research.* 2010;1(3):161-169.

102. Koch S, Della-Morte D, Dave KR, Sacco RL, Perez-Pinzon MA. Biomarkers for ischemic preconditioning: finding the responders. *Journal of Cerebral Blood Flow & Metabolism.* 2014;34(6):933-941.

103. Shimizu M, Tropak M, Diaz RJ, et al. Transient limb ischaemia remotely preconditions through a humoral mechanism acting directly on the myocardium: evidence suggesting cross-species protection. *Clinical Science.* 2009;117(5):191-200.

104. Redington KL, Disenhouse T, Strantzas SC, et al. Remote cardioprotection by direct peripheral nerve stimulation and topical capsaicin is mediated by circulating humoral factors. *Basic research in cardiology.* 2012;107(2):1-10.

105. Jensen RV, Støttrup NB, Kristiansen SB, Bøtker HE. Release of a humoral circulating cardioprotective factor by remote ischemic preconditioning is dependent on preserved neural pathways in diabetic patients. *Basic research in cardiology.* 2012;107(5):1-9.

106. Brand D, Ratan RR. Epigenetics and the environment: In search of the "toleroasome" vital to execution of ischemic preconditioning. *Translational stroke research.* 2013;4(1):56-62.

107. Stowell C, Wang L, Arbogast B, et al. Retinal proteomic changes under different ischemic conditions–implication of an epigenetic regulatory mechanism. *International journal of physiology, pathophysiology and pharmacology.* 2010;2(2):148.

108. Thompson JW, Narayanan SV, Koronowski KB, Morris-Blanco K, Dave KR, Perez-Pinzon MA. Signaling pathways leading to ischemic mitochondrial neuroprotection. *Journal of bioenergetics and biomembranes.* 2015;47(1-2):101-110.

109. Konstantinov IE, Arab S, Kharbanda RK, et al. The remote ischemic preconditioning stimulus modifies inflammatory gene expression in humans. *Physiological genomics.* 2004;19(1):143-150.

110. Zhao Y, Li J, Lin A, Xiao M, Xiao B, Wan C. Improving angiogenesis and muscle performance in the ischemic limb model by physiological ischemic training in rabbits. *American Journal of Physical Medicine & Rehabilitation.* 2011;90(12):1020-1029.

111. Shen M, Gao J, Li J, Su J. Effect of ischaemic exercise training of a normal limb on angiogenesis of a pathological ischaemic limb in rabbits. *Clinical Science.* 2009;117(5):201-208.

112. Lin S, Lu X, Chen S, et al. Human coronary collateral recruitment is facilitated by isometric exercise during acute coronary occlusion. *Journal of rehabilitation medicine.* 2012;44(8):691-695.

113. Liu Y, Li J, Lu P, Wang J, Jin T. The spatial pattern of VEGF expression after transient myocardial ischemia in rabbits. *Chin. J. Rehabil. Med.* 2004;19:422-425.

114. Gao J, Shen M, Guo X, Li X, Li J. Proteomic mechanism of myocardial angiogenesis augmented by remote ischemic training of skeletal muscle in rabbit. *Cardiovascular therapeutics.* 2011;29(3):199-210.

115. Wan C, Li J, Yi L. Enhancement of homing capability of endothelial progenitor cells to ischaemic myocardium through physiological ischaemia training. *Journal of rehabilitation medicine.* 2011;43(6):550-555.

116. Meng R, Ding Y, Asmaro K, et al. Ischemic conditioning is safe and effective for octo-and nonagenarians in stroke prevention and treatment. *Neurotherapeutics.* 2015;12(3):667-677.

117. Olher RdRV, Bocalini DS, Bacurau RF, et al. Isometric handgrip does not elicit cardiovascular overload or post-exercise hypotension in hypertensive older women. *Clinical interventions in aging.* 2013;8:649.

118. McGowan CL, Levy AS, Millar PJ, et al. Acute vascular responses to isometric handgrip exercise and effects of training in persons medicated for hypertension. *American Journal of Physiology-Heart and Circulatory Physiology.* 2006;291(4):H1797-H1802.

119. Carlson DJ, Dieberg G, Hess NC, Millar PJ, Smart NA. Isometric Exercise Training for Blood Pressure Management: A Systematic Review and Meta-analysis. *Mayo Clinic Proceedings.* MAR 2014 2014;89(3):327-334.

120. Wong GW, Wright JM. Blood pressure lowering efficacy of nonselective beta-blockers for primary hypertension. *The Cochrane Library.* 2014.

121. Barnes WS. The relationship between maximum isometric strength and intramuscular circulatory occlusion. *Ergonomics.* Apr 1980;23(4):351-357.

122. Stiller-Moldovan C, Kenno K, McGowan CL. Effects of isometric handgrip training on blood pressure (resting and 24 h ambulatory) and heart rate variability in medicated hypertensive patients. *Blood Pressure Monitoring.* 2012;17(2):55-61.

123. Wong GW, Laugerotte A, Wright JM. Blood pressure lowering efficacy of non-selective beta blockers for primary hypertension. *The Cochrane Library.* 2008.

124. Cabot PJ, Carter L, Gaiddon C, et al. Immune cell-derived beta-endorphin. Production, release, and control of inflammatory pain in rats. *Journal of Clinical Investigation.* 1997;100(1):142.

125. Davidge ST. Prostaglandin H synthase and vascular function. *Circulation research.* 2001;89(8):650-660.

126. Wang T, Zhou Y, Chen X, Zhu A. Putative role of ischemic postconditioning in a rat model of limb ischemia and reperfusion: involvement of hypoxia-inducible factor-1? expression. *Brazilian Journal of Medical and Biological Research.* 2014;47(9):738-745.

127. Hess NC, Carlson D, Inder J, Jesulola E, McFarlane J, Smart N. Clinically Meaningful Blood Pressure Reductions with Low Intensity Isometric Handgrip Exercise. A Randomized Trial. *Physiological research* 2016;65.

128. Font MA, Arboix A, Krupinski J. Angiogenesis, neurogenesis and neuroplasticity in ischemic stroke. *Current cardiology reviews.* 2010;6(3):238.

129. Ahlskog JE, Geda YE, Graff-Radford NR, Petersen RC. Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. Paper presented at: Mayo Clinic Proceedings2011.

130. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. 1980.

Higher Degree Research Thesis by Publication
University of New England

STATEMENT OF AUTHORS' CONTRIBUTION

(To appear at the end of each thesis chapter submitted as an article/paper)

We, the Research Master/PhD candidate and the candidate's Principal Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated in the *Statement of Originality*.

	Author's Name (please print clearly)	**contribution**
Candidate	Nicole Hess	Literature review, format, content and writing
Other Authors	Neil Smart	Editorial feedback, format, writing suggestions as to content.

Name of Student/Candidate: Nicole Hess

Name/title of Principal Supervisor: Neil Smart

[redacted]

18.09.2016
Date

[redacted]

Principal Supervisor

19.09.2016
Date

Higher Degree Research Thesis by Publication
University of New England

STATEMENT OF ORIGINALITY

(To appear at the end of each thesis chapter submitted as an article/paper)

We, the Research Master/PhD candidate and the candidate's Principal Supervisor, certify that the following text, figures and diagrams are the candidate's original work.

Type of work	Page numbers
All text, tables and diagrams	Chapter 5 pp 75–103

Name of Student/Candidate: Nicole Hess

Name/title of Principal Supervisor: Neil Smart

[redacted]

18.09.2016
Date

[redacted]

Principal Supervisor

19.09.2016
Date

Chapter 6 : Isometric Exercise Training to Manage Blood Pressure and Improve Cognitive Performance: Pilot Case-Studies

N. C. L. Hess, D. Dunstan and N. A. Smart

Manuscript in preparation for journal submission

Candidate Signature

Principal Supervisor Signature

Abstract

Background: There is considerable research linking untreated hypertension with cognitive decline, dementia, and Alzheimer's disease (AD). Whilst the current literature suggests that various forms of exercise improves cognitive performance and reduces the effects of hypertension, the effect of isometric exercise training (IET) on cognitive performance outcomes has not been tested. **Objective:** To investigate the impact of IET on resting systolic and diastolic blood pressure (BP), mean arterial pressure (MAP), pulse pressure (PP), and cognitive performance in elderly individuals with cognitive impairment or AD. **Design:** A *single case, multiple baseline, across-subjects experimental design* was employed in a 6 week isometric hand grip (IHG) training pilot case-study. **Participants and methods:** Four older adults (M_{age} = 77.8 years; *SD* = 7.9) with cognitive impairment or AD ($M_{RBANS\ total\ score}$ = 60.6; *SD* = 9.8) participated in 6 weeks of unilateral IHG training performed in four, 2 min bouts three times per week at 20% of their maximal voluntary effort. Systolic and diastolic BP was measured pre-training, during training, and post-training. Cognitive performance was assessed using the Repeatable Battery for the Assessment of Neurological Status (RBANS) administered twice pre-training, once post training, and once at follow up. **Results:** No participant evidenced improvement in systolic or diastolic BP, MAP, or PP. A clinical improvement in cognitive performance was observed in one participant. **Conclusion:** Our data suggests that IET does not reduce resting BP in elderly medicated hypertensives after 3 weeks, 5 weeks or 6 weeks of IET at 20% maximal voluntary effort. Improvements in cognitive performance measures were not attributed to the anti-hypertensive effects of isometric exercise. Cognitive improvements may have been attributed to increased social engagement of the participants during the study or to neurohormonal pathways not necessarily associated with BP reduction.

6.1 Introduction

There is considerable research linking untreated hypertension with cognitive decline, dementia, and Alzheimer's disease (AD) [1-4]. From a physiological perspective, hypertension promotes vascular inflammation, vascular damage, and activated astrocytes and microglia [5]. These events stimulate dysfunctional arterial dilation, the generation of pro-inflammatory stimuli and enhanced levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS) [5]. As a consequence, cerebral blood flow is significantly reduced and mitochondrial damage is pervasive. Ultimately, these physiological cascades manifest in neuronal damage, neuronal energy crisis, cell death, neuro-degeneration, inflammation and finally, AD [5]. The harmful structural and functional alterations to cerebral circulation that are associated with hypertension are potentially reversible [6], subsequently, improving cerebral blood flow is thought to stimulate improvements in cognitive performance [7,8]. Antihypertensive treatment utilising pharmacotherapy has been shown to increase the velocity of cerebral blood flow and improve the distensibility of the carotid artery, supporting a correlation between blood pressure (BP) reduction and increased cerebral blood flow [6]. Moreover, antihypertensive medication has also been shown to offer protection against dementia in elderly individuals with hypertension [9]. It seems likely that improving neurovascular circulation might be a catalyst to enhance cognitive performance in individuals complaining of memory issues or diagnosed with mild cognitive impairment (MCI) or AD. Addressing modifiable risk factors, such as hypertension, at the MCI stage of AD may ameliorate or attenuate their deleterious effects on cerebral vasculature and possibly slow down or impede the progression to AD.

6.2 Isometric exercise training as a modifier of hypertension and Alzheimer's disease

Whilst the current literature suggests that participation in various forms of exercise improves cognitive performance [10-18] and manages hypertension [19,20], to our knowledge there has been

no investigation into the effects of Isometric exercise training (IET) on cognitive performance outcomes. IET has been successfully demonstrated to manage BP in both hypertensive and normotensive individuals [21-23] and to improve endothelial distensiblity [24,25]. An isometric contraction involves a single sustained muscle contraction against an immovable load or resistance with no, or minimal, change in length of the involved muscle group. Whilst the physiological mechanisms elicited by IET are not entirely clear there is a growing body of evidence that supports the role of IET to accommodate significant reductions in resting systolic BP (SBP) and resting diastolic BP (DBP) in both hypertensive and normotensive men and women [26-30]. It seems feasible that the anti-hypertensive effects elicited through IET might be a stimulus for improvements in neurovascular systemic circulation and as a result, enhanced cognitive performance.

6.3 Isometric exercise for elderly adults

Over the past thirteen years, the efficacy of isometric exercise training for the management of BP in hypertensive older adults (with an average age ≥ 55 years) has received some, yet limited, attention [24,25,27,31-34]. Four of these studies have reported decreases in resting BP [25,27,31,33], however, these findings have not been equivocal with Stiller-Moldovan et al. [32] reporting null results after 8 weeks of IHG training at 30% MVC. Ohler et al. [34] reported that IET in the elderly was safe and did not elicit cardiovascular overload or post-exercise hypotension, and the findings of McGowan et al. [25] suggest that isometric exercise can improve local flow-mediated dilatation (FMD). The physiological basis that might underpin the potential benefits of IET in individuals with MCI and AD may be that IET provides the stimulus to reduce resting BP, and changes in blood flow and volume are linked with transient changes in cognition. It could be that the repeated increases in cerebral blood flow (CBF) and the associated nutrient and oxygen delivery that result from the sustained

isometric exercise trigger (primary or secondary) the subsequent cascade of structural, biochemical and functional adaptations that increase brain plasticity and function, and cognition. Supporting this proposition is evidence that exercise induces increases in neurotrophins (such as BDNF, IGF-1), angiogenesis, neuro-endocrine function, and causes vascular wall changes (such as endothelial Nitric Oxide) [35-38]. A plausible hypothesis is that IET leads to a reduction in BP that is associated with a cascade of vascular, neurotrophic and neuro-endocrine events that lead to an improvement of cognitive function. Adding weight to the feasibility of this hypothesis are the clinical findings that inducing ischemia in healthy limbs, either via tourniquet or isometric contraction, utilising techniques such as remote ischemic conditioning (RIC) and physiological ischemic training (PIT) stimulates endogenous signalling and protective pathways that support and repair distant organs such as the heart, kidneys, and brain [39,40].

6.4 Cognitive function in the elderly

Cognitive impairment without dementia, such as age-associated cognitive decline (AACD) and age-associated memory impairment (AAMI), is considered to fall within the normative realms of brain aging [41,42], whereas, MCI and dementia are not. The differentiation between AACD, AAMI, MCI or early stage dementia is intrinsically a clinical judgement made by a skilled clinician and is couched on the magnitude to which an individual's ability to function at work or in activities of daily living is impacted [43].

MCI is not classified as dementia rather, it is a condition that is characterised by a deterioration in cognitive abilities and memory that are beyond that which would be expected for a person's age and level of education, but without notable loss of global cognition or activities of daily living [42,44-46]. Between 10% and 15% of MCI cases will progress to a diagnosis of AD. Alzheimer's disease is a progressive neurodegenerative dementing disorder

responsible for severe cortical atrophy in selective regions of the brain such as the temporal, medial-temporal, limbic, frontal and prefrontal cortices [45,47,48]. The Cognitive and functional domains impacted (to differing extents) by both MCI and AD include learning, memory, attention, motivation, executive function, the sequencing of complex tasks, and judgment and decision making [45,49]. Psychometric tools such as the *Mini Mental State Exam* (MMSE) and the *Repeatable Battery for the Assessment of Neurological Status* (RBANS) are frequently employed in clinical practice and in research to screen for dysfunction in cognitive performance in adults, and to facilitate the detection and characterisation of dementia in older adults [50]. Both the MMSE and the RBANS contribute to the assessment and diagnosis of MCI and probable AD or dementia [50,51]. Neither of these assessment protocols functions to identify the causative factors underlying cognitive impairment symptoms. Consequently, non-organic disorders such as depression, that also affect cognitive function [52], are likely to remain undetected and unidentified as the possible root of the cognitive-impairment-like symptoms. Screening tools such as the *Geriatric Depression Scale* (GDS) are useful in identifying depressive symptoms in the elderly [53].

6.5 Psychometric screening and testing protocols

The MMSE is a screening tool that gauges the severity of cognitive impairment by measuring subsets of cognitive functions such as registration, attention, calculation, recall and language [54,55]. The MMSE is scored out of 30; scores are interpreted as follows, $\geq$ 24 suggests no cognitive impairment, 19 to 23 suggests mild cognitive impairment, 10 to 18 suggests moderate cognitive impairment and $\leq$ 9 is indicative of severe cognitive impairment [56]. The MMSE is sensitive to cognitive impairment in diseased or very old populations, however, it does not specifically characterise cognitive impairment or dementia [57] and attaining a maximum score of 30 cannot rule out dementia as the raw scores do not take into

consideration a person's age or level of education [58]; whereas, the RBANS , a brief, individually administered test, was developed specifically to aid in the diagnosis and characterisation of dementia and factors into the scoring process a person's age and level of education [50]. Importantly, the RBANS test battery is suitably sensitive to screen for MCI up to moderately severe dementia. The RBANS measures cognitive function in the domains of immediate and delayed memory, attention, language, and visuospatial/constructional abilities. This test battery provides for up to four equivalent tests that can be administered at four different time points for repeat evaluations while controlling for content practice effects.

Non-organic/functional disorders in the elderly, such as depression, often produce cognitive impairment and are frequently confused with other conditions such as MCI or dementia [52]. Within the research setting, to avoid these confounding factors it is necessary to identify and exclude individuals who display depressive symptoms; otherwise their cognitive functioning might improve for reasons other than the intervention. The GDS is a 30 item questionnaire that is used to screen for and identify depressive symptoms in the elderly [53]; scores are interpreted as follows, 0 to 9 normal, 10 to 19 mild depressive, and 20 to 30 severe depressive [59].

6.6 The single case experimental design

Single case study designs provide reliable and robust research protocols for experimentation with individual subjects [60-62] and allow for the detection of changes that would otherwise go unnoticed in the traditional group design [61,63]. Specifically, the *single case, multiple baseline, across-subject experimental design* facilitates carefully controlled experimentation on a small scale, providing an ideal platform to run pilot projects of a psychophysiological nature [61,63,64]. Multiple baseline study designs allow researchers to document the controlling effects of a treatment by identifying and measuring a number of variables over time [60-62,65]. The effect of

the intervention is demonstrated by showing that the dependent variables of interest are stable over time and change only after the introduction of the intervention, which occurs sequentially, at different time points, for each participant [60-62]. The design addresses threats to internal validity through the staggered commencement of the intervention and each participant functioning as their own control [60]. Two baselines (participants) are a minimum to adequately demonstrate the effect of an intervention [61].

Generally, inferences are made through non-statistical evaluation or visual inspection of the data and take into account aspects such as changes in means, changes in levels/between phases (e.g. changes between baseline vs treatment vs follow up), a change in slope/trend and the latency of change across conditions [60-62]. When considering time series data of a psychophysiological nature, it may also be prudent to employ non-parametric statistical analytic approaches such as *Split-Middle and Percentage of Data Points Exceeding the Median (PEM)* [66] methods or *Improvement Rate Difference (IRD)* [67] analysis to enhance the ability to investigate experimental effectiveness, clinical significance and effect size [68,69]. Single case experimental design techniques provide a unique platform from which to present new, validated, and empirically supported clinical treatments to the broader literature. Moreover, these experimental techniques are a substantive alternative to large sample size, randomised controlled trials which are not always practical or the best research model for clinical psychophysiology [69].

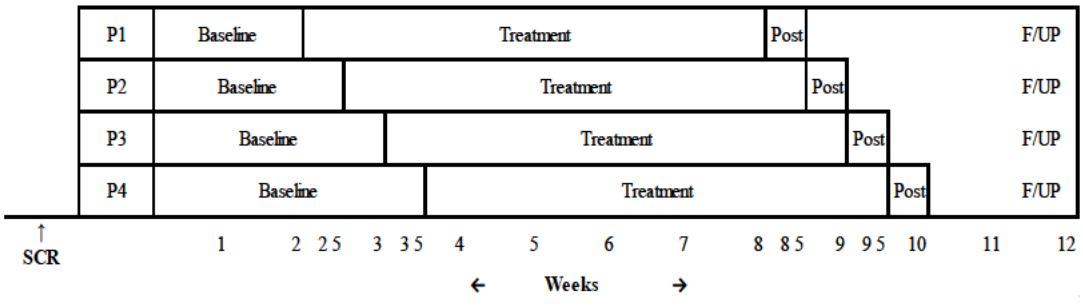
The purpose of this study was to investigate the impact of IET on resting systolic and diastolic BP, mean arterial pressure (MAP), pulse pressure (PP) and cognitive performance in elderly individuals experiencing cognitive impairment or diagnosed with AD. The MMSE and the GDS were used as screening tools to determine participant eligibility. Resting BP within the normal range was characterised as ($> \frac{90}{60}$ mmHg to $\leq \frac{120}{80}$ mmHg) pre-hypertensive

was characterised as ($> \frac{120}{80}$ mmHg to $\leq \frac{139}{90}$ mmHg) hypertensive was characterised as $\geq \frac{140}{90}$ mmHg. Using a *single case, multiple baseline, experimental design* we conducted a small pilot study comprising of four participants. This provided four baselines from which to gauge any effects of intervention, the minimum suggested number is two[61]. Pre-training we applied a temporal sequence of measurement, as described above, and presented in Figure 6.1. below, to establish stability across our two dependent variables which were cognitive performance operationalised as RBANS test scores and resting systolic and diastolic BP. We hypothesised that IET would elicit improvements in resting BP and cognitive performance in elderly individuals experiencing cognitive impairment or diagnosed with AD, and that these changes would be linked with anti-hypertensive effects.

6.7 Materials and Methods

6.7.1 Design

A *single case, multiple baseline, across-subjects experimental design* was utilised to investigate haemodynamic and cognitive responses in four participants experiencing cognitive impairment or diagnosed with AD. An overview of the study design is presented below in Figure 6.1. Baseline measurements were administered in a temporal sequence over a 2 to 3 week time-period which enabled the participants to function as their own control. Each intervention consisted of four sets of 2 minute isometric hand grip (IHG) contractions 3 days per week for 6 weeks. All Participants completed IHG training at 20% maximal voluntary contraction (MVC).



SCR = Initial screening prior to intervention
P1 - **P4** = Participants 1 to 4
Baseline = RBANS at time 1 (first day of baseline) and time 2 (last day of baseline) and daily BP measurements
Treatment = Four bouts of IET performed 3 times per week at 20% MVC and twice weekly BP measurements
Post = Post-test 1 day after final treatment (RBANS time 3 and BP measurements)
F/UP = Follow up at week 12 for all participants (RBANS time 4 and BP measurements)

Figure 6.1. An overview of the study design.

6.7.2 Recruitment of participants

Following approval by the University's Human Research Ethics Committee (Approval Number HE14-047) participants were recruited at an information session held at a residential facility for elderly adults. Ten potential volunteers were identified.

At a screening session prior to commencement of the isometric exercise program all potential volunteers (N = 10) were asked to complete a participant history questionnaire which also included a medical questionnaire, an adult exercise screening questionnaire, a written consent. The MMSE and GDS were also administered. At this time participant eligibility was assessed and (n = 4) were identified as meeting the following inclusion and exclusion criteria: aged between 55 and 85 years; returned a MMSE score >16; returned a GDS score of between 0 to 9; reported experiencing difficulties in cognition and/or memory or had received a diagnosis of either MCI or early stage AD; were non-smokers; had no significant psychiatric or substance abuse history; were able to complete cognitive tasks (no significant

verbal, visual, or motor impairment); and, were able to respond to visual and verbal commands.

6.7.3 Participants

Four participants, two males and two females, with ages ranging from 67 to 85 years, (M_{age} = 77.8 years; *SD* = 7.9), met the inclusion criteria and agreed to participate in the study. All participants were medicated for hypertension. All participants resided in a city in rural Australia. Two participants resided at a community residential facility for older adults and two participants resided with family. At the commencement of the study Participant 4 had received a diagnosis of Alzheimer's disease. During the study phase Participant 3 received a diagnosis of *posterior cortical atrophy* (a form of dementia). For personal reasons, two participants completed the study early: one after a treatment phase of 3 weeks and the other after a treatment phase of 5 weeks.

6.7.4 Measures

6.7.4.1 Neuropsychological assessment

The RBANS were administered by provisional psychologists enrolled in the Clinical Psychology program at the University of New England, Armidale. The RBANS were administered on four separate occasions throughout the study at the time points outlined in the *study design* above. The RBANS consists of 12 subtests which yield 5 Index scores (see below) and a Total scale score with a mean of 100 and a standard deviation of 15 index points. All subtests were administered and scored as prescribed in the RBANS manual[50]. The battery indexes are:

(1) Immediate memory

Identifies an examinee's aptitude to recall information immediately after it is given. The subtests that contribute to this index are List Learning and Story Memory.

(2) Visuospatial/constructional

Identifies an examinee's aptitude to perceive spatial relations and to construct a spatially accurate copy of drawing. The subtests that contribute to this index are Copy and Line Orientation.

(3) Language

Identifies an examinee's aptitude to respond verbally to either naming or recalling learned material. The subtests that contribute to this index are Picture Naming and Semantic Fluency.

(4) Attention

Identifies an examinee's aptitude to remember and manipulate both visually and orally presented information in short-term memory storage. The subtests that contribute to this index are Digit Span and Coding.

(5) Delayed memory

Identifies an examinee's anterograde memory capacity. The subtests that contribute to this index are List Recall, List Recognition, Story Memory, and Figure Recall.

A Total Scale score is calculated by adding together the five index scores.

6.7.4.2 Arterial BP

Arterial SBP and DBP was monitored using the Omron Automatic Blood Pressure Monitor with Fit Cuff (Omron Healthcare Co., Ltd, Kyoto, Japan) Model-IA1B. A wrap around cuff equip with air bladder was placed around the bicep and over the brachial artery of the dominant arm. Care was taken when selecting and fitting an appropriate size cuff for each

participant. The Omron Automatic Blood Pressure Monitor measured systolic and diastolic BP. Three BP measurements were taken each time that BP was assessed; readings were separated by a two minute rest period. The average of these three readings was recorded and utilised for the purposes of data analysis.

To minimise the influence of external variables on BP measurements, participants were asked to refrain from vigorous exercise and alcohol for 24 hours prior to each scheduled BP measurement; to abstain from caffeine for 12 hours prior; and to fast for 4 hours prior. Before resting BP measures were taken participants were asked to sit quietly for at least 10 minutes. Blood pressure measurements were taken at the same time each day. Prior to the commencement of BP measurements and IET participants were familiarised with all equipment and IET and BP measurement procedures.

6.7.5 Procedure

6.7.5.1 IET training protocol

Participants completed four sets of 2 minute isometric hand grip (IHG) contractions 3 days per week for 6 weeks with the aid of a programmed dynamometer (DHD-3 Digital Hand Dynamometer, Saehan Corp, South Korea). Isometric contractions were performed using the dominant hand at 20% MVC separated by a 2 minute rest period. A direct-reading light box was attached directly to the dynamometer to provide visual feedback to assist participants in maintaining the desired contraction force. The light box was calibrated to 20% MVC for every participant every session, furthermore, the dynomometer display was monitored by an investigator each time to ensure that 20% MVC was mantained for the duration of the 2 minute contraction period.

To avoid Valsalva manoeuvres participants were instructed to breathe at a normal rhythm and depth. Participants were seated in an erect position so that the shoulder was adducted and neutrally rotated, the elbow was flexed at a 90° angle and the forearm and wrist were in a neutral position. The dynamometer was arranged in the participants' hand to ensure that it fitted comfortably, where necessary, the handle of the dynamometer was adjusted to the desired fit. Participants were instructed to apply grip force gently and smoothly and were advised by the researcher to hold their contraction once they had reached the desired IHG intensity. Participants trained every other weekday (Monday, Wednesday and Friday) with rest days in between. MVC was determined at the beginning of each training session (via imbedded electronic linear load cells contained within each handgrip); participants were asked to perform three MVCs with their dominant hand. The three measurements were then averaged to arrive at the MVC. Twice each week, and prior to commencement of IHG training, resting systolic and diastolic BP measurements were recorded. All sessions were supervised in a common room area of the aged care facility in rural Australia.

6.7.5.2 Data handling and analysis

The data for each participant was assessed individually for changes in RBANS scores, systolic and diastolic BP, PP and MAP. Blood pressure data and RBANS data was recorded on Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) spread sheets and converted into graphical representation for observational analysis. RBANS subtest Indexes and Total scale scores were cross referenced and interpreted utilising standardised tables for clinical interpretation [50], these are displayed in Table 6.1. Non-parametric statistical analytics, IRD analysis, was used to assess changes in both SBP and DBP. IRD scores are calculated as the improvement rate observed in the experimental phase less the improvement rate observed in the baseline phase. The formula for calculating IRD is:

$IRD = IR_T - IR_B$

Where:

$$IR_T = \frac{N\ improved\ data\ treatment\ phase}{Total\ data\ points\ treatment\ phase}$$

$$IR_B = \frac{N\ improved\ data\ points\ baseline\ phase}{Total\ data\ points\ baseline\ phase}$$

The maximum IRD score is 100% (1.00) indicating that all of the scores in the treatment phase exceed all of the scores in the base-line phase in an improved direction. An IRD of 50% (.50) indicates that half of the scores are overlapping and represents a chance level of change and signifies that no improvement was evident. A negative score indicates deterioration below baseline.

Table 6.1. Qualitative and clinical descriptions of RBANS index scores

Index score	Percentile bands	Classification	Clinical descriptor
130 and above	≥ 98th	Very superior	
120-129	91st - 97th	Superior	
110-119	75th - 90th	High Average	(Above average)
90-109	25th - 74th	Average	
80-89	10th - 24th	Low Average	(Mildly Impaired)
70-79	3rd - 9th	Borderline	(Moderately Impaired)
69 and below	≤ 2nd	Extremely low	(Severely Impaired)

6.8 Results

6.8.1 Participant 1

Baseline measurements were taken across a 10 day period. Participant 1 completed 3 weeks of IET. The adherence to IET over this time frame was 100%. Baseline data is shown in Table 6.2.

Table 6.2. Participant 1 baseline characteristics

Anthropometric		
Age		77
Gender		Female
Height (M)		1.53
Weight (Kg)		71.5
BMI		30.5
Psychological		
GDS at screening (score and descriptor)	5	Normal
MMSE at screening (score and descriptor)	23	Mildly impaired
RBANS time 1 (total scale score & descriptor)	72	Moderately impaired
RBANS time 2 (total scale score & descriptor)	72	Moderately impaired
Hemodynamic		
RSBP (mmHg)		169 ± 12
RDBP (mmHg)		73 ± 5
MAP (mmHg)		105 ± 7.13
PP (mmHg)		96 ± 7.83
Medicine		
Angiotensin **II** antagonist receptor		

Note: Values expressed as the mean ± standard deviation unless otherwise specified. Abbreviations: BMI, body mass index; GDS, geriatric depression scale; MMSE, mini mental state exam; RBANS, repeatable battery for the assessment of neurological status; RSBP, resting systolic blood pressure; RDBP, resting diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure.

6.8.1.1 Systolic and diastolic blood pressure

Observational analysis of Figure 6.2. suggests that SBP did not improve during the intervention phase compared to the baseline phase. IRD analysis supports these observations

IRD = -73%. Further graphical analysis does not depict improvements in SBP at either the completion of IET or at follow up compared to baseline measurements.

Observational analysis of Figure 6.2. depicts DBP remaining constant within the range of > 60mmHg < 90mmHg throughout the study, at the completion of the study and at follow up. Subsequently, no improvement was observed during the intervention phase. IRD analysis supports these observations *IRD* = - 47%.

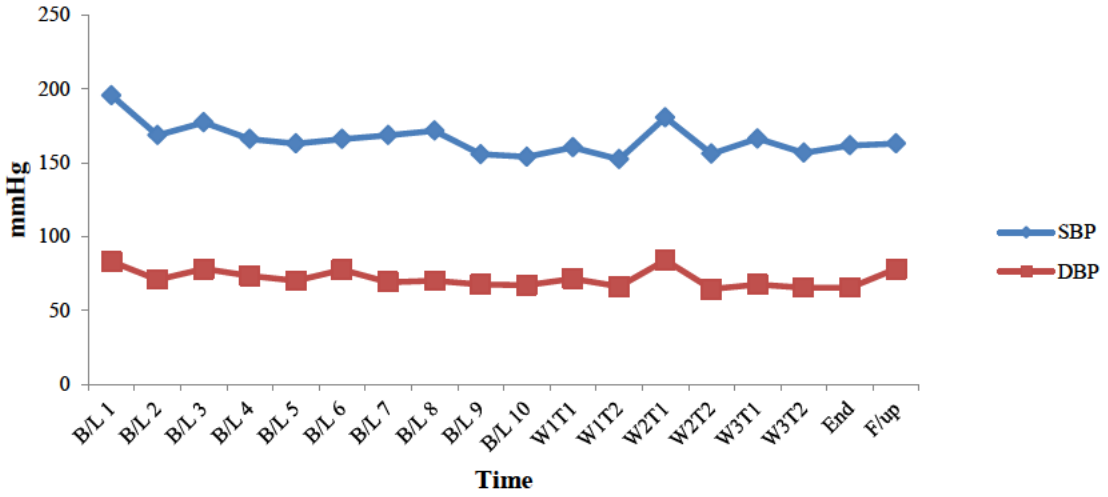


Figure 6.2. Participant 1 systolic and diastolic BP over time.

Mean arterial pressure and pulse pressure

There was no improvement in either MAP or PP as outlined in Figure 6.3.

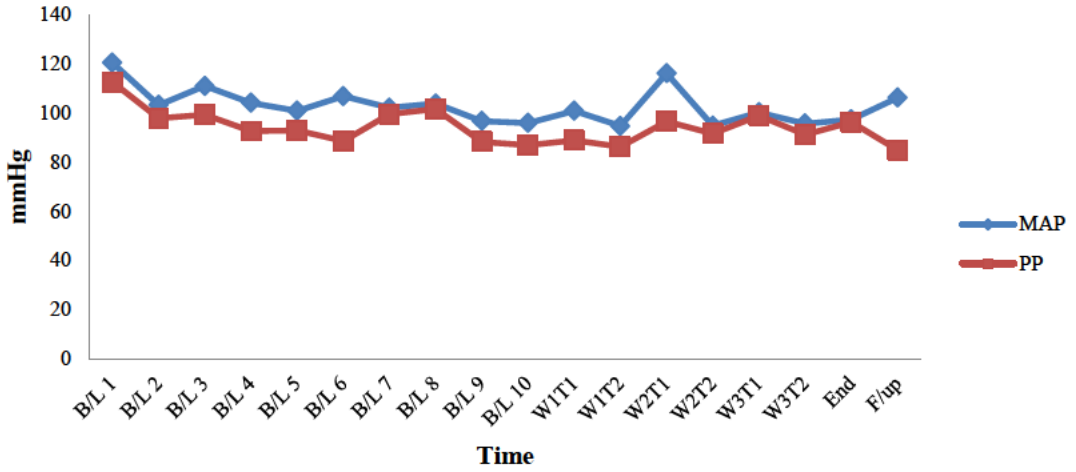


Figure 6.3. Participant 1 MAP and PP over time.

6.8.1.2 Neuropsychological analysis

The RBANS Total Scale score is a composite of all of the indexes within the test battery and is the most reliable score and strongest indicator of cognitive functioning[50]. Stability in cognitive functioning at baseline was determined by comparing the RBANS (Time 1) with the RBANS (Time 2) Total Scale scores. The impact of the intervention was determined by examining the difference between the RBANS (Time 2) and RBANS (Time 3) Total Scale scores. Finally, the stability of gains was determined by comparing the RBANS (Time 3) with the RBANS (Time 4) Total Scale scores. Changes across all Index and Total Scales scores are presented in Table 6.3.

Table 6.3. Participant 1 RBANS index scores and clinical descriptors

	Immediate memory	Index score	Visuospatial/ constructional	Index score	Language	Index score	Attention	Index score	Delayed memory	Index score	Total scale	Index score
Time 1	Average	100	Severe	53	Mild	85	Severe	53	Average	98	Moderate	72
Time 2	Mild	83	Severe	62	Mild	83	Severe	68	Average	95	Moderate	72
Time 3	Average	94	Severe	69	Average	105	Mild	82	Average	95	Mild	85
Time 4	Mild	87	Severe	64	Average	96	Mild	85	Average	95	Mild	81

As shown in Table 6.3., the overall cognitive functioning of Participant 1 was stable until the intervention commenced. Thereafter, an improvement in functioning occurred and was maintained at follow-up.

6.8.1.3 General Observations

Participant 1 regularly reported to the experimenter that they enjoyed participating in the study and they looked forward to each session. In terms of daily routine and lifestyle this participant did not engage in regular social activities and had a social network.

6.8.2 Participant 2

Baseline measurements were taken across a 12 day period. Participant 2 completed 6 weeks of IET. The adherence to IET over this time frame was 100%. Baseline data is shown in Table 6.4.

Table 6.4. Participant 2 baseline characteristics

Anthropometric		
Age		85
Gender		Male
Height (M)		1.68
Weight (Kg)		60.8
BMI (Kg/cm²)		21.5
Psychological		
GDS at screening (score and descriptor)	1	Normal
MMSE at screening (score and descriptor)	28	No impairment
RBANS time 1 (total scale score & descriptor)	71	Moderately impaired
RBANS time 2 (total scale score & descriptor)	73	Moderately impaired
Hemodynamic		
RSBP (mmHg)		124 ± 11
RDBP (mmHg)		76 ± 9
MAP (mmHg)		92 ± 9.4
PP (mmHg)		48 ± 6.6
Medicine		
ACE inhibitor		

Note: Values expressed as the mean ± standard deviation unless otherwise specified. Abbreviations: BMI, body mass index; GDS, geriatric depression scale; MMSE, mini mental state exam; RBANS, repeatable battery for the assessment of neurological status; RSBP, resting systolic blood pressure; RDBP, resting diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; ACE, angiotensin-converting-enzyme.

6.8.2.1 Systolic and diastolic blood pressure

There was no improvement in SBP during the intervention phase compared to the baseline phase, *IRD* = - 83%. Observational analysis of Figure 6.4. depicts that although SBP predominately remained within the range of > 90mmHg < 139mmHg for the duration of the

study, at completion and at follow up; SBP tended to be higher during the intervention phase compared to the baseline phase.

There was no improvement in DBP during the intervention phase compared to the baseline phase, *IRD* = - 75%. Observational analysis of Figure 6.4. suggests that although DBP predominately remained constant within the range of > 60mmHg < 90mmHg throughout the study, at the completion of the study and at follow up; DBP tended to be higher during the intervention phase compared to the baseline phase.

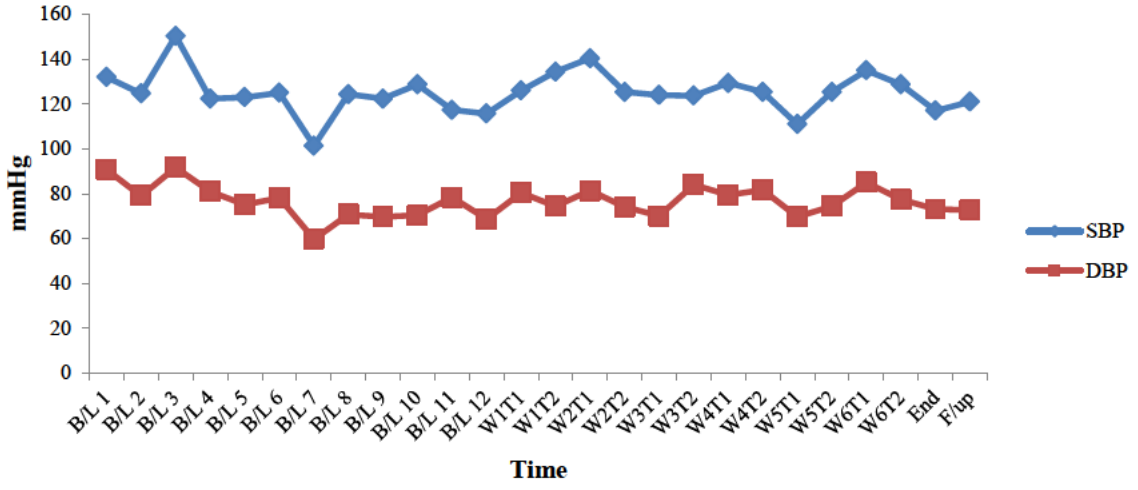


Figure 6.4. Participant 2 systolic and diastolic BP over time.

Mean arterial pressure and pulse pressure

There was no improvement in either MAP or PP as outlined in Figure 6.5.

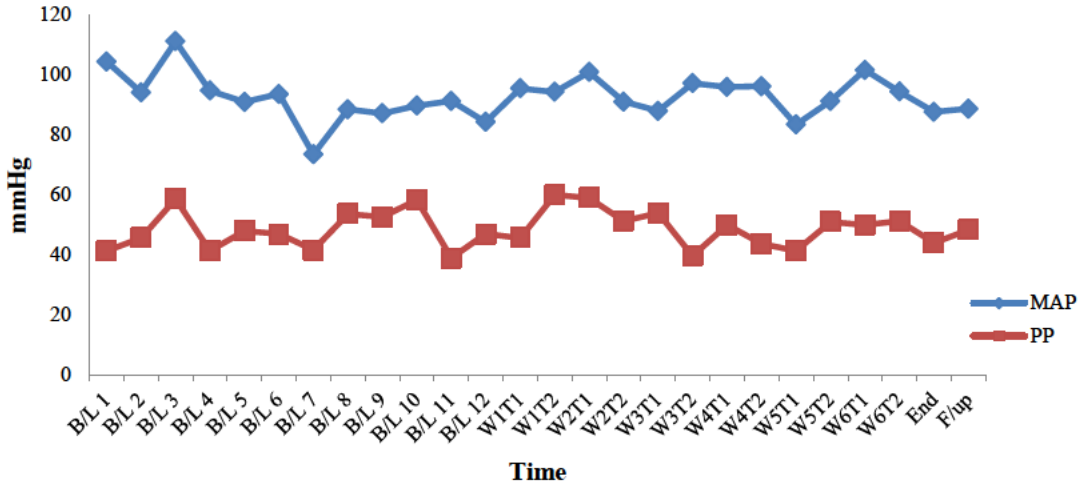


Figure 6.5. Participant 2 MAP and PP over time.

6.8.2.2 Neuropsychological analysis

The RBANS scores for Participant 2 are presented in Table 6.5. below.

Table 6.5. Participant 2 RBANS index scores and clinical descriptors

	Immediate memory	Index score	Visuospatial/ constructional	Index score	Language	Index score	Attention	Index score	Delayed memory	Index score	Total scale	Index score
Time 1	Severe	53	Mild	87	Mild	89	Mild	88	Severe	68	Moderate	71
Time 2	Severe	65	Average	96	Average	92	Moderate	72	Severe	64	Moderate	73
Time 3	Average	94	Moderate	78	Severe	68	Mild	88	Severe	64	Moderate	73
Time 4	Severe	49	Mild	87	Average	107	Moderate	79	Moderate	71	Moderate	73

As shown in Table 6.5., despite some variability in the Index scores, the overall cognitive functioning of Participant 2 remained unchanged throughout the study.

During the RBANS testing at Time 3, Participant 2 became distressed and teary at his inability to perform some tasks. He told the psychologist that the harder he tried to recall information the more elusive it became.

6.8.3 Participant 3

Baseline measurements were taken across a 14 day period. Participant 3 completed 6 weeks of IET. The adherence to IET over this time frame was 100%. Participant 3 received a diagnosis of *posterior cortical atrophy* two weeks after the study commenced. Baseline data is shown in Table 6.6.

Table 6.6. Participant 3 baseline characteristics

Anthropometric		
Age		67
Gender		Male
Height (M)		1.74
Weight (Kg)		84.9
BMI (Kg/cm²)		28
Psychological		
GDS at screening (score and descriptor)	3	Normal
MMSE at screening (score and descriptor)	17	Moderately impaired
RBANS time 1 (total scale score & descriptor)	55	Severely impaired
RBANS time 2 (total scale score & descriptor)	58	Severely impaired
Hemodynamic		
RSBP (mmHg)		135 ± 7
RDBP (mmHg)		83 ± 4
MAP (mmHg)		100 ± 4.6
PP (mmHg)		52 ± 5
Medicine		
ACE inhibitor		

Note: Values expressed as the mean ± standard deviation unless otherwise specified. Abbreviations: BMI, body mass index; GDS, geriatric depression scale; MMSE, mini mental state exam; RBANS, repeatable battery for the assessment of neurological status; RSBP, resting systolic blood pressure; RDBP, resting diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; ACE, angiotensin-converting-enzyme.

6.8.3.1 Systolic and diastolic blood pressure

There was no improvement in SBP from baseline to intervention phase, IRD = - 25%. Observational analysis of Figure 6.6. depicts that SBP tended to be higher during the intervention phase, at completion, and at follow up compared to the baseline phase.

Observational analysis of Figure 6.6. depicts that other than the final DBP measurement of the intervention phase and the DBP measurement at completion ,overall, DBP remained constant within the of > 60mmHg < 90mmHg throughout the study.

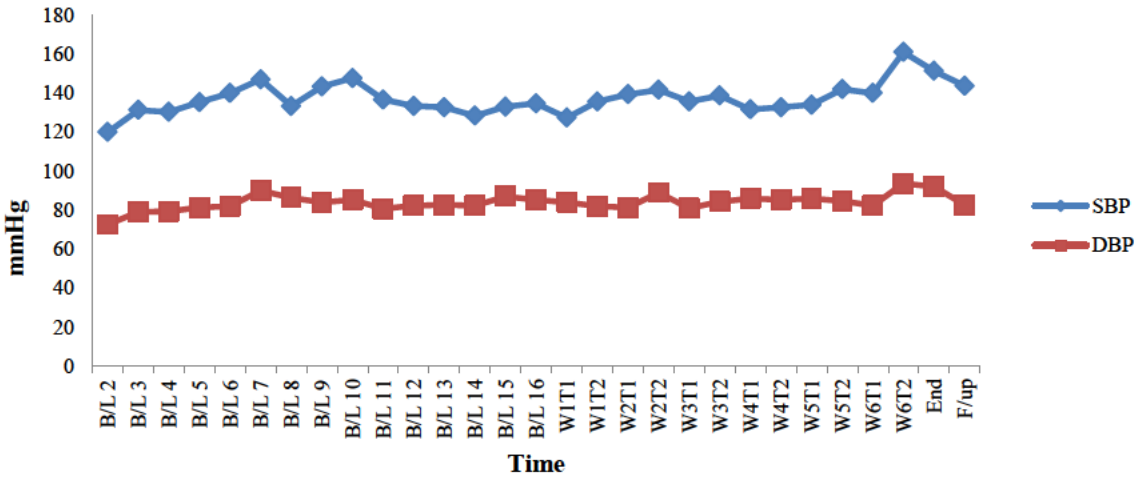


Figure 6.6. Participant 3 systolic and diastolic BP over time.

At time *B/L 7*, for personal reasons, participant 3 reported feeling highly distressed. At time *B/L 14*, on physician's advice, participant ceased taking BP medication; this continued for the duration of the study and through to follow up. At times *W2T1* and *W2T2* participant 3 had consumed alcohol within 12 hours prior to having BP measured.

6.8.3.2 Mean arterial pressure and pulse pressure

There was no improvement in either MAP or PP as outlined in Figure 6.7.

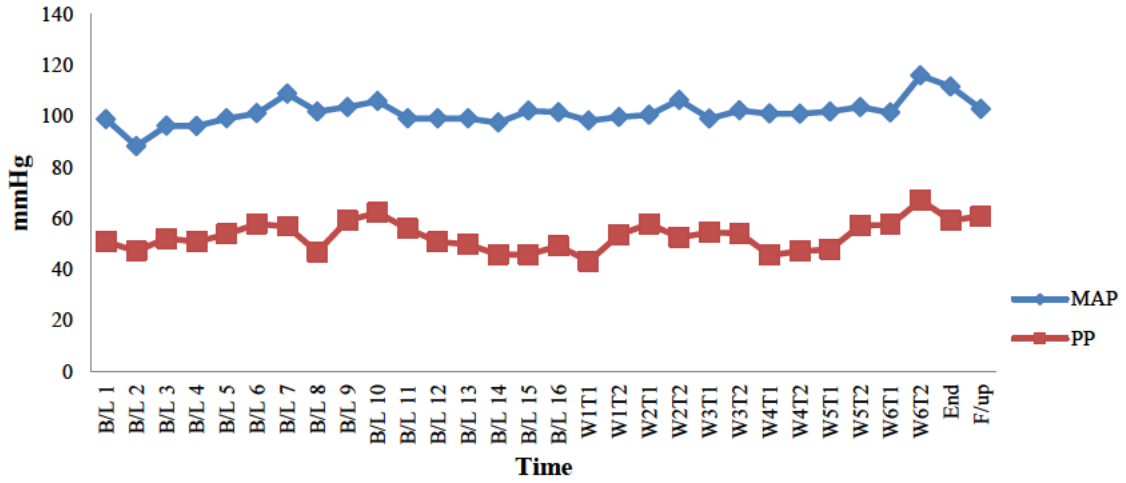


Figure 6.7. Participant 3 MAP and PP over time.

6.8.3.3 Neuropsychological analysis

The RBANS scores for Participant 3 are presented in Table 6.7. below.

Table 6.7. Participant 3 RBANS index scores and clinical descriptors

	Immediate memory	Index score	Visuospatial/ constructional	Index score	Language	Index score	Attention	Index score	Delayed memory	Index score	Total scale	Index score
Time 1	Severe	53	Severe	50	Mild	85	Moderate	79	Severe	56	Severe	55
Time 2	Severe	65	Severe	50	Average	96	Moderate	75	Severe	48	Severe	58
Time 3	Severe	57	Severe	50	Mild	83	Severe	64	Severe	48	Severe	52
Time 4	Moderate	73	Severe	50	Mild	87	Severe	49	Severe	60	Severe	54

As shown in Table 6.7., despite some variability in Index scores, the overall cognitive functioning of Participant 3 remained unchanged throughout the study.

During the RBANS testing at Time 1, Participant 3 was significantly distressed and teary about undertaking the RBANS assessment and needed to take a break from testing part way through the test before continuing to complete the assessment in full. At RBANS Time 2 Participant 3 reported that although anxious they felt more at ease than at Time 1. At RBANS

Time 3 Participant 3 reported experiencing increased perceptual and visual difficulties due to visual deterioration in the left eye.

6.8.3.4 General Observations

Initially Participant 3 had difficulty understanding the relationship between the lights on the light box visual aid and the intensity of the isometric contraction being performed. By week 3 the participant was having further difficulties maintaining focus on the light box due to deterioration in vision. With the combined assistance of the light box and verbal feedback from the experimenter the participant was always able to sustain an isometric contraction continuously for 2 minutes.

Participant 4

Baseline measurements were taken across a 16 day period. Participant 4 completed 5 weeks of IET. The adherence to IET over this time frame was 100%. Participant had received a diagnosis of early stage Alzheimer's disease prior to the commencement of the study. Baseline data is shown in Table 6.8.

Table 6.8. Participant 4 baseline characteristics

Anthropometric		
Age		82
Gender		Female
Height (M)		1.65
Weight (Kg)		48.1
BMI (Kg/cm²)		17.6
Psychological		
GDS at screening (score and descriptor)	9	Normal
MMSE at screening (score and descriptor)	20	Mildly impaired
RBANS time 1 (total scale score & descriptor)	52	Severely impaired
RBANS time 2 (total scale score & descriptor)	49	Severely impaired
Hemodynamic		
RSBP (mmHg)		153 ± 13
RDBP (mmHg)		87 ± 4
MAP (mmHg)		109 ± 5.8
PP (mmHg)		66 ± 11.7
Medicine		
β-blocker		
ACE inhibitor		

Note: Values expressed as the mean ± standard deviation unless otherwise specified. Abbreviations: BMI, body mass index; GDS, geriatric depression scale; MMSE, mini mental state exam; RBANS, repeatable battery for the assessment of neurological status; RSBP, resting systolic blood pressure; RDBP, resting diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; ACE, angiotensin-converting-enzyme.

6.8.3.5 Systolic and diastolic blood pressure

Observational analysis of Figure 6.8. suggests that SBP did not improve significantly during the intervention phase compared to the baseline phase. IRD analysis supports these

observations *IRD* = 12%. Further graphical analysis does not suggest improvements in SBP at either the completion of IET or at follow up compared to baseline measurements.

Observational analysis of Figure 6.8. suggests that DBP did not improve during the intervention phase compared to the baseline phase. IRD analysis supports these observations *IRD* = - 38%. Further graphical analysis does not suggest improvements in SBP at either the completion of IET or at follow up compared to baseline measurements.

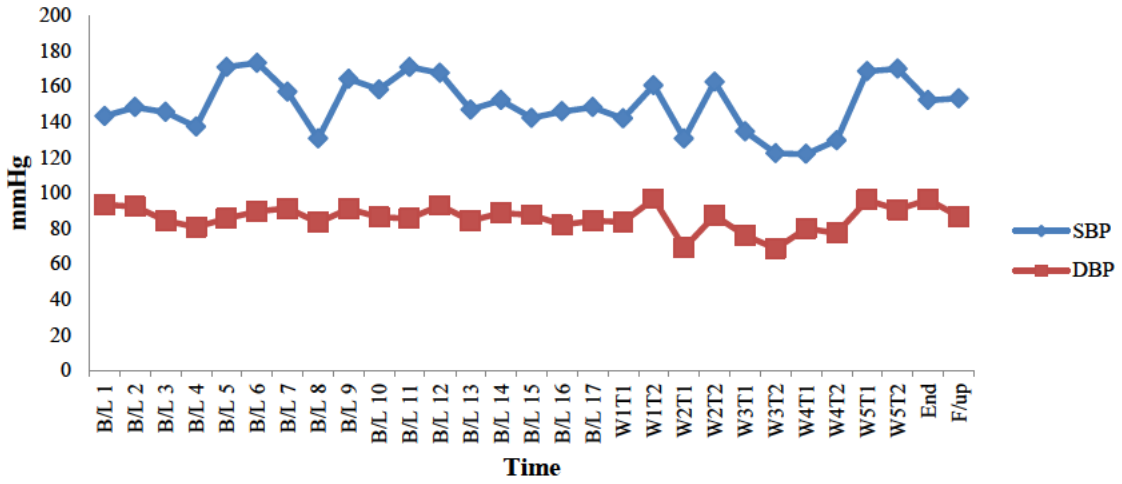


Figure 6.8. Participant 4 systolic and diastolic BP over time.

6.8.3.6 Mean arterial pressure and pulse pressure

There was no improvement in either MAP or PP as observed in Figure 6.9.

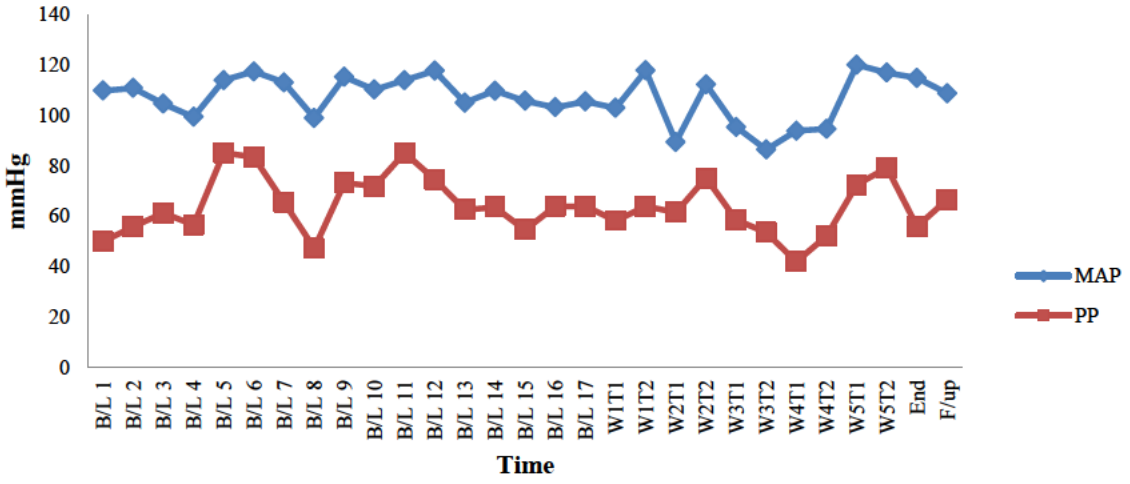


Figure 6.9. Participant 4 systolic MAP and PP over time.

6.8.3.7 Neuropsychological analysis

The RBANS scores for Participant 4 are presented in Table 6.9. below.

Table 6.9. Participant 4 RBANS index scores and clinical descriptors

	Immediate memory	Index score	Visuospatial/ constructional	Index score	Language	Index score	Attention	Index score	Delayed memory	Index score	Total scale	Index score
Time 1	Severe	40	Severe	69	Mild	80	Severe	56	Severe	44	Severe	50
Time 2	Severe	40	Severe	66	Severe	54	Severe	68	Severe	44	Severe	49
Time 3	Severe	44	Severe	69	Average	92	Severe	68	Severe	56	Severe	56
Time 4	Severe	44	Moderate	75	Severe	57	Severe	53	Severe	44	Severe	49

As shown in Table 6.9., despite some variability within Index scores, the overall cognitive functioning of Participant 4 remained unchanged throughout the study.

Throughout RBANS Time 2 testing Participant 4 regularly apologised to the psychologist as they were anxious that they were not performing so well.

6.8.3.8 General Observations

Initially Participant 4 had difficulty understanding and performing the isometric exercise task, specifically, they were confused by the relationship of the light box visual aid to the isometric handgrip task and were distracted by the lights. By day 1 of week 3 the participant had come to understand the association between the light box visual cue providing feedback, and maintaining the correct intensity contraction on the dynamometer. Subsequently, for the first 2 weeks it was difficult for Participant 4 to sustain an isometric contraction continuously for 2 minutes.

6.9 Discussion

The objectives of the current study were to investigate the impact of IET on resting systolic and diastolic BP, MAP, PP and cognitive performance in elderly individuals experiencing cognitive impairment or diagnosed with AD. We hypothesised that IET would elicit improvements in resting BP and in cognitive performance in elderly individuals experiencing cognitive impairment or diagnosed with AD, and that these changes would be linked with anti-hypertensive effects.

6.9.1 Isometric exercise and blood pressure

Contrary to our hypothesis and to the findings presented within the broader literature we observed no improvement in resting BP after IET. We found five other studies that investigated the effects of IET on resting BP in older adults aged ≥ 55 [25,27,31,33,34] and all but one of these studies [32] reported significant reductions in resting BP after IET. In all five of these studies the participants were medicated hypertensives engaging in isometric hand grip training three times per week for a minimum of 8 weeks at an intensity of 30% MVC. Thus the null findings of Stiller-Moldovant et al. [32] suggest that outside of the rigor of the isometric

training protocol there exists an interplay of unique individual characteristics influencing BP responses to IET. In the current 6 week study two participants completed early; one after 3 weeks of IET and the other after 5 weeks of IET. These training periods are considerably less than the 8 week IET period administered by the five studies noted above and may account for our null results. However, based on the findings of other IET research protocols, this factor alone may not be sufficient to explain away our neutral results with reports that isometric exercise can elicit BP reductions in as little as 3 to 4 weeks. Howden et al. [70] observed statistically significant reductions in SBP after 3 weeks of isometric leg exercise at ~20% MVC and after 4 weeks of isometric arm training at 30% MVC, Gill et al. [71] hypothesised that reductions in resting BP from IET would be intensity dependent, they compared the effects of low (~23% MVC) and moderate (~34% MVC) IET over a 3 week period and reported a reduction in SBP in the moderate intensity group only, and Peters et al. [72] reported significant reductions in both SBP and DBP after 6 weeks of IHG training at 50% MVC. Whilst these studies suggest that IET may have the propensity to manage BP in as little as 3 weeks they also highlight a relationship between IET intensity, study duration, and reductions in resting BP. They suggest that the magnitude and rate at which resting BP is reduced increases as exercise intensity increases and that where present these reductions will continue to increase over time.

Previous work has postulated that in response to ischemia induced by IHG activity a number of metabolites are produced; these include prostaglandins, beta-endorphins and HIF-alpha. [32,73,74]. It may be that the presence or absence of reactive hyperaemia is determined by the MVC intensity during isometric exercise. The work of Hess et al. [21], Wiles et al. [75] and Baross et al. [76] suggests that MVC intensities as little as 5-14% may induce sufficient, albeit partial, occlusion to blood flow to induce ischemia and the subsequent metabolite production that may be contributing to BP reductions. Nonetheless, IET response rates are highly

variable between individual participants whereby some respond to IET (in highly varying degrees) and others do not [32,77]. Whilst the reasons for this are not fully understood there are a number of variables that are likely to affect the magnitude of reduction in resting BP. For instance, the greatest isometric exercise reductions in resting BP have been observed in pre-hypertensive and hypertensive individuals [33,78] and magnitude of change in BP has been associated with initial resting BP values such that greater reductions are observed in individuals with higher pre-IET BP [79]. More specific to the current study, hypertensive medication status [24,25,32] and participant age [21] have also been identified as possible co-variates affecting the magnitude of reduction in resting BP in response to IET. It is likely that hypertensive medication and IET share overlapping mechanisms responsible for BP reductions and that this might account for lower IET responder rates in medicated hypertensives. Furthermore, age is related to arterial stiffness and hypertension [80] and is also likely to impact on the magnitude of the anti-hypertensive effects of IET. A further consideration that is unique to the current study was that the severity of cognitive impairment significantly impacted on participants' ability to understand and effectively perform the prescribed isometric exercise task. None-the-less, while this observation is a pertinent consideration in the contemplation of our results, it was only applicable to two out of the four participants (P3 and P4) and cannot account for the null results of the other two participants.

Whilst the normal BP range of ($> \frac{\mathbf{90}}{\mathbf{60}}$ mmHg to $\leq \frac{\mathbf{120}}{\mathbf{80}}$ mmHg) is ideal for both and older and younger adults, higher blood pressure in the elderly is common and is less likely to be indicative of cardiovascular complications than it would be in younger individuals; often, increased arterial stiffness in the elderly can be erroneously diagnosed as hypertension, this is referred to a pseudohypertension [80], for example, a 40 year old with BP of $\frac{\mathbf{150}}{\mathbf{80}}$ mmHg is more likely to suffer complications than a 70 year old with the same reading. In this regard, of

greater concern in the elderly is the management of PP [81,82]. PP represents the force that the heart generates each time it contracts and it provides an indication of the extent of stiffness and damage in the blood vessels [80]. Arterial stiffness both exacerbates and promotes vessel endothelial dysfunction inhibiting healthy vasoactivity [80]. PP is calculated as SBP minus DBP. Consequently, a PP reading above 40mmHg is considered above average and potentially problematic. In the current study, all four participant started with baseline PPs in excess of 40mmHg, ranging between 48mmHg and 98mmHg. Considering the concomitant relationship between age, PP status, arterial stiffness, and endothelial dysfunction it is a reasonable hypothesis that in the current study arterial stiffness (as suggested by the high PP readings) inhibited vascular endothelial responses to the reactive hyperaemia caused by repeated bouts of isometric handgrip training. On this premise, it is unsurprising that none of the participants recorded reductions in BP in response to IET.

Whilst the McGowan [24,25] studies found that IET elicited reductions in SBP and improvements in vessel endothelial functioning in an elderly cohort there are a number of significant variations between our studies that might account for our differing results; duration of the intervention, exercise intensity and age cohort potentially account for our null results when compared to the McGowan studies. Whilst our study and the McGowan studies all investigated IET responses in medicated hypertensive elderly individuals, participant age was not matched between studies with the current study investigating a considerably older population (M_{age} = 77.8 years; SD = 7.9) compared to McGowan (M_{age} = 66.1 years; SD = 6.3) [25] and (M_{age} = 67 years; SD = 6) [24]. One might expect that older individuals would suffer greater arterial rigidity and as a consequence take longer to respond to the antihypertensive effects that have been attributed to isometric exercise training. Subsequently, in terms of the current study, it could be the case that at an intensity of 20% MVC that 3 weeks, 5 weeks,

and 6 weeks of IHG training is not a sufficiently long enough training period to elicit improvements in resting PP and BP in hypertensive elderly individuals.

6.9.2 Cognitive function

The second aspect of our hypothesis postulated that cognitive improvement would be dependent on the BP lowering effects of IET; however, as our results indicate, resting BP was not affected. Subsequently, with our secondary outcome concomitant on the significant findings of our primary outcome any improvements in cognitive performance could not be attributed to the antihypertensive effects of the IET protocol.

Despite all four participants demonstrating some variability in certain RBANS Index scores, overall cognitive functioning remained stable for all but one of these participants. The neurological status of Participant 1 improved from a clinical rating of moderate cognitive impairment to mild cognitive impairment both at post-training and at follow up, whereas, the other three participant's did not demonstrate improvement in overall cognitive status post-training. Presumably, attributes of IET were not responsible for this outcome; the most likely therapeutic mechanism responsible for Participant 1's overall improvement in cognitive performance was the increased social contact that they were exposed to through participation in the study. Social contact is widely believed to exert a beneficial effect on cognition and is also considered to be a modifiable risk factor of cognitive impairment and dementia [83-85]. On the other hand, it may also be possible that the neurohormonal pathways activated by IET are responsible for stimulating enhancements in cognitive performance.

Although the RBANS Total Scale score represents a composite of all of the indexes within the test battery and is the most reliable score and strongest indicator of cognitive functioning [50], for a number of reasons it is not uncommon to observe seemingly erratic fluctuations in

the Index scores (that comprise the Total Scale score) over subsequent re-test times and yet observe no change in the Total Scale score. Index scores can be significantly impacted by seemingly minor changes within subtest performance, consequently, a gain or a loss of only a few points on re-test attempts may result in a rapid drop or increase of the associated index [50]. Outside of the event that clinical change in neurological performance is actually responsible for the variability in change scores there are a number of other reasons that might account for Index variability; firstly, inherent in all test scores are systematic variance (participant ability and procedure related variance) and error variance (attributable specific factors affecting the examiner, examinee, environment, the context of each individual testing session) which is very difficult to identify and to control for, and may potentially skew results; secondly, change or lack of change in Index scores may be explained by person-specific motivational factors accounting for poor test-taking effort on some testing occasions but not on others [86]. Furthermore, in the early stages of dementia variability in scores is more likely to be observed than in the more advanced stages [50] Across repeated testing this may give the impression of erratically fluctuating change scores, for this reason subtest indexes should be interpreted holistically and contextually taking into account patient history, any previous diagnoses, clinical interviews, and the Total Scale score and not be interpreted as standalone neuro-cognitive measures [50].

Applicable to the current study, standard variance, error variance, neurological status and person-specific motivational factors, possibly exacerbated by stress and anxiety, may all reasonably account for the observed variabilities in Index scores. Across the four testing times, as much as possible, we tried to maintain consistency in the administration procedures of the RBANS, however, it was not always possible to ensure that participants experienced the same test administrator (psychologist) on each occasion. This factor may have added to the distress and anxiety that some participants reported or were observed to experience on

certain testing occasions. Excessive cortisol response resulting from stress and anxiety can significantly impede efficient cognitive performance [87], particularly when one is attempting to encode and then subsequently retrieve information from memory [88]. Systematic error (procedure related variance) may also account for variations across certain Index scores. At the commencement of the study all four psychologists were inexperienced at administering and scoring the RBANS, thus it is likely that as the study progressed psychologists became increasingly more proficient at administering and scoring the RBANS.

6.10 Limitations

Although we employed a robust study design and reviewed each case based on its own unique variables, our pilot-case study has several limitations. Small sample size, the varying characterisations of cognitive impairment and dementias experienced amongst the participants, inadequate study duration and insufficient IET intensity were the perceived limitations.

6.11 Recommendations for future research

Pharmacological management of hypertension [9] and stenting of the carotid artery [7,89] have both been demonstrated to improve cognitive performance outcomes in the elderly and limb ischemia induced by tourniquet has been shown to improve CBF [90], and enhance neuroplasticity [91]. Similarly, the anti-hypertensive effects of IET reported in the broader literature and the concomitant improvements in FMD and endothelial function should also be expected to elicit improvements in cognitive performance. Considering that arterial stiffness, and consequently, endothelial dysfunction are associated with aging it is intuitive that hypertension in the elderly is potentially more resistant to improvement than it might be in younger cohorts. To provide a greater insight into the potential cognitive improvements and

health and lifestyle benefits of IET in medicated hypertensive elderly cohorts (between the ages of 75 years to 85 years) we suggest that future studies look to increase both the training intensity and protocol duration. In the current study it was evident that the severity and characterisation of dementia significantly affected participants' ability to understand and effectively participate in the isometric exercise task required of them. Subsequently, we would also recommend that future studies narrow their eligibility criteria to only include individuals with MCI.

6.12 Conclusion

Isometric exercise at 20% maximal voluntary effort does not reduce resting BP in elderly medicated hypertensives after 3 weeks, 5 weeks or 6 weeks of training. Improvements in cognitive performance measures were not attributed to the anti-hypertensive effects of isometric exercise and may be attributed to an increased social interaction or to neurohormonal pathways not necessarily associated with BP reduction. In a cohort of elderly individuals with above average to very high pulse pressure, endothelial dysfunction would likely need to be addressed before improvements in overall BP are affected.

Acknowledgements

Margret and Michael Hill, management of Sunny Cove Village, Armidale: for allowing access to Sunny Cove facilities and residents.

References

1. Power MC, Weuve J, Gagne JJ, McQueen MB, Viswanathan A, Blacker D. The association between blood pressure and incident Alzheimer disease: a systematic review and meta-analysis. *Epidemiology (Cambridge, Mass.).* 2011;22(5):646.

2. Kivipelto M, Helkala E-L, Laakso MP, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *Bmj.* 2001;322(7300):1447-1451.

3. Korf ES, White LR, Scheltens P, Launer LJ. Midlife Blood Pressure and the Risk of Hippocampal Atrophy The Honolulu Asia Aging Study. *Hypertension.* 2004;44(1):29-34.

4. Skoog I, Nilsson L, Persson G, et al. 15-year longitudinal study of blood pressure and dementia. *The Lancet.* 1996;347(9009):1141-1145.

5. Iadecola C, Park L, Capone C. Threats to the mind aging, amyloid, and hypertension. *Stroke.* 2009;40(3 suppl 1):S40-S44.

6. Lipsitz LA, Gagnon M, Vyas M, et al. Antihypertensive therapy increases cerebral blood flow and carotid distensibility in hypertensive elderly subjects. *Hypertension.* 2005;45(2):216-221.

7. Lin M-S, Chiu M-J, Wu Y-W, et al. Neurocognitive improvement after carotid artery stenting in patients with chronic internal carotid artery occlusion and cerebral ischemia. *Stroke.* 2011;42(10):2850-2854.

8. Li J, Wang Y, Zhang M, et al. Vascular risk factors promote conversion from mild cognitive impairment to Alzheimer disease. *Neurology.* 2011;76(17):1485-1491.

9. Forette F, Seux M-L, Staessen JA, et al. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. *Archives of internal medicine.* 2002;162(18):2046-2052.

10. Smith PJ, Blumenthal JA, Hoffman BM, et al. Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. *Psychosom Med.* Apr 2010;72(3):239-252.

11. Aarsland D, Sardahaee FS, Anderssen S, Ballard C, group tAsSSR. Is physical activity a potential preventive factor for vascular dementia? A systematic review. *Aging & mental health.* 2010;14(4):386-395.

12. Heyn P, Abreu BC, Ottenbacher KJ. The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis. *Archives of physical medicine and rehabilitation.* 2004;85(10):1694-1704.

13. Sofi F, Valecchi D, Bacci D, et al. Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. *Journal of internal medicine.* 2011;269(1):107-117.

14. van Uffelen JG, Paw MJCA, Hopman-Rock M, van Mechelen W. The effects of exercise on cognition in older adults with and without cognitive decline: a systematic review. *Clinical Journal of Sport Medicine.* 2008;18(6):486-500.

15. Baker LD, Frank LL, Foster-Schubert K, et al. Effects of aerobic exercise on mild cognitive impairment: a controlled trial. *Archives of neurology.* 2010;67(1):71.

16. Colcombe S, Kramer AF. Fitness Effects on the Cognitive Function of Older Adults A Meta-Analytic Study. *Psychological science.* 2003;14(2):125-130.

17. Groot C, Hooghiemstra A, Raijmakers P, et al. The effect of physical activity on cognitive function in patients with dementia: A meta-analysis of randomized control trials. *Ageing research reviews.* 2016;25:13-23.

18. Hess NC, Dieberg G, McFarlane JR, Smart NA. The effect of exercise intervention on cognitive performance in persons at risk of, or with, dementia: A systematic review and meta-analysis. *Healthy Aging Research.* 2014;3(3):1-10.

19. Cornelissen V, Smart N. Exercise Training for Blood Pressure: A Systematic Review and Meta-analysis. *Journal of the American Heart Association.* 2013;2(1).

20. Cardoso Jr CG, Gomides RS, Queiroz A, et al. Acute and chronic effects of aerobic and resistance exercise on ambulatory blood pressure. *Clinics.* 2010;65(3):317-325.

21. Hess NC, Carlson D, Inder J, Jesulola E, McFarlane J, Smart N. Clinically Meaningful Blood Pressure Reductions with Low Intensity Isometric Handgrip Exercise. A Randomized Trial. *Physiological research* 2016;65.

22. Carlson DJ, Dieberg G, Hess NC, Millar PJ, Smart NA. Isometric exercise training for blood pressure management: a systematic review and meta-analysis. Paper presented at: Mayo Clinic Proceedings2014.

23. Inder JD, Carlson DJ, Dieberg G, McFarlane JR, Hess NC, Smart NA. Isometric exercise training for blood pressure management: a systematic review and meta-analysis to optimize benefit. *Hypertension Research.* 2015.

24. McGowan CL, Levy AS, Millar PJ, et al. Acute vascular responses to isometric handgrip exercise and effects of training in persons medicated for hypertension. *American Journal of Physiology-Heart and Circulatory Physiology.* 2006;291(4):H1797-H1802.

25. McGowan CL, Visocchi A, Faulkner M, et al. Isometric handgrip training improves local flow-mediated dilation in medicated hypertensives. *European journal of applied physiology.* 2006;98(4):355-362.

26. Badrov MB, Bartol CL, Dibartolomeo MA, Millar PJ, McNevin NH, McGowan CL. Effects of isometric handgrip training dose on resting blood pressure and resistance vessel endothelial function in normotensive women. *Eur J Appl Physiol.* Aug 2013;113(8):2091-2100.

27. Badrov MB, Horton S, Millar PJ, McGowan CL. Cardiovascular stress reactivity tasks successfully predict the hypotensive response of isometric handgrip training in hypertensives. *Psychophysiology.* 2013;50(4):407-414.

28. Wiles JD, Coleman DA, Swaine IL. The effects of performing isometric training at two exercise intensities in healthy young males. *Eur J Appl Physiol.* Feb 2010;108(3):419-428.

29. Devereux GR, Wiles JD, Swaine I. Markers of isometric training intensity and reductions in resting blood pressure. *J Sports Sci.* Apr 2011;29(7):715-724.

30. Millar PJ, Bray SR, MacDonald MJ, McCartney N. The hypotensive effects of isometric handgrip training using an inexpensive spring handgrip training device. *J Cardiopulm Rehabil Prev.* May-Jun 2008;28(3):203-207.

31. Millar P, Levy A, McGowan C, McCartney N, MacDonald M. Isometric handgrip training lowers blood pressure and increases heart rate complexity in medicated hypertensive patients. *Scandinavian journal of medicine & science in sports.* 2013;23(5):620-626.

32. Stiller-Moldovan C, Kenno K, McGowan CL. Effects of isometric handgrip training on blood pressure (resting and 24 h ambulatory) and heart rate variability in medicated hypertensive patients. *Blood Pressure Monitoring.* 2012;17(2):55-61.

33. Taylor AC, McCartney N, Kamath MV, Wiley RL. Isometric training lowers resting blood pressure and modulates autonomic control. *Medicine and science in sports and exercise.* 2003;35(2):251-256.

34. Olher RdRV, Bocalini DS, Bacurau RF, et al. Isometric handgrip does not elicit cardiovascular overload or post-exercise hypotension in hypertensive older women. *Clinical interventions in aging.* 2013;8:649.

35. Font MA, Arboix A, Krupinski J. Angiogenesis, neurogenesis and neuroplasticity in ischemic stroke. *Current cardiology reviews.* 2010;6(3):238.

36. Ahlskog JE, Geda YE, Graff-Radford NR, Petersen RC. Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. Paper presented at: Mayo Clinic Proceedings2011.

37. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. 1980.

38. DeSouza CA, Shapiro LF, Clevenger CM, et al. Regular aerobic exercise prevents and restores age-related declines in endothelium-dependent vasodilation in healthy men. *Circulation.* 2000;102(12):1351-1357.

39. Hess DC, Blauenfeldt RA, Andersen G, et al. Remote ischaemic conditioning [mdash] a new paradigm of self-protection in the brain. *Nature Reviews Neurology.* 2015;11(12):698-710.

40. Ni J, Lu H, Lu X, et al. The evolving concept of physiological ischemia training vs. ischemia preconditioning. *Journal of biomedical research.* 2015;29(6):445.

41. Ritchie K, Artero S, Touchon J. Classification criteria for mild cognitive impairment: A population-based validation study. *Neurology.* 2001;56(37):37-42.

42. Alzheimers Association. Mild Cognitive Impairment (MCI). 2012; http://www.alz.org/dementia/mild-cognitive-impairment-mci.asp. Accessed 25.02.2013.

43. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia.* 2011;7(3):263-269.

44. Etgen T, Sander D, Bickel H, Förstl H. Mild cognitive impairment and dementia: the importance of modifiable risk factors. *Deutsches Ärzteblatt International.* 2011;108(44):743.

45. Archer T, Kostrzewa R, Beninger R, Palomo T. Staging Neurodegenerative Disorders: Structural, Regional, Biomarker, and Functional Progressions. *Neurotoxicity Research.* 2011/02/01 2011;19(2):211-234.

46. Duara R, Loewenstein DA, Greig-Custo MT, et al. Diagnosis and staging of mild cognitive impairment, using a modification of the clinical dementia rating scale: the mCDR. *Int J Geriatr Psychiatry.* 2010;25(3):282-289.

47. Querfurth HW, LaFerla FM. Alzheimer's DiseaseMechanisms of Disease. *The New England Journal of Medicine.* 2010;362(4):329-344.

48. Braak H, Alafuzoff I, Arzberger T, Kretzschmar H, Del Tredici K. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta neuropathologica.* 2006;112(4):389-404.

49. Archer T. Physical exercise alleviates debilities of normal aging and Alzheimer's disease. *Acta Neurol Scand.* Apr 2011;123(4):221-238.

50. Randolph C. *RBANS update Repeatable Battery for the Assessment of Neuropsychological Status manual*. Bloomington, MN: Pearson; 1998.

51. Monroe T, Carter M. Using the Folstein Mini Mental State Exam (MMSE) to explore methodological issues in cognitive aging research. *European Journal of Ageing.* 2012;9(3):265-274.

52. Boone KB, Lesser IM, Miller BL, et al. Cognitive functioning in older depressed outpatients: Relationship of presence and severity of depression to neuropsychological test scores. *Neuropsychology.* 1995;9(3):390.

53. Brink TL, Yesavage JA, Lum O, Heersema PH, Adey M, Rose TL. Screening tests for geriatric depression. *Clinical gerontologist.* 1982;1(1):37-43.

54. Tuijl JP, Scholte EM, Craen AJ, Mast RC. Screening for cognitive impairment in older general hospital patients: comparison of the Six-Item Cognitive Impairment Test with the Mini-Mental State Examination. *International journal of geriatric psychiatry.* 2012;27(7):755-762.

55. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *Journal of psychiatric research.* 1975;12(3):189-198.

56. Mungas D. Iii-office mental status testing: A practical guide. *Geriatrics.* 1991;46(7).

57. Cockrell JR, Folstein MF. Mini-mental state examination. *Geriatric Psychiatry.* 2002:140.

58. Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-Based Norms for the Mini-Mental State Examination by Age and Education Level. *Journal of Occupational and Environmental Medicine.* 1994;36(1):13-14.

59. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *Journal of psychiatric research.* 1983;17(1):37-49.

60. Kratochwill TR, Hitchcock J, Horner R, et al. Single-case designs technical documentation. *What Works Clearinghouse.* 2010.

61. Kazdin AE. *Research Design in Clinical Psychology: Pearson New International Edition.* Pearson Education, Limited; 2013.

62. Barlow D, Nock M, Hersen M. *Single case experimental designs : strategies for studying behavior for change. 3rd ed.* Boston, MA: Pearson; 2009.

63. Gustafson SA, Nassar SL, Waddell DE. Single-case design in psychophysiological research. part I: Context, structure, and techniques. *Journal of Neurotherapy.* 2011;15(1):18-34.

64. Kratochwill TR, Hitchcock JH, Horner RH, et al. Single-case intervention research design standards. *Remedial and Special Education.* 2012:0741932512452794.

65. Shadish WR, Sullivan KJ. Characteristics of single-case designs used to assess intervention effects in 2008. *Behavior Research Methods.* 2011;43(4):971-980.

66. Ma H-H. An alternative method for quantitative synthesis of single-subject researches percentage of data points exceeding the median. *Behavior modification.* 2006;30(5):598-617.

67. Parker RI, Hagan-Burke S. Median-Based Overlap Analysis for Single Case Data A Second Study. *Behavior modification.* 2007;31(6):919-936.

68. Jenson WR, Clark E, Kircher JC, Kristjansson SD. Statistical reform: Evidence-based practice, meta-analyses, and single subject designs. *Psychology in the Schools.* 2007;44(5):483-493.

69. Waddell DE, Nassar SL, Gustafson SA. Single-case design in psychophysiological research: Part II: Statistical analytic approaches. *Journal of Neurotherapy.* 2011;15(2):160-169.

70. Howden R, Lightfoot JT, Brown SJ, Swaine IL. The effects of isometric exercise training on resting blood pressure and orthostatic tolerance in humans. *Experimental physiology.* 2002;87(4):507-515.

71. Gill KF, Arthur ST, Swaine I, et al. Intensity-dependent reductions in resting blood pressure following short-term isometric exercise training. *Journal of sports sciences.* 2014(ahead-of-print):1-6.

72. Peters PG, Alessio HM, Hagerman AE, Ashton T, Nagy S, Wiley RL. Short-term isometric exercise reduces systolic blood pressure in hypertensive adults: possible role of reactive oxygen species. *International journal of cardiology.* 2006;110(2):199-205.

73. Wong GW, Wright JM. Blood pressure lowering efficacy of nonselective beta-blockers for primary hypertension. *The Cochrane Library.* 2014.

74. Wong GW, Laugerotte A, Wright JM. Blood pressure lowering efficacy of non-selective beta blockers for primary hypertension. *The Cochrane Library.* 2008.

75. Wiles JD, Coleman DA, Swaine IL. The effects of performing isometric training at two exercise intensities in healthy young males. *European journal of applied physiology.* 2010;108(3):419-428.

76. Baross AW, Wiles JD, Swaine IL. Effects of the intensity of leg isometric training on the vasculature of trained and untrained limbs and resting blood pressure in middle-aged men. *International journal of vascular medicine.* 2012;2012.

77. Mcgowan C, Levy A, Mccartney N, Macdonald M. Isometric handgrip training does not improve flow-mediated dilation in subjects with normal blood pressure. *Clinical Science.* 2007;112:403-409.

78. Wiley RL, Dunn CL, Cox RH, Hueppchen NA, Scott MS. Isometric exercise training lowers resting blood pressure. *Medicine and science in sports and exercise.* 1992;24(7):749-754.

79. Millar PJ, Bray SR, McGowan CL, MacDonald MJ, McCartney N. Effects of isometric handgrip training among people medicated for hypertension: a multilevel analysis. *Blood Pressure Monitoring.* 2007;12(5):307-314.

80. Pimenta E, Oparil S. Management of hypertension in the elderly. *Nature Reviews Cardiology.* 2012;9(5):286-296.

81. Blacher J, Staessen JA, Girerd X, et al. Pulse pressure not mean pressure determines cardiovascular risk in older hypertensive patients. *Archives of internal medicine.* 2000;160(8):1085-1089.

82. Glynn RJ, Chae CU, Guralnik JM, Taylor JO, Hennekens CH. Pulse pressure and mortality in older people. *Archives of internal medicine.* 2000;160(18):2765-2772.

83. Fratiglioni L, Paillard-Borg S, Winblad B. An active and socially integrated lifestyle in late life might protect against dementia. *The Lancet Neurology.* 2004;3(6):343-353.

84. Crooks VC, Lubben J, Petitti DB, Little D, Chiu V. Social network, cognitive function, and dementia incidence among elderly women. *American Journal of Public Health.* 2008;98(7):1221-1227.

85. Shankar A, Hamer M, McMunn A, Steptoe A. Social isolation and loneliness: relationships with cognitive function during 4 years of follow-up in the English Longitudinal Study of Ageing. *Psychosomatic Medicine.* 2013;75(2):161-170.

86. Heilbronner RL, Sweet JJ, Attix DK, Krull KR, Henry GK, Hart RP. Official position of the American Academy of Clinical Neuropsychology on serial neuropsychological assessments: the utility and challenges of repeat test administrations in clinical and forensic contexts. *The Clinical Neuropsychologist.* 2010;24(8):1267-1278.

87. Buchanan TW, Tranel D, Adolphs R. Impaired memory retrieval correlates with individual differences in cortisol response but not autonomic response. *Learning & Memory.* 2006;13(3):382-387.

88. Galvin JA, Benson H, Deckro GR, Fricchione GL, Dusek JA. The relaxation response: reducing stress and improving cognition in healthy aging adults. *Complementary therapies in clinical practice.* 2006;12(3):186-191.

89. Fan Y-L, Wan J-Q, Zhou Z-W, et al. Neurocognitive improvement after carotid artery stenting in patients with chronic internal carotid artery occlusion: a prospective, controlled, single-center study. *Vascular and endovascular surgery.* 2014:1538574414525863.

90. Hess DC, Hoda MN, Khan MB. Humoral mediators of remote ischemic conditioning: important role of eNOS/NO/nitrite. *Brain Edema XVI*: Springer; 2016:45-48.

91. Cherry-Allen KM, Gidday JM, Lee J-M, Hershey T, Lang CE. Remote limb ischemic conditioning enhances motor learning in healthy humans. *Journal of neurophysiology.* 2015;113(10):3708-3719.

Higher Degree Research Thesis by Publication
University of New England

STATEMENT OF AUTHORS' CONTRIBUTION

(To appear at the end of each thesis chapter submitted as an article/paper)

We, the Research Master/PhD candidate and the candidate's Principal Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated in the *Statement of Originality*.

	Author's Name (please print clearly)	**contribution**
Candidate	Nicole Hess	Study design, recruitment of participants, coordinating the study, data collection, data handling, statistical analysis, writing paper.
Other Authors	Debra Dunstan	Study design, editorial feedback, and suggestions as to content.
	Neil Smart	Study design, editorial feedback, and suggestions as to content.

Name of Student/Candidate: Nicole Hess

Name/title of Principal Supervisor: Neil Smart

[redacted]

18.09.2016
Date

[redacted]

Principal Supervisor

19.09.2016
Date

Higher Degree Research Thesis by Publication
University of New England

STATEMENT OF ORIGINALITY

(To appear at the end of each thesis chapter submitted as an article/paper)

We, the Research Master/PhD candidate and the candidate's Principal Supervisor, certify that the following text, figures and diagrams are the candidate's original work.

Type of work	Page numbers
All text, tables and diagrams	Chapter 6 pp 107–150

Name of Student/Candidate: Nicole Hess

Name/title of Principal Supervisor: Neil Smart

[redacted]

18.09.2016
Date

[redacted]

Principal Supervisor

19.09.2016
Date

Chapter 7 : Conclusions

7.1 The problem and the research questions

Dementia is not considered to be a part of the normal aging process, however, age does appear to be the principle risk factor with the majority of people diagnosed with Alzheimer's disease (AD) 65 years or older [1-3] and the incidence of the disease doubling every 5 years thereafter [2]. Cognitive impairment without dementia, such as age-associated cognitive decline (AACD) and age-associated memory impairment (AAMI) is considered to fall within the normative realms of brain aging [4,5], whereas, mild cognitive impairment (MCI) and dementia are not. The differentiation between AACD, AAMI, MCI or early stage dementia is intrinsically a clinical judgement made by a skilled clinician and is couched on the magnitude to which an individual's ability to function at work or in activities of daily living is impacted [6].

MCI is a condition that is characterised by a deterioration in cognitive abilities and memory that are beyond that expected for a person's age and level of education, and without notable loss of global cognition or impairment in activities of daily living [5,7-9]. Between 10% and 15% of MCI cases will progress to a diagnosis of AD; AD is a progressive neurodegenerative dementing disorder responsible for severe cortical atrophy in selective regions of the brain such as the temporal, medial-temporal, limbic, frontal and prefrontal cortices [2,8,10]. AD is an irrevocable condition, therefore, there is an urgent need for therapeutic treatments that may prevent, attenuate or slow down the progression of MCI to AD, and from early stage AD to more advanced stages. Furthermore, it is believed that preventative actions and treatments are most likely to be effective in the early stages of AD and other dementing disorders.

The etiology of AD is believed to be multifaceted, encompassing both genetic and vascular contributors [11,12]. Vascular theories of AD cite vascular risk factors (VRF) such as hypertension, atherosclerosis, cardiac disease, stroke, and diabetes as contributing to chronic

brain hypoperfusion and as major contributors to the development of sporadic AD [13,14]. Specifically, untreated hypertension at mid-life [15] and cerebral hypoperfusion [16] are recognised as predictors for developing AD.

Exercise and physical activity are modifiable lifestyle factors that have been found to moderate and attenuate the deleterious effects of age-associated cognitive decline and pathological cognitive decline such as AD[17]. A growing body of literature supports the notion that physical activity bestows therapeutic benefits on cognitive performance outcomes [18-21] and plays a protective role in the preservation of brain functioning in the elderly. Moreover, taken together, these studies tend to suggest that cognitive improvements are not necessarily specific to increases in cardio respiratory fitness alone (VO_{2max}). Several mechanisms have been identified that underlie the neurocognitive benefits of physical activity. These include the promotion of neurogenesis, angiogenesis, synaptogenesis, neurotrophin production [22], the upregulation of catecholamines [23,24] and anti-inflammatory cytokines [25], and the mitigation of vascular risk factors that promote increased cerebral perfusion.

An increasing body of evidence supports the role of isometric exercise training (IET) to affect significant reductions in resting systolic and diastolic blood pressures in both hypertensive and normotensive men and women [26-31]. Unlike aerobic exercise, the potential for IET to assist with improvements in cognitive performance have not yet been investigated in the broader literature, though the feasibility of inducing limb ischemia to support and repair distant organs such as the heart and the brain has been successfully demonstrated through the application of techniques such as remote ischemic conditioning (RIC) [32] and physiological ischemic training (PIT) [33].

The physiological mechanisms elicited by IET are not fully understood and are still under investigation. However, it may be the case that repeated exposure to ischemia, hypoxia, and

reactive hyperaemia resulting from IET elicits increases in angiogenesis, neuro-endocrine function, and metabolites such as beta endorphins and prostaglandins. Edwards et al. [34] suggest that reduced peripheral vascular resistance facilitated via neurohormonal and structural adaptations might also explain the anti-hypertensive effects of exercise. Subsequently, it may be the case that in conjunction with its anti-hypertensive effects, isometric exercise may also offer the potential to elicit improvements in cognitive performance. It could be that the repeated increases in cerebral blood flow (CBF) and the associated nutrient and oxygen delivery that result from the sustained isometric exercise trigger the subsequent cascade of structural, biochemical and functional adaptations that increase brain plasticity, function, and cognition. Supporting this proposition is evidence that exercise induces increases in neurotrophins, angiogenesis, neuro-endocrine function, and causes vascular wall changes [35-38]. Therefore a plausible hypothesis is that IET initiates a cascade of vascular, neurotrophic, and neuro-endocrine events that lead to an improvement of cognitive function.

Cognitive deficits and compromised mobility and balance are significant inhibitors to participation in physical activity for the elderly, as are the logistical arrangements involved in attending a gymnasium or a similar situation. Subsequently, an activity such as isometric exercise that does not necessitate these demands yet is able to stimulate the numerous physiological benefits of more traditional aerobic and resistance styles of exercise might be a viable substitute for the elderly. Specifically, IET may prevent, attenuate, or delay the onset of cognitive decline and the progression of MCI to incidence of sporadic AD.

The current thesis investigated the issues presented above by addressing the following questions:

1. To what extent does physical activity confer neurocognitive benefits on individuals with cognitive decline and/or dementia?
2. Is isometric exercise, utilizing isometric hand grip (IHG) training, at 10% maximum voluntary contraction (MVC) and 5% MVC above the BP lowering threshold in normotensive adult men and women?
3. Is IET a viable non-pharmacological therapy for preventing and/or attenuating the progression of MCI to incidence of sporadic AD and for preventing and/or attenuating the progression of early stage AD to more advanced stages?
4. Can IET elicit improvements in resting BP and cognitive performance in elderly individuals experiencing cognitive impairment or diagnosed with AD and would changes in cognitive performance be linked with anti-hypertensive effects?

7.2 How the research was conducted

7.2.1 Meta-analysis

Firstly, in chapter 3, we conducted a meta-analysis focusing on recent studies that investigated the impact of exercise on cognitive performance outcomes. We conducted a systematic search of PubMed, the Cumulative Index to Nursing and Allied Health Literature, and the Cochrane Central Register of Controlled Trials (1966–2014) using the concepts of dementia, cognitive impairment, cognitive function, and exercise.

7.2.2 Randomised trial

Secondly, in chapter 4, we conducted a randomised study to try to establish the minimum anti-hypertensive threshold intensity for isometric exercise as the current literature had not reported on this. The reason we were interested in a minimum anti-hypertensive threshold for IET was in consideration of the frail or elderly. The frail and elderly may initially struggle

with IET at 30% MVC, yet are more likely to be hypertensive and therefore exude most benefit from IET.

Twenty participants were randomly allocated to either IHG training at 10% MVC (n = 10) or IHG training at 5% MVC (n = 10). Each intervention consisted of four sets of 2 minute IHG contractions 3 days per week for 6 weeks. Subsequent to group assignment all participants underwent baseline cardiovascular measures (heart rate , systolic, diastolic, and mean arterial blood pressure) which were repeated each week for the duration of the training program.

7.2.3 Review of literature

Thirdly, in chapter 5, we aimed to build a solid rationale that would support the hypothesis that IET has the potential to improve cognitive performance outcomes in elderly individuals with cognitive impairment or AD. To this end we reviewed (1) the purported linkages between VRF and cognitive impairment; (2) the shared pathological events prevalent in hypertension and AD; and (3) considered the potential benefits and efficacy of utilising IET as a non-pharmacological therapy for preventing and/or attenuating the progression of MCI to incidence of sporadic AD and early stage AD to more advanced stages of the disease.

7.2.4 Single-case multiple base-line across subjects pilot study

Finally, in chapter 6, we ran a small pilot-case-study to assess the impact of IET on cognitive performance outcomes in elderly individuals experiencing memory impairment or diagnosed with AD. Four participants, two males and two females, with ages ranging from 67 to 85 years, (M_{age} = 77.8 years; SD = 7.9), participated in IHG at 20% MVC. Baseline measurements were administered in a temporal sequence over a 2 to 3 week time-period which enabled the participants to function as their own control. Each intervention consisted of four sets of 2 minute IHG contractions 3 days per week for 6 weeks. All Participants

completed IHG training at 20% MVC. At the commencement of the study all participants were assessed as not suffering from depression and as presenting with some extent of cognitive impairment.

7.3 Findings

The results of our meta-analysis supported the implication that physical activity might be an effective lifestyle modification and non-pharmacological intervention for individuals diagnosed with cognitive impairment and dementia. The spectrum of physical activities encompassed by our meta-analysis included Tai Chi, flexibility, relaxation, balancing techniques, and varying intensities of aerobic exercise and strength training. Consequently, not all of the physical activities reported could be considered aerobic in nature, yet despite this there was still evidence of improvement in certain domains of cognitive function. The notable variation in the modalities of physical intervention prevented speculation regarding which exercise modality was optimal. These findings supported the proposal that IET might also elicit improvements in cognitive performance in individuals diagnosed with cognitive impairment and dementia.

In consideration of the potential difficulties that the frail and elderly may encounter when attempting to maintain IHG contractions at intensities ≥ 30% MVC we were interested in determining the minimum anti-hypertensive threshold intensity for isometric exercise. The primary finding was that IHG training performed at either 5% MVC or 10% MVC elicited no statistically significant reduction on either SBP or DBP after 6 weeks of training in normotensive adult men and women. However, our results did show a clinically meaningful reduction in SBP in both the 5% and 10% groups and this was supported by medium to large effect sizes suggesting that IHG training at both intensities has a clinically meaningful impact. The results of this study demonstrated that after 6 weeks of low intensity IHG

training reductions in SBP were similar to the antihypertensive effects observed in monotherapy of 5 – 7 mmHg [39].

A review of the current literature supported both a strong relationship between the contribution of cerebral hypoperfusion to the development of MCI and AD and [13,40] a strong link between untreated hypertension and neurodegenerative processes [14,41]. In sporadic AD cognitive decline was directly related to the neurodegenerative process of the diseases and not amyloidosis [42-44]. Moreover, the neurodegenerative process of AD is heavily driven by VRF [13,45]. Hypertension is responsible for promoting cerebral ischemia, neurovascular dysfunction and cognitive decline [41], consequently, it would make sense that ameliorating and attenuating the effects of hypertension and increasing cerebral perfusion might also slow down the neurodegenerative processes related to MCI and dementia in AD. We were able to conclude that there is considerable and growing evidence to suggest that BP reduction in elderly hypertensive adults might reduce the development of incident AD and cognitive decline.

Our final case study investigated whether IET could elicit improvements in resting BP and cognitive performance in elderly individuals experiencing cognitive impairment or diagnosed with AD and whether any changes in cognitive performance could be linked with anti-hypertensive effects? Overall cognitive functioning remained stable for all but one participant, the neurological status of Participant 1 improved from a clinical rating of moderate cognitive impairment to mild cognitive impairment. Our primary finding was that IET did not reduce resting BP in elderly medicated hypertensives after 3 weeks, 5 weeks or 6 weeks of IET at 20% maximal voluntary effort. Subsequently, any of our observed improvements in cognitive performance could not be attributed to the anti-hypertensive effects of isometric exercise. Cognitive improvements may have been associated with the

increased social contact that the participants experienced or other neurohormonal mechanisms that are mutually exclusive to changes in BP.

7.4 Discussion of findings

Pharmacological management of hypertension [46] and stenting of the carotid artery [47,48] have both been demonstrated to improve cognitive performance outcomes in the elderly and limb ischemia induced by tourniquet has been shown to improve CBF [49] and enhance neuroplasticity [50]. Subsequently, the feasibility of limb ischemia to support and repair distant organs such as the heart and the brain has been demonstrated through the application of techniques such as RIC [32] and more recently PIT [33]. Whilst the protocols between these two techniques differ from each other, and the extent of the commonality of shared signalling and protective mechanisms is still the subject of investigation, it is likely that there is a cross over whereby some of these mechanisms are shared. Encouragingly RIC administered to elderly patients aged 80-95 years old with intracranial atherosclerosis stenosis was found to be both safe and effective in stroke prevention and treatment [51]. Moreover, the principles that support the efficacy of RIC and PIT also support the feasibility of a hypothesis that IET performed by elderly individuals might promote healthy neural functioning and boost cognitive performance. Similarly, the anti-hypertensive effects of IET reported in the broader literature [52,53] and the concomitant improvements in flow mediated dilation and endothelial function should also be expected to elicit improvements in cognitive performance [54,55]. The reactive hyperaemia elicited during a two minute bout of IHG training may occur due to either partial or full occlusion of the brachial artery. The production of a number of metabolites such as beta endorphins, prostaglandins and hypoxia-inducible factor – 1 α (HIF 1 α) are postulated to result from ischemia induced by full or partial restriction of the brachial artery during IHG exercises [39,56,57]. These metabolites play a number of roles including, supporting the immune

system, managing inflammation [58,59], vasodilation and vasoconstriction [60], stimulating angiogenesis, and tissue repair and regeneration [61]. Previous isometric exercise research suggests that full occlusion of blood flow occurs at approximately 55-75% of MVC with higher occlusion thresholds evident in individuals who were able to exert a greater handgrip force [62] and PIT administered using isometric contraction at 50% MVC stimulated a sufficient ischemic response to induce cardiovascular angiogenesis [33]. It may be that the intensity of the hand grip contraction employed during IHG exercise determines the existence or absence of reactive hyperaemia. Intuitively, even at intensities less than 55% of MVC partial occlusion of blood flow is likely; however, lower intensities may be insufficient to affect BP and cognitive changes in the elderly.

Considering that arterial stiffness and, consequently, endothelial dysfunction are associated with aging, it is intuitive that hypertension in the elderly is potentially more resistant to improvement than it might be in younger adult cohorts. Although we concluded from the results of our randomised trial that those people unable to complete IET at the traditional intensity of 30% MVC may still benefit from clinically relevant anti-hyertensive effects at IET intensities of both 5% and 10% MVC, in terms of BP management in the elderly it would appear that a maximal force less than or equal to 20% is insufficient to elicit improvements in BP. It might be the case that amongst this cohort, in order to elicit change in both BP and in neurocognitive measures that IET equal to or greater than 50% MVC is required. PIT protocols utilising IHG at a MVC of 50% have elicited significant increases in collateral blood flow in the myocardium of patients with coronary artery disease and a coronary artery occlusion [63] and high intensity IHG training has been shown as safely tolerated in elderly participants [64]. It may be that the underlying principles of performing high intensity bouts of IET are similar to those underlying high intensity interval training (HIIT) whereby brief intermittent bursts of high intensity physical activity are interspersed with rest periods. As

with IET, the physiological adaptations arising from HIIT are highly variable and are determined by factors such as intensity, duration, and number of intervals performed [65].

7.5 Addressing a gap in current literature

Our research was the first to investigate the minimum anti-hypertensive threshold intensity for isometric exercise. Although the study duration and the sample size may have been insufficient to demonstrate a statistically significant reduction in resting BP at these low intensities our findings were able to demonstrate clinically meaningful results. Furthermore, our case-study was the first study to review and examine the potential cognitive benefits of IET in elderly individuals with memory impairment and/or dementia.

7.6 Limitations of this study

7.6.1 Randomised trial

Our randomised controlled study investigating the minimum anti-hypertensive threshold intensity for isometric exercise was the first study of its kind; subsequently, we felt that the study duration and the sample size may have been insufficient to demonstrate a statistically significant reduction in resting BP at these low intensities.

7.6.2 Single-case multiple base-line across subjects pilot study

Although we employed a robust study design and reviewed each case based on its own unique variables, our pilot-case study has several limitations. Small sample size, the varying characterisations of cognitive impairment and dementias experienced amongst the participants, inadequate study duration, and insufficient IET intensity were the perceived limitations.

7.7 Moving forward; future research potential

7.7.1 Randomised trial

Further research involving a larger participant cohort, conducted over a longer period of time is required to determine a minimum therapeutic threshold for antihypertensive response. This determination would aid in the design of future RCTs to determine if sham groups are truly that. Moreover, ascertaining the minimum IET intensity for BP reduction may also be important in terms of designing exercise programs for the frail and rehabilitating. Individuals defined in this cohort may struggle to complete IHG exercise at 30% MVC, and might not be required in light of our clinically meaningful findings.

7.7.2 Single-case multiple base-line across subjects pilot study

To provide a greater insight into the potential cognitive improvements and health and lifestyle benefits of IET in medicated hypertensive elderly cohorts (between the ages of 75 years to 85 years) we suggest that future studies look to increase both the training intensity and protocol duration. IET at intensities of 50% and 70% MVC has been demonstrated to be well tolerated in elderly individuals with no adverse effects reported [51,64]. It may be the case that IET at intensities of 50% MVC may stimulate improvements in cognitive performance in elderly individuals with cognitive impairment or AD.

Unfortunately, we were unable to run a large scale study investigating the effects of IET on elderly individuals with cognitive impairment or AD. However, we recommend that future large scale studies look to investigate the implications of a more diverse array of subgroups. Possible subgroups include groups that are gender specific; groups that constrain age ranges to within ± 5 years, this may help to elucidate the effects of age on IET protocols and any derived benefits; classifying/defining activity levels of participants; and the uniform

characterisation of dementia across participants, as different dementias are likely to respond differently to the same treatment. Incorporating techniques such as magnetic resonance imaging, blood analysis, and genotype profiling would further assist in our understanding of the mechanisms of ischemic training on the brain, BP, and cognition.

A further recommendation for future research would be a large scale RCT to investigate recent suggestions that RIC might be beneficial in neurological disorders such as AD. Maybe the ischemic effects elicited by IET at less than 50% maximal effort are not adequate to trigger the endogenous neuroprotective pathways that are activated by RIC. Consequently, those who are unable to perform IET at intensities of 50% MVC or greater might experience haemodynamic and cognitive benefits from a program of RIC.

7.8 Closing comments

The potential for limb ischemia to trigger neuroprotective physiological responses to support and repair the brain has been demonstrated via RIC protocols and introduces exciting therapeutic potential for individuals with MCI and AD. The application of IET at ≥ 50% MVC may be sufficient to create an ischemic event that is adequate to confer neuroprotective benefits and anti-hypertensive effects in elderly adults with cognitive impairment or AD. Further investigations within this domain have the potential to yield life-changing results for many individuals.

References

1. Alzheimer's Association. What is Alzheimer's. 2012; http://www.alz.org/alzheimers_disease_what_is_alzheimers.asp.Accessed 25.02.2013.
2. Querfurth HW, LaFerla FM. Alzheimer's DiseaseMechanisms of Disease. *The New England Journal of Medicine.* 2010;362(4):329-344.
3. Middleton LE, Yaffe K. Targets for the prevention of dementia. *J Alzheimers Dis.* 2010;20(3):915-924.
4. Ritchie K, Artero S, Touchon J. Classification criteria for mild cognitive impairment: A population-based validation study. *Neurology.* 2001;56(37):37-42.
5. Alzheimers Association. Mild Cognitive Impairment (MCI). 2012; http://www.alz.org/dementia/mild-cognitive-impairment-mci.asp. Accessed 25.02.2013.
6. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer’s disease: Recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia.* 2011;7(3):263-269.
7. Etgen T, Sander D, Bickel H, Förstl H. Mild cognitive impairment and dementia: the importance of modifiable risk factors. *Deutsches Ärzteblatt International.* 2011;108(44):743.
8. Archer T, Kostrzewa R, Beninger R, Palomo T. Staging Neurodegenerative Disorders: Structural, Regional, Biomarker, and Functional Progressions. *Neurotoxicity Research.* 2011/02/01 2011;19(2):211-234.
9. Duara R, Loewenstein DA, Greig-Custo MT, et al. Diagnosis and staging of mild cognitive impairment, using a modification of the clinical dementia rating scale: the mCDR. *Int J Geriatr Psychiatry.* 2010;25(3):282-289.
10. Braak H, Alafuzoff I, Arzberger T, Kretzschmar H, Del Tredici K. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta neuropathologica.* 2006;112(4):389-404.
11. Imtiaz B, Tolppanen A-M, Kivipelto M, Soininen H. Future directions in Alzheimer's disease from risk factors to prevention. *Biochemical Pharmacology.* 2014;In press.
12. Wang C, Yu J-T, Wang H-F, et al. Meta-analysis of peripheral blood apolipoprotein E levels in Alzheimer’s disease. *PloS one.* 2014;9(2):e89041.

13. Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nature Reviews Neuroscience.* 2011;12(12):723-738.
14. Li J, Wang Y, Zhang M, et al. Vascular risk factors promote conversion from mild cognitive impairment to Alzheimer disease. *Neurology.* 2011;76(17):1485-1491.
15. Korf ES, White LR, Scheltens P, Launer LJ. Midlife Blood Pressure and the Risk of Hippocampal Atrophy The Honolulu Asia Aging Study. *Hypertension.* 2004;44(1):29-34.
16. Brown W, Thore C. Review: cerebral microvascular pathology in ageing and neurodegeneration. *Neuropathology and applied neurobiology.* 2011;37(1):56-74.
17. Rolland Y, van Kan GA, Vellas B. Healthy brain aging: role of exercise and physical activity. *Clinics in geriatric medicine.* 2010;26(1):75-87.
18. Colcombe S, Kramer AF. Fitness Effects on the Cognitive Function of Older Adults A Meta-Analytic Study. *Psychological science.* 2003;14(2):125-130.
19. Heyn P, Abreu BC, Ottenbacher KJ. The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis. *Archives of physical medicine and rehabilitation.* 2004;85(10):1694-1704.
20. Smith PJ, Blumenthal JA, Hoffman BM, et al. Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. *Psychosom Med.* 2010;72(3):239-252.
21. van Uffelen JG, Paw MJCA, Hopman-Rock M, van Mechelen W. The effects of exercise on cognition in older adults with and without cognitive decline: a systematic review. *Clinical Journal of Sport Medicine.* 2008;18(6):486-500.
22. Greenwood PM, Parasuraman R. Neuronal and cognitive plasticity: a neurocognitive framework for ameliorating cognitive aging. *Frontiers in aging neuroscience.* 2010;2.
23. McMorris T, Hale BJ. Differential effects of differing intensities of acute exercise on speed and accuracy of cognition: A meta-analytical investigation. *Brain and cognition.* 2012;80(3):338-351.
24. Tomporowski PD. Effects of acute bouts of exercise on cognition. *Acta psychologica.* 2003;112(3):297-324.
25. Petersen AMW, Pedersen BK. The anti-inflammatory effect of exercise. *Journal of applied physiology.* 2005;98(4):1154-1162.

26. Baross AW, Wiles JD, Swaine IL. Effects of the intensity of leg isometric training on the vasculature of trained and untrained limbs and resting blood pressure in middle-aged men. *International journal of vascular medicine.* 2012;2012.
27. Millar P, Levy A, McGowan C, McCartney N, MacDonald M. Isometric handgrip training lowers blood pressure and increases heart rate complexity in medicated hypertensive patients. *Scandinavian journal of medicine & science in sports.* 2013;23(5):620-626.
28. Devereux GR, Wiles JD, Swaine IL. Reductions in resting blood pressure after 4 weeks of isometric exercise training. *European journal of applied physiology.* 2010;109(4):601-606.
29. Wiles JD, Coleman DA, Swaine IL. The effects of performing isometric training at two exercise intensities in healthy young males. *European journal of applied physiology.* 2010;108(3):419-428.
30. Badrov MB, Bartol CL, Dibartolomeo MA, Millar PJ, McNevin NH, McGowan CL. Effects of isometric handgrip training dose on resting blood pressure and resistance vessel endothelial function in normotensive women. *Eur J Appl Physiol.* Aug 2013;113(8):2091-2100.
31. Badrov MB, Horton S, Millar PJ, McGowan CL. Cardiovascular stress reactivity tasks successfully predict the hypotensive response of isometric handgrip training in hypertensives. *Psychophysiology.* Apr 2013;50(4):407-414.
32. Hess DC, Blauenfeldt RA, Andersen G, et al. Remote ischaemic conditioning [mdash] a new paradigm of self-protection in the brain. *Nature Reviews Neurology.* 2015;11(12):698-710.
33. Ni J, Lu H, Lu X, et al. The evolving concept of physiological ischemia training vs. ischemia preconditioning. *Journal of biomedical research.* 2015;29(6):445.
34. Edwards KM, Ziegler MG, Mills PJ. The potential anti-inflammatory benefits of improving physical fitness in hypertension. *Journal of hypertension.* 2007;25(8):1533-1542.
35. Font MA, Arboix A, Krupinski J. Angiogenesis, neurogenesis and neuroplasticity in ischemic stroke. *Current cardiology reviews.* 2010;6(3):238.
36. Ahlskog JE, Geda YE, Graff-Radford NR, Petersen RC. Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. Paper presented at: Mayo Clinic Proceedings2011.

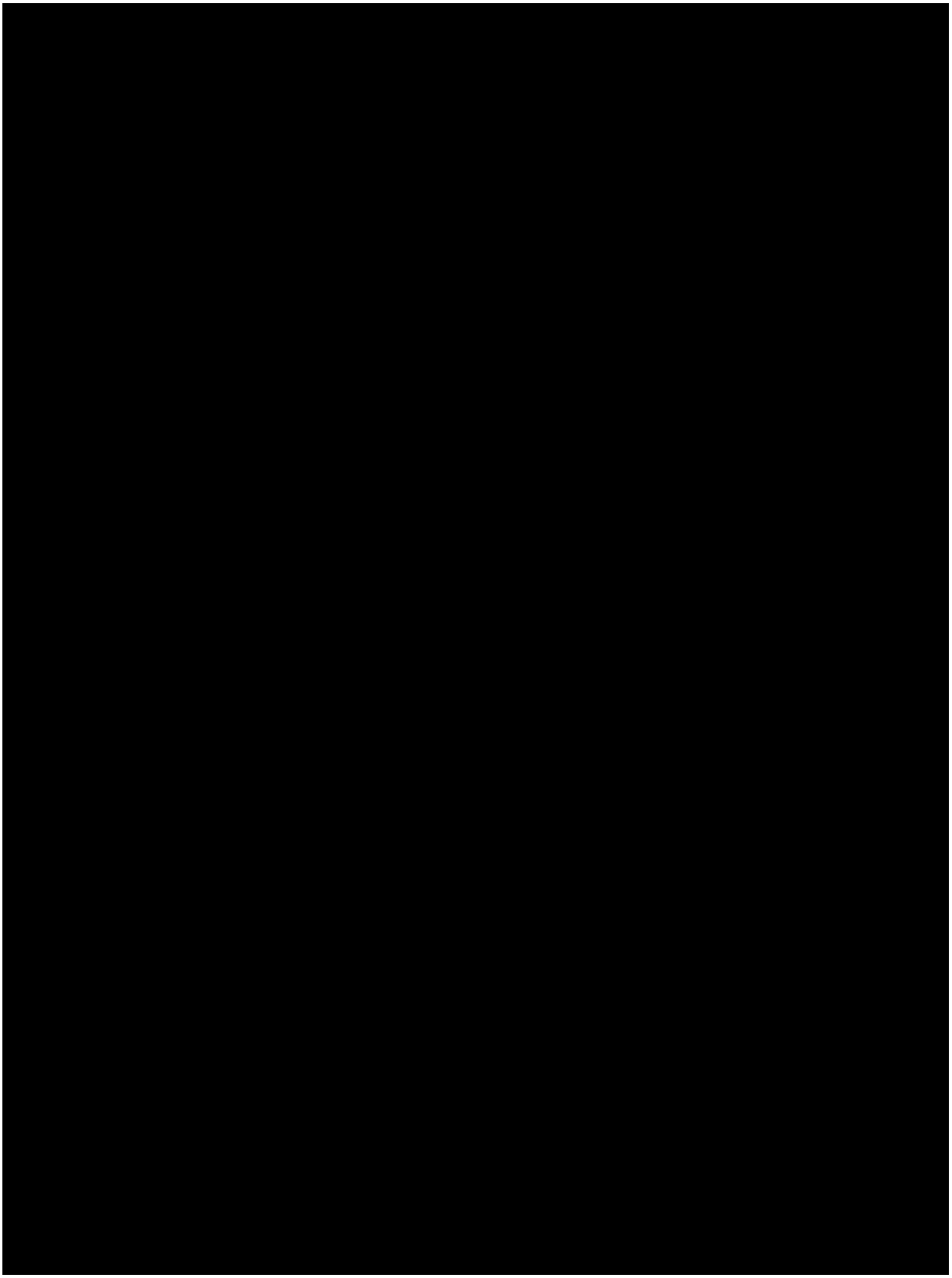
37. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. 1980.
38. DeSouza CA, Shapiro LF, Clevenger CM, et al. Regular aerobic exercise prevents and restores age-related declines in endothelium-dependent vasodilation in healthy men. *Circulation.* 2000;102(12):1351-1357.
39. Wong GW, Wright JM. Blood pressure lowering efficacy of nonselective beta-blockers for primary hypertension. *The Cochrane Library.* 2014.
40. de la Torre JC, Mussivand T. Can disturbed brain microcirculation cause Alzheimer's disease? *Neurological research.* 1993;15(3):146.
41. Iadecola C, Park L, Capone C. Threats to the mind aging, amyloid, and hypertension. *Stroke.* 2009;40(3 suppl 1):S40-S44.
42. Pedersen B, Steensberg A, Fischer C, et al. Searching for the exercise factor: is IL-6 a candidate? *Journal of Muscle Research & Cell Motility.* 2003;24(2-3):113-119.
43. Jack C, Lowe VJ, Weigand SD, et al. Serial PIB and MRI in normal, mild cognitive impairment and Alzheimer's disease: implications for sequence of pathological events in Alzheimer's disease. *Brain.* 2009:awp062.
44. Hiscock N, Chan MS, Bisucci T, Darby IA, Febbraio MA. Skeletal myocytes are a source of interleukin-6 mRNA expression and protein release during contraction: evidence of fiber type specificity. *The FASEB Journal.* 2004;18(9):992-994.
45. Schneider JA, Arvanitakis Z, Leurgans SE, Bennett DA. The neuropathology of probable Alzheimer disease and mild cognitive impairment. *Annals of neurology.* 2009;66(2):200-208.
46. Forette F, Seux M-L, Staessen JA, et al. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. *Archives of internal medicine.* 2002;162(18):2046-2052.
47. Fan Y-L, Wan J-Q, Zhou Z-W, et al. Neurocognitive improvement after carotid artery stenting in patients with chronic internal carotid artery occlusion: a prospective, controlled, single-center study. *Vascular and endovascular surgery.* 2014:1538574414525863.
48. Lin M-S, Chiu M-J, Wu Y-W, et al. Neurocognitive improvement after carotid artery stenting in patients with chronic internal carotid artery occlusion and cerebral ischemia. *Stroke.* 2011;42(10):2850-2854.

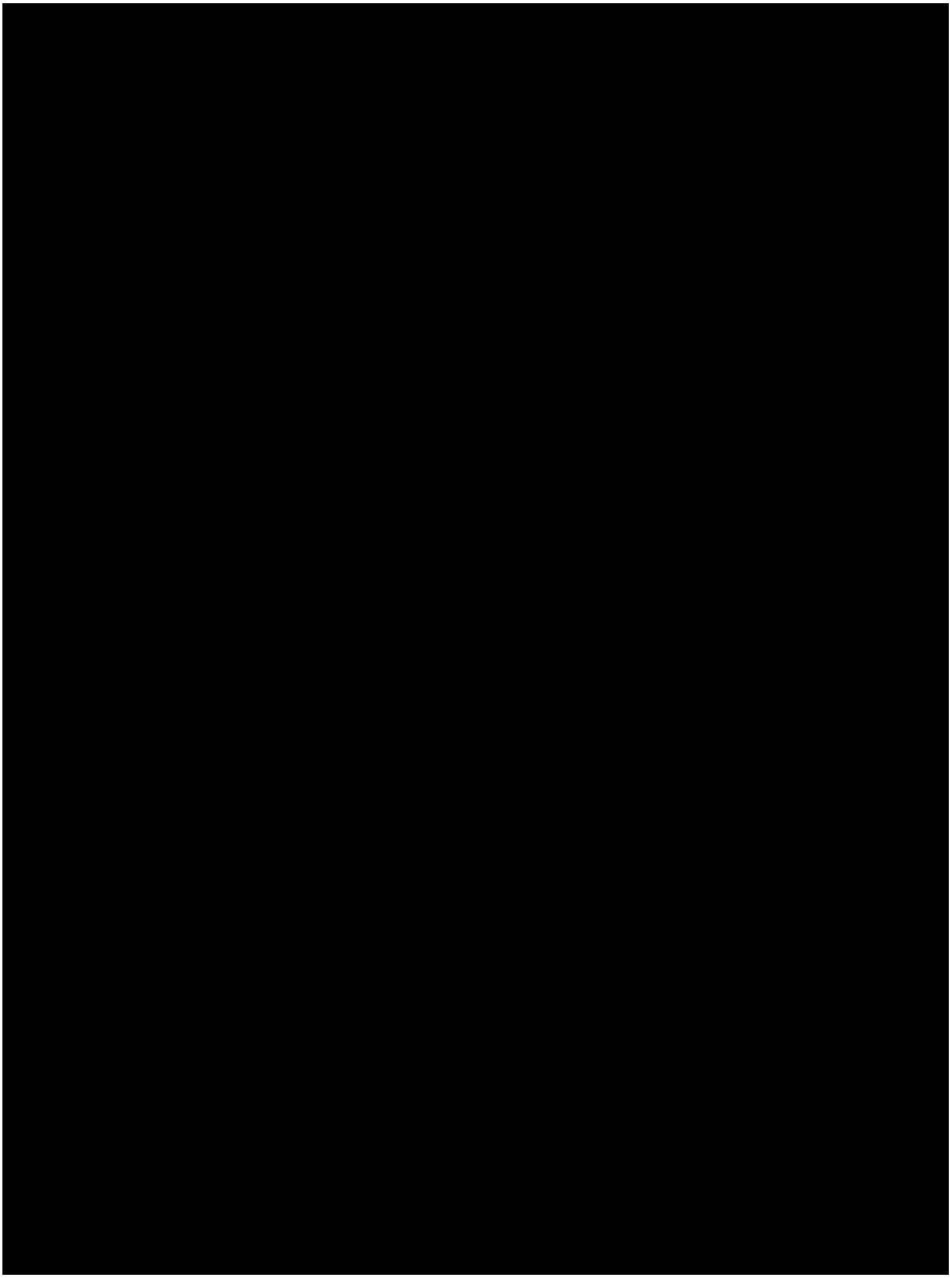
49. Hess DC, Hoda MN, Khan MB. Humoral mediators of remote ischemic conditioning: important role of eNOS/NO/nitrite. *Brain Edema XVI*: Springer; 2016:45-48.
50. Cherry-Allen KM, Gidday JM, Lee J-M, Hershey T, Lang CE. Remote limb ischemic conditioning enhances motor learning in healthy humans. *Journal of neurophysiology.* 2015;113(10):3708-3719.
51. Meng R, Ding Y, Asmaro K, et al. Ischemic conditioning is safe and effective for octo-and nonagenarians in stroke prevention and treatment. *Neurotherapeutics.* 2015;12(3):667-677.
52. Cornelissen V, Smart N. Exercise Training for Blood Pressure: A Systematic Review and Meta-analysis. *Journal of the American Heart Association.* 2013;2(1).
53. Carlson DJ, Dieberg G, Hess NC, Millar PJ, Smart NA. Isometric exercise training for blood pressure management: a systematic review and meta-analysis. Paper presented at: Mayo Clinic Proceedings2014.
54. McGowan CL, Levy AS, Millar PJ, et al. Acute vascular responses to isometric handgrip exercise and effects of training in persons medicated for hypertension. *American Journal of Physiology-Heart and Circulatory Physiology.* 2006;291(4):H1797-H1802.
55. McGowan CL, Visocchi A, Faulkner M, et al. Isometric handgrip training improves local flow-mediated dilation in medicated hypertensives. *European journal of applied physiology.* 2006;98(4):355-362.
56. Stiller-Moldovan C, Kenno K, McGowan CL. Effects of isometric handgrip training on blood pressure (resting and 24 h ambulatory) and heart rate variability in medicated hypertensive patients. *Blood Pressure Monitoring.* 2012;17(2):55-61.
57. Wong GW, Laugerotte A, Wright JM. Blood pressure lowering efficacy of non-selective beta blockers for primary hypertension. *The Cochrane Library.* 2008.
58. Cabot PJ, Carter L, Gaiddon C, et al. Immune cell-derived beta-endorphin. Production, release, and control of inflammatory pain in rats. *Journal of Clinical Investigation.* 1997;100(1):142.
59. Pedersen BK, Hoffman-Goetz L. Exercise and the immune system: regulation, integration, and adaptation. *Physiological reviews.* 2000;80(3):1055-1081.
60. Davidge ST. Prostaglandin H synthase and vascular function. *Circulation research.* 2001;89(8):650-660.

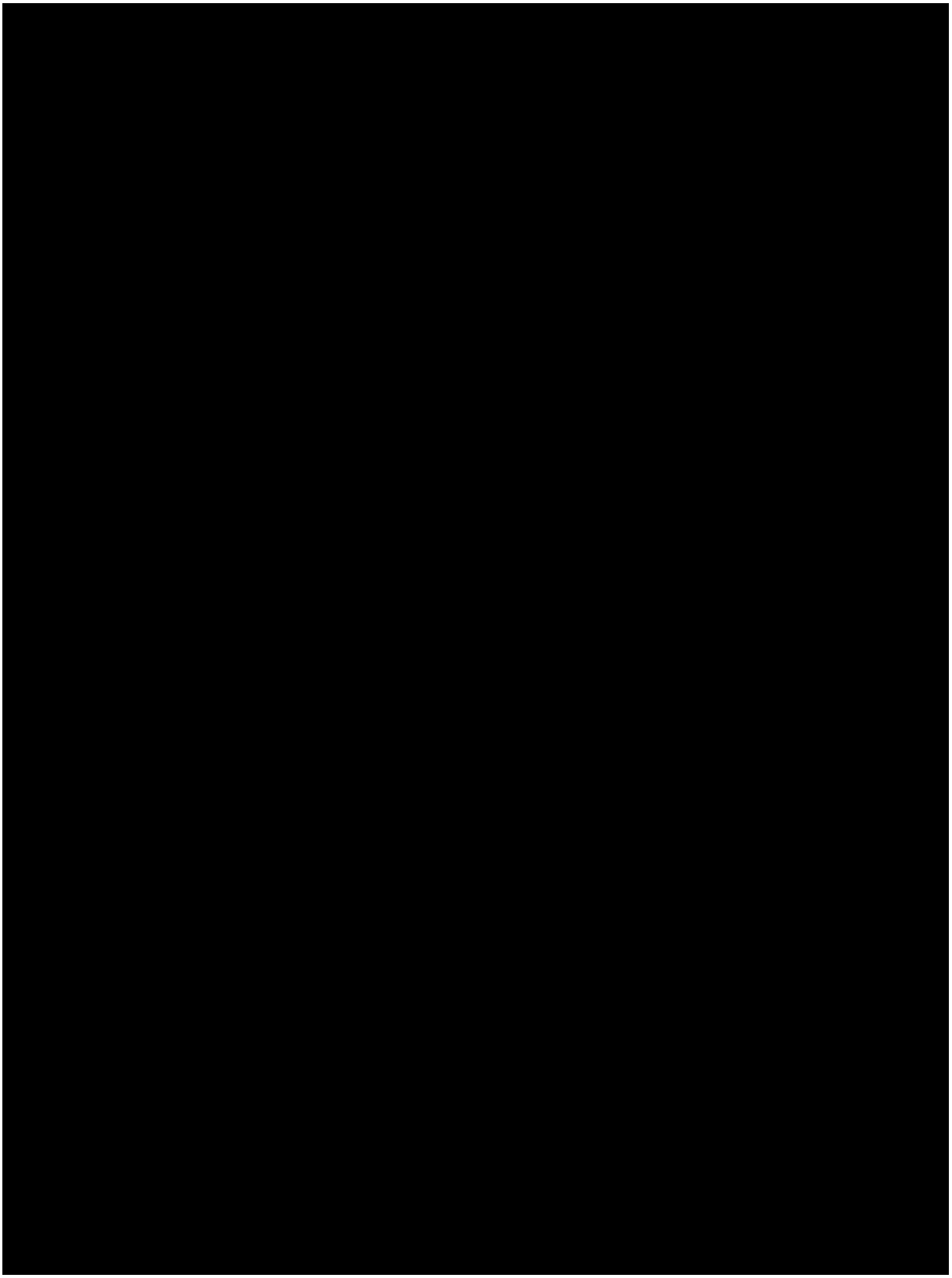
61. Wang T, Zhou Y, Chen X, Zhu A. Putative role of ischemic postconditioning in a rat model of limb ischemia and reperfusion: involvement of hypoxia-inducible factor-1? expression. *Brazilian Journal of Medical and Biological Research.* 2014;47(9):738-745.
62. Barnes WS. The relationship between maximum isometric strength and intramuscular circulatory occlusion. *Ergonomics.* Apr 1980;23(4):351-357.
63. Lin S, Lu X, Chen S, et al. Human coronary collateral recruitment is facilitated by isometric exercise during acute coronary occlusion. *Journal of rehabilitation medicine.* 2012;44(8):691-695.
64. Olher RdRV, Bocalini DS, Bacurau RF, et al. Isometric handgrip does not elicit cardiovascular overload or post-exercise hypotension in hypertensive older women. *Clinical interventions in aging.* 2013;8:649.
65. Gibala MJ, Little JP, MacDonald MJ, Hawley JA. Physiological adaptations to low-volume, high-intensity interval training in health and disease. *The Journal of physiology.* 2012;590(5):1077-1084.

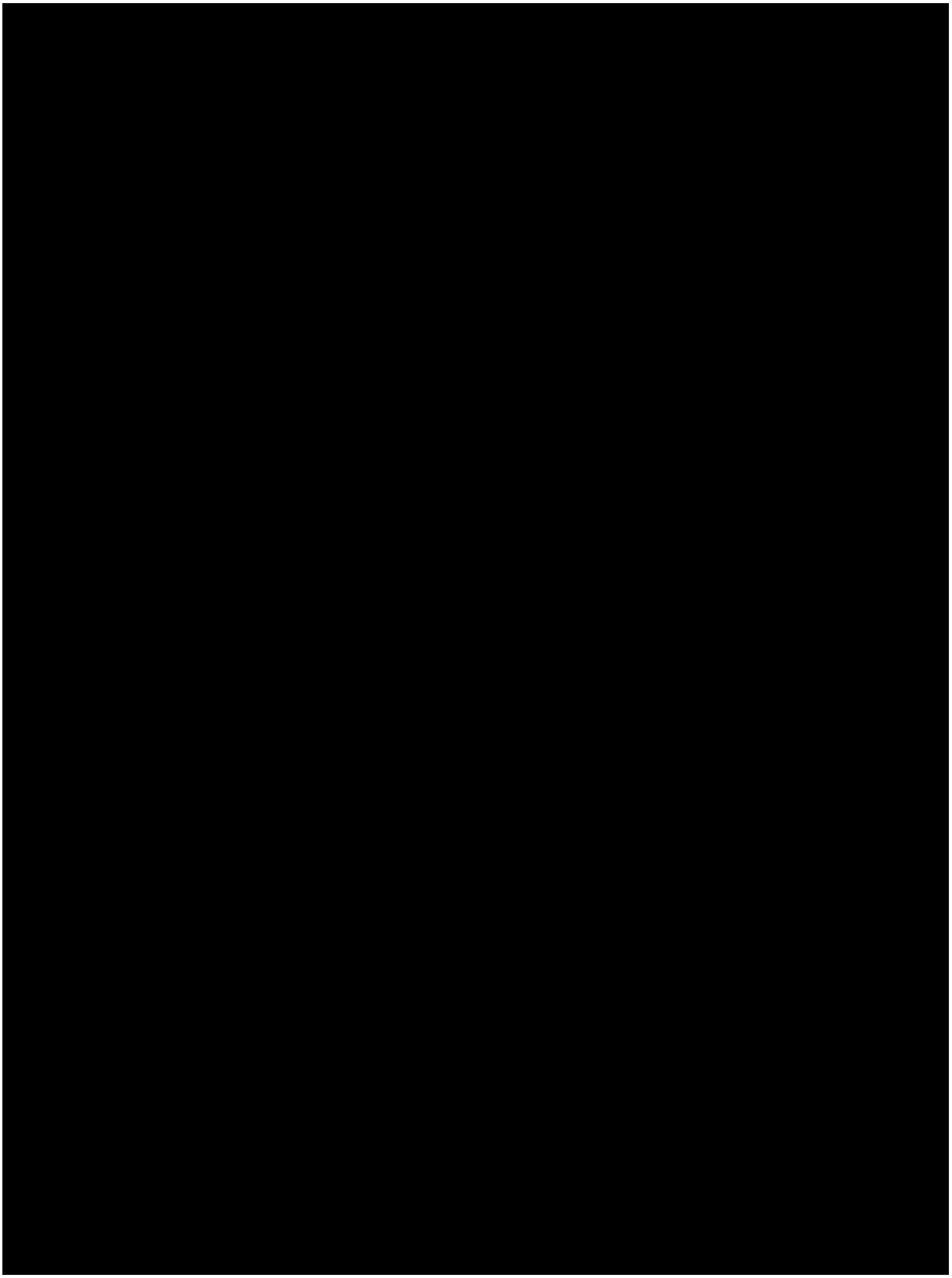
Appendix A: Published articles contributed to as a co-author

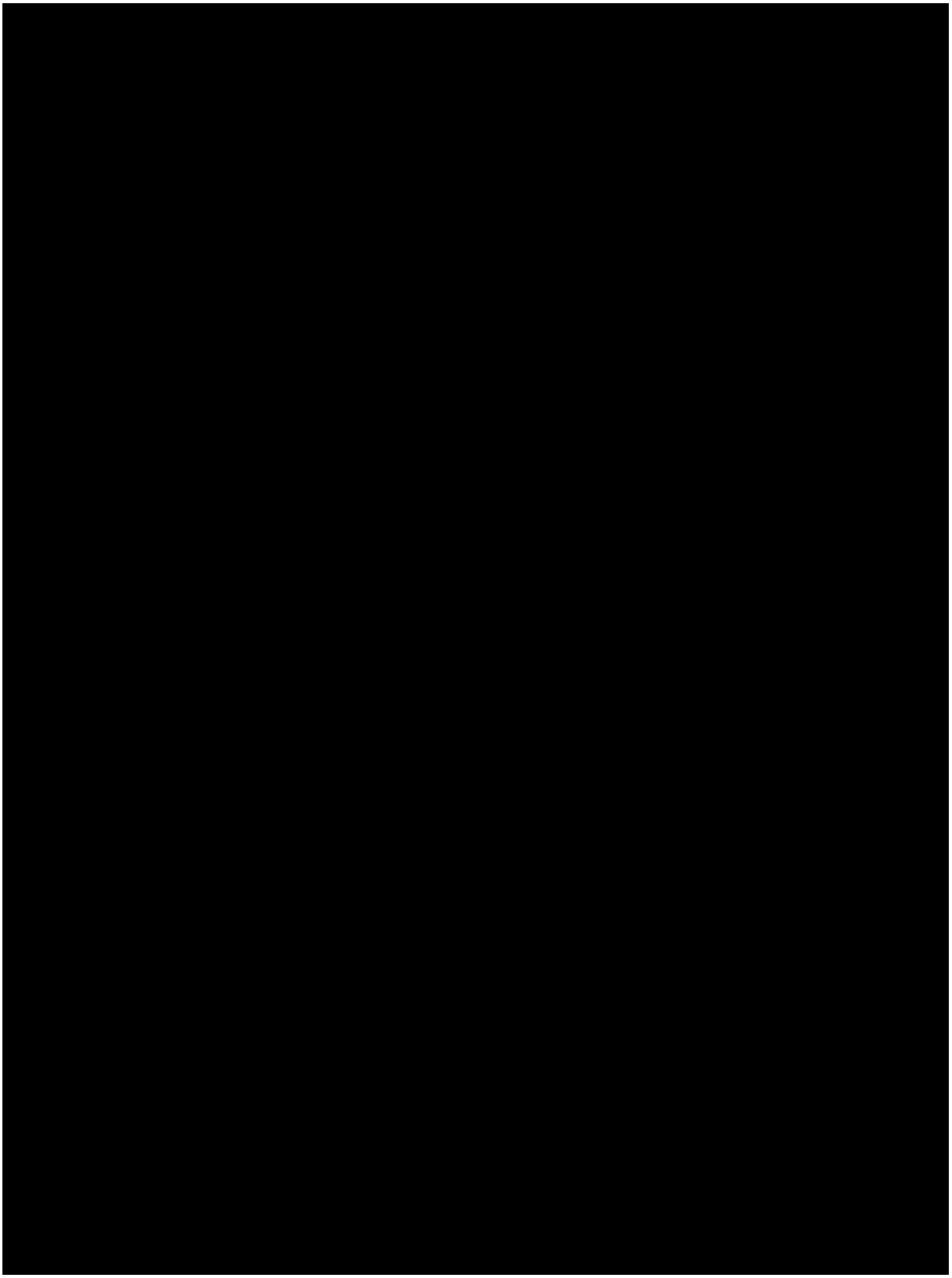
The following two published articles did not contribute to the main body of my doctoral work; however, they review and discuss the antihypertensive effects of isometric exercise training and this was relevant to my dissertation research topic.

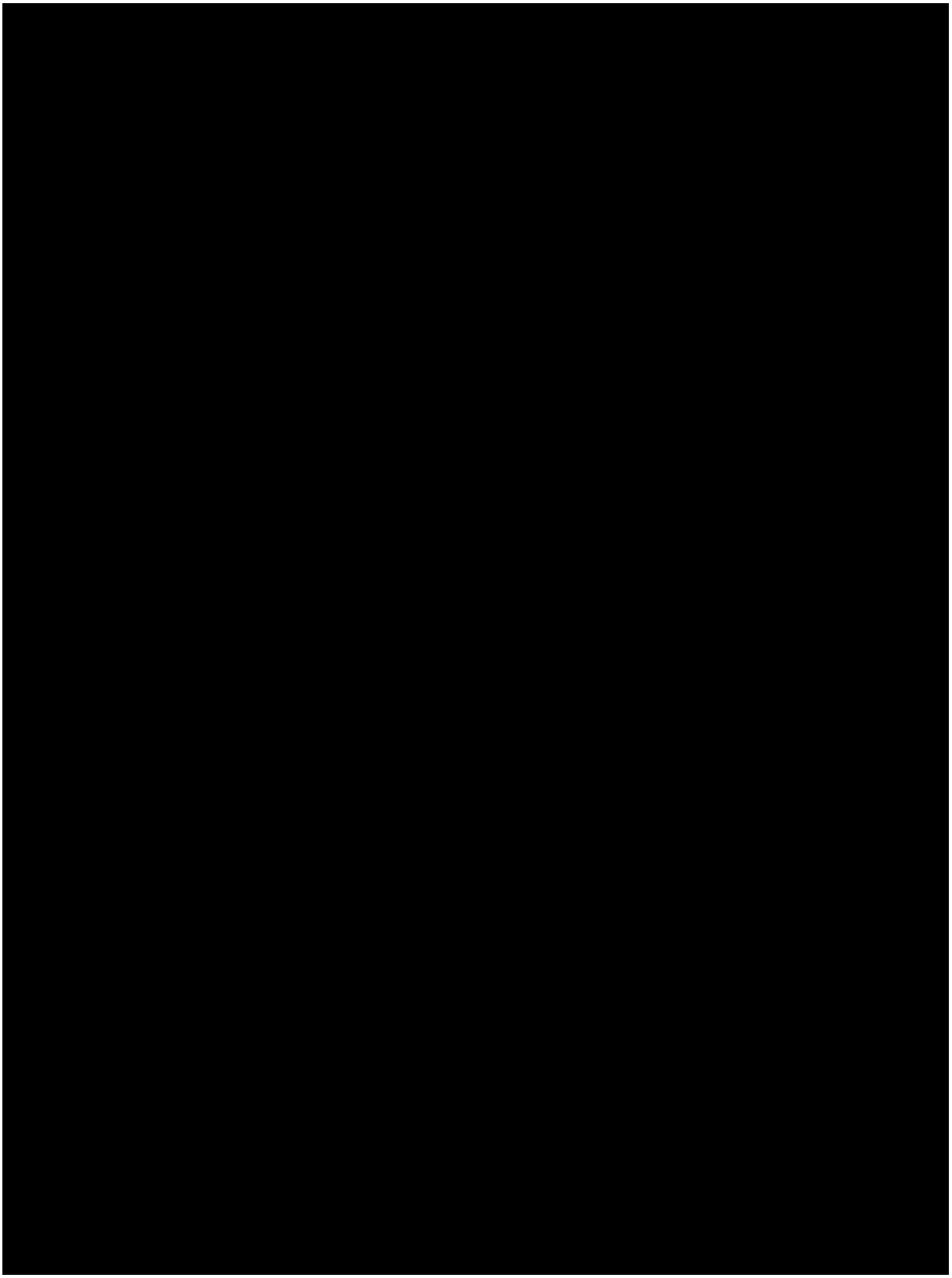


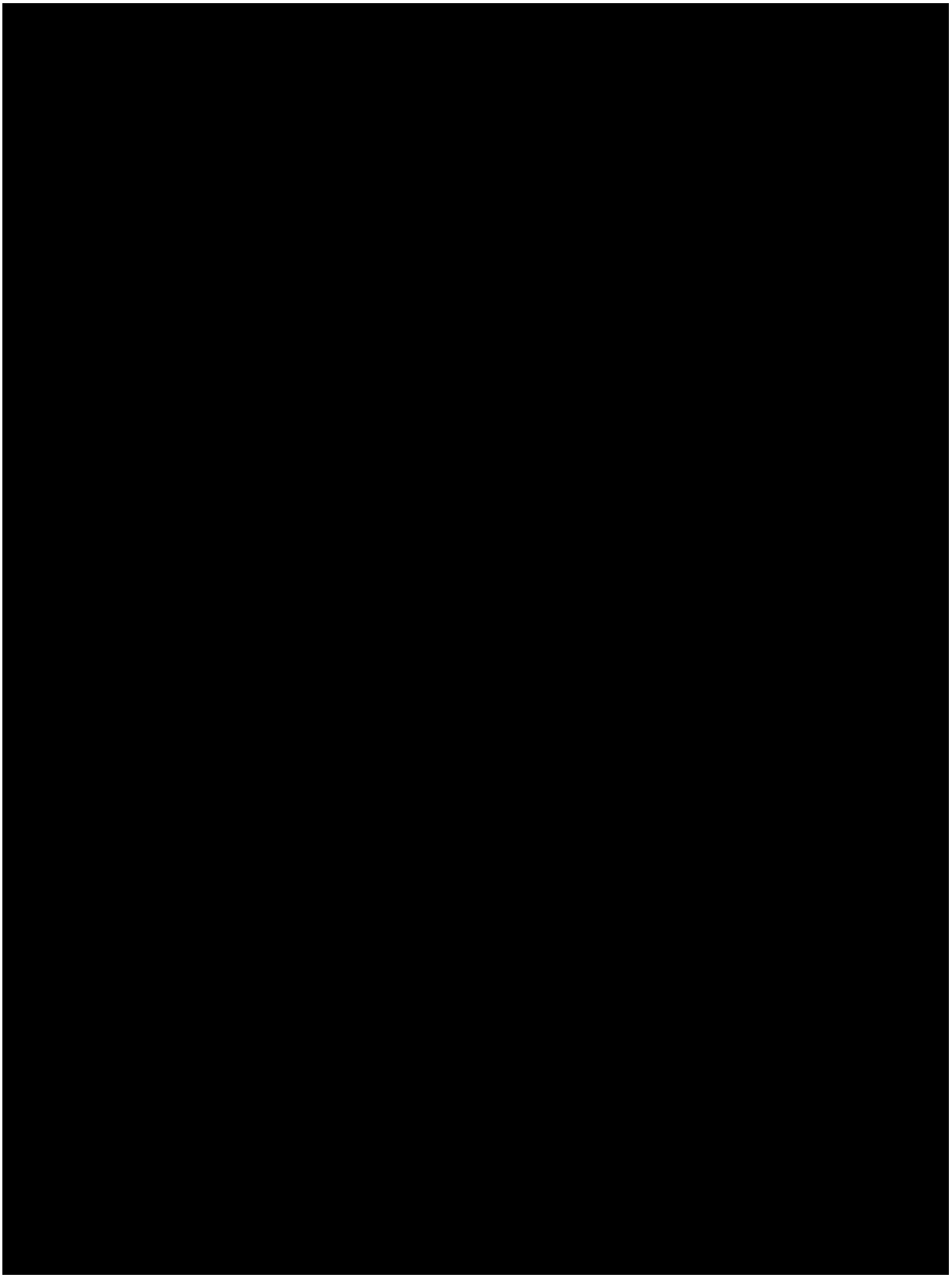


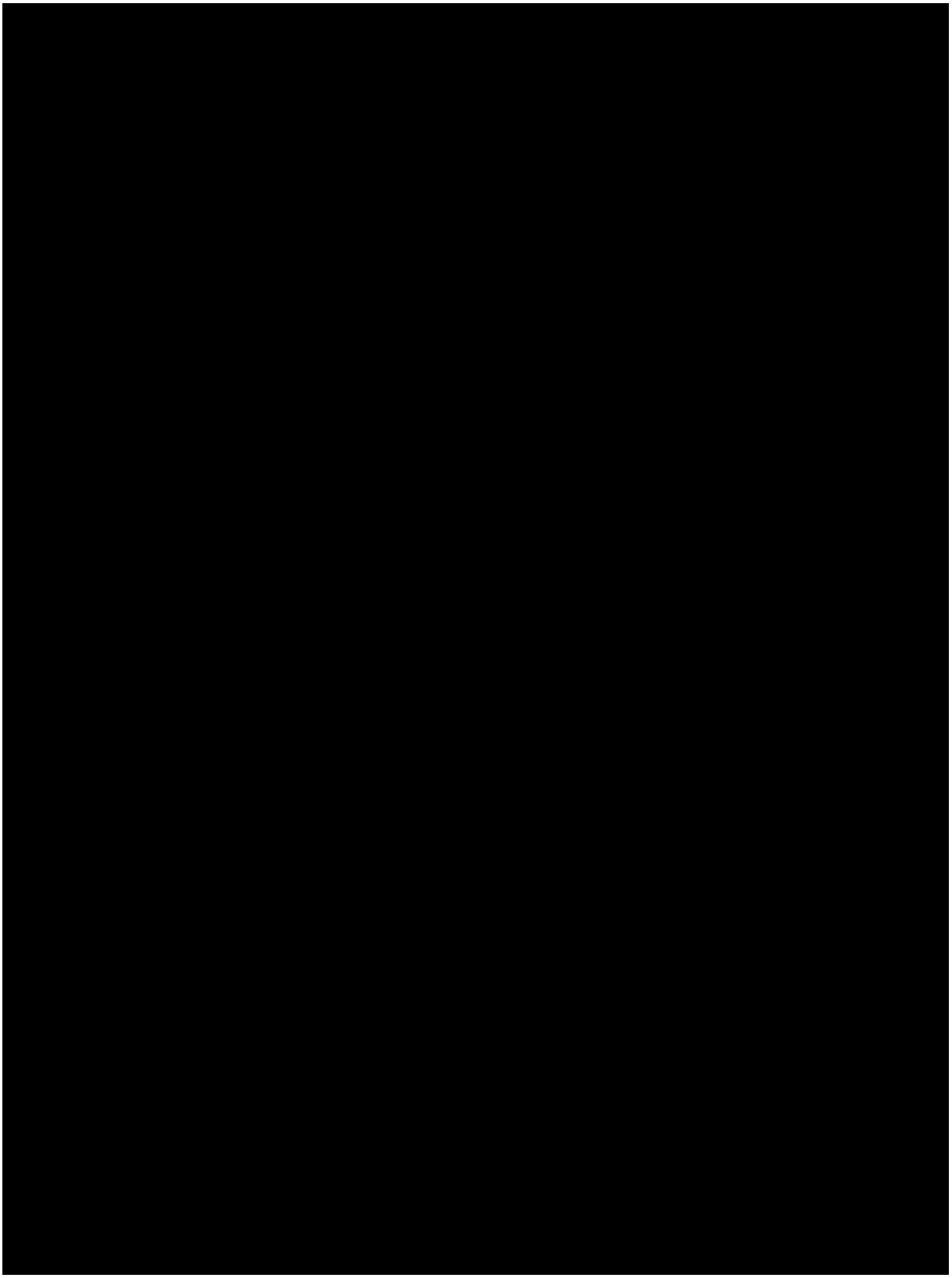


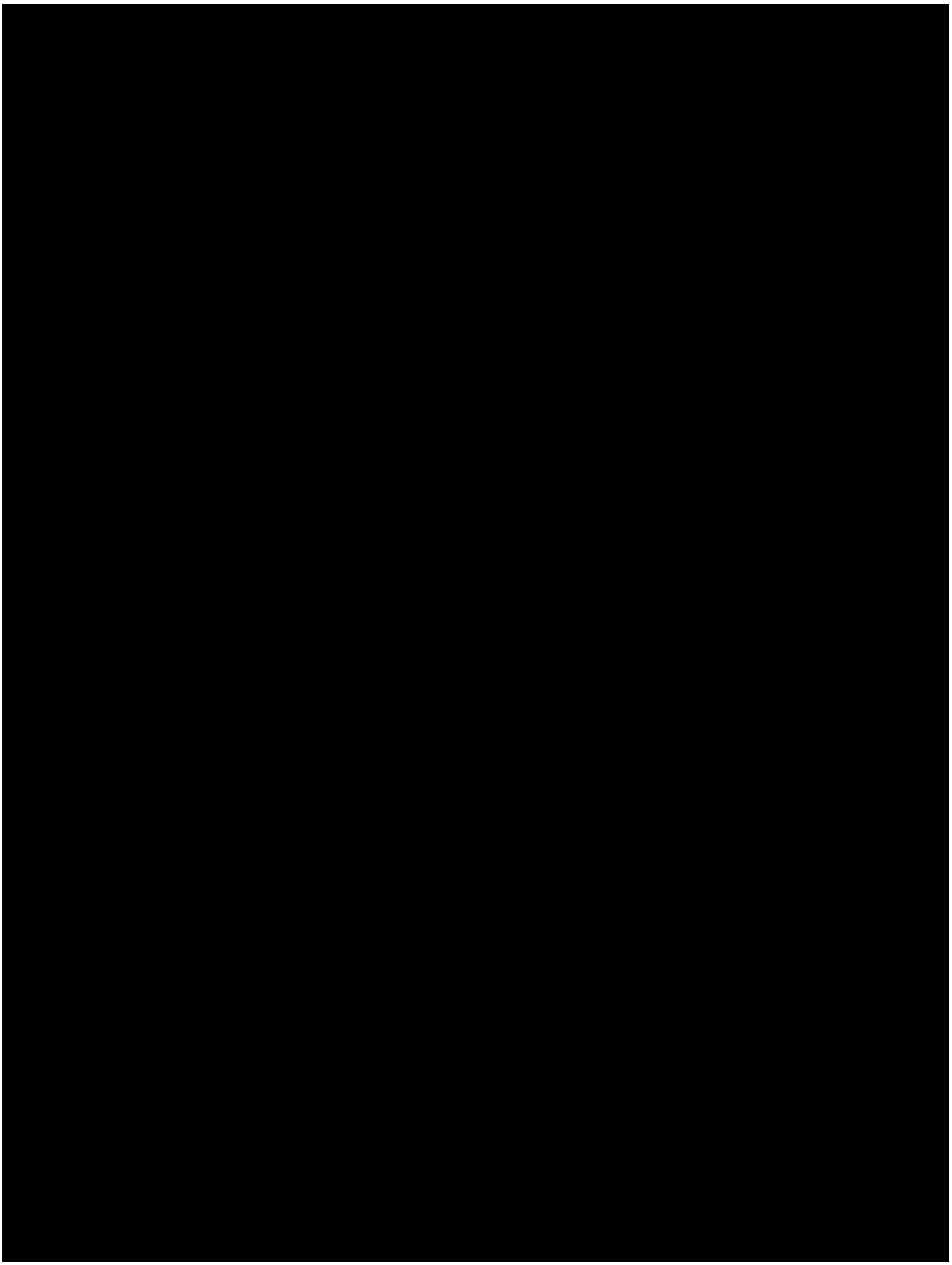


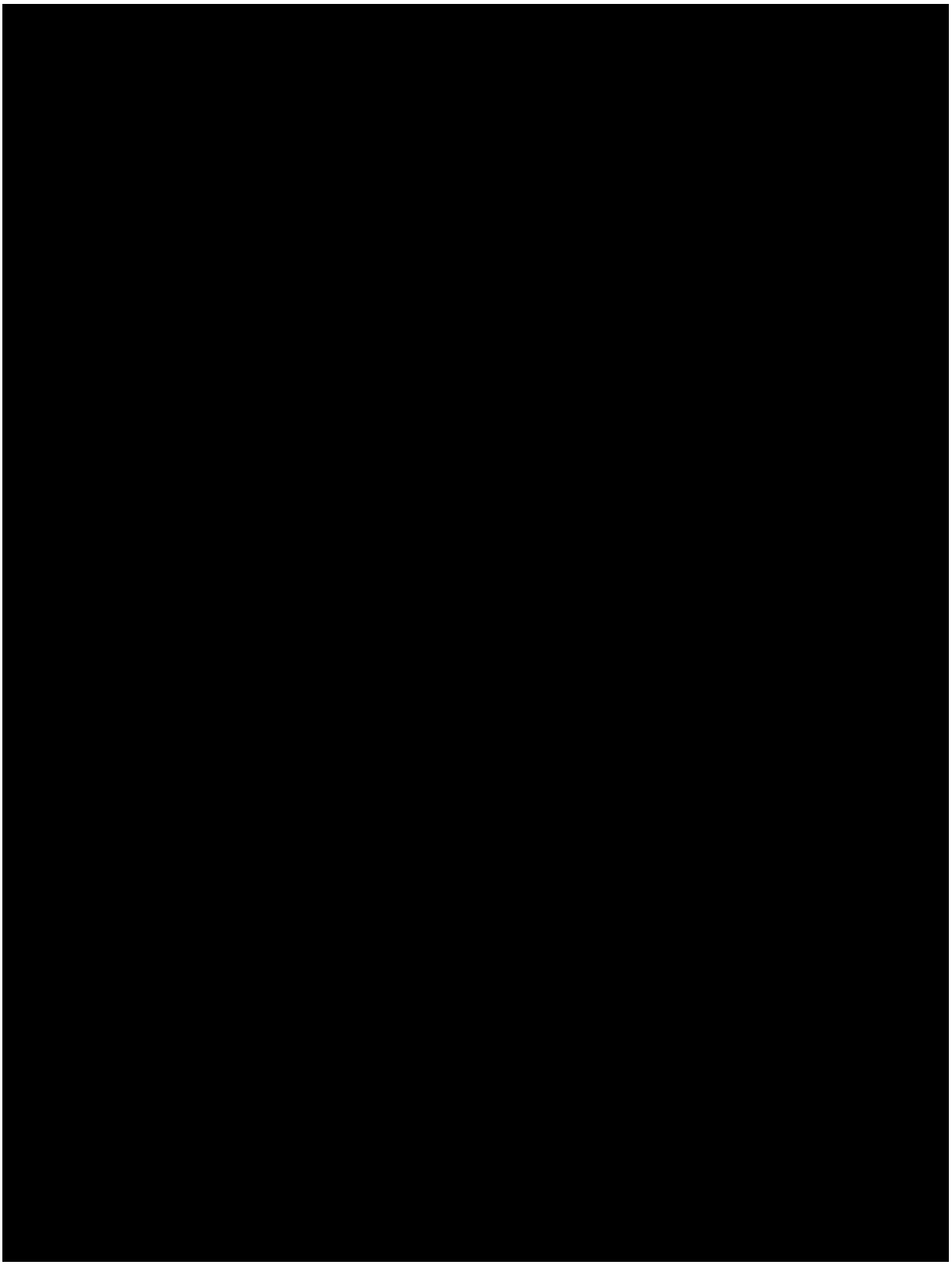


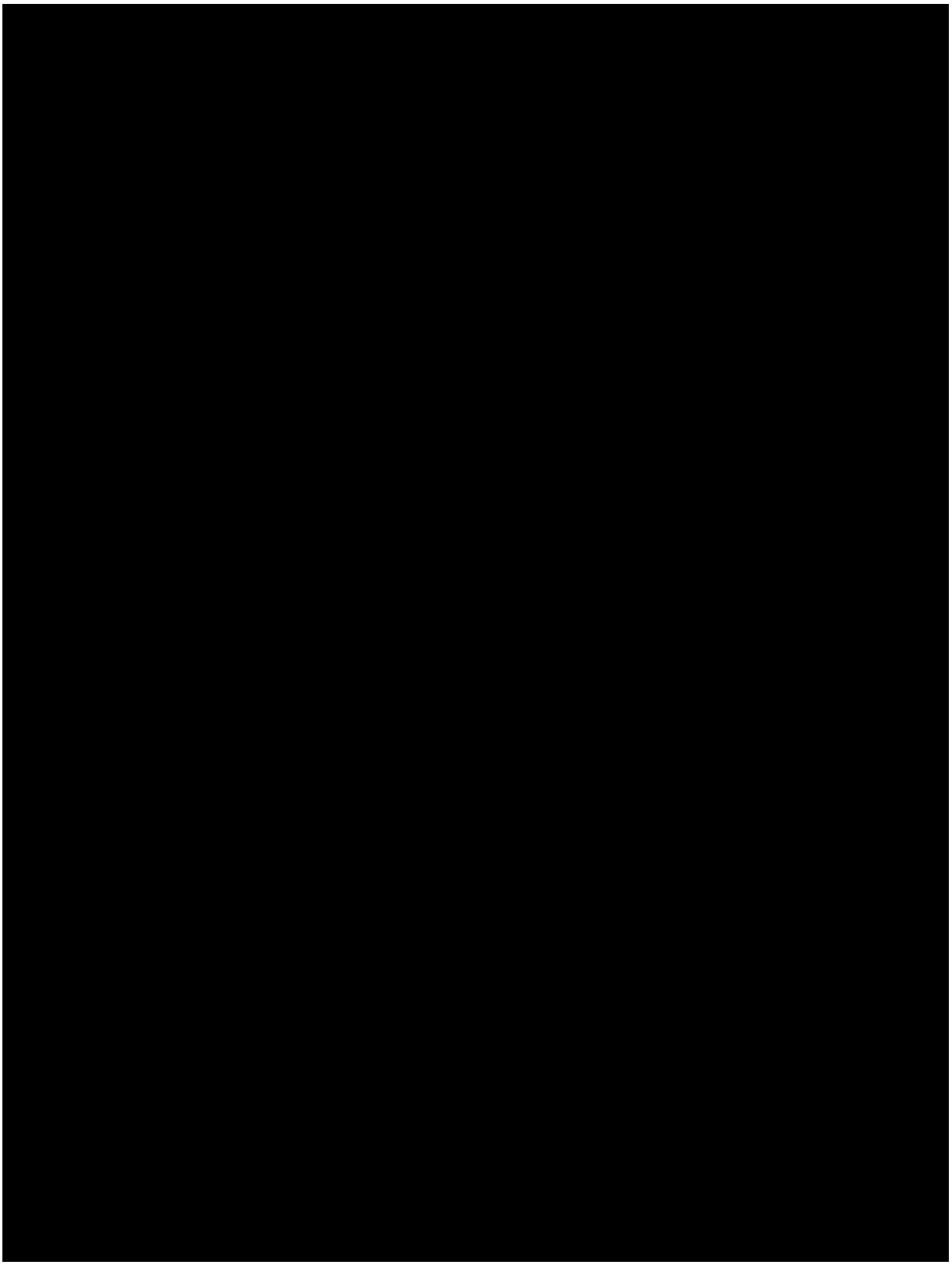


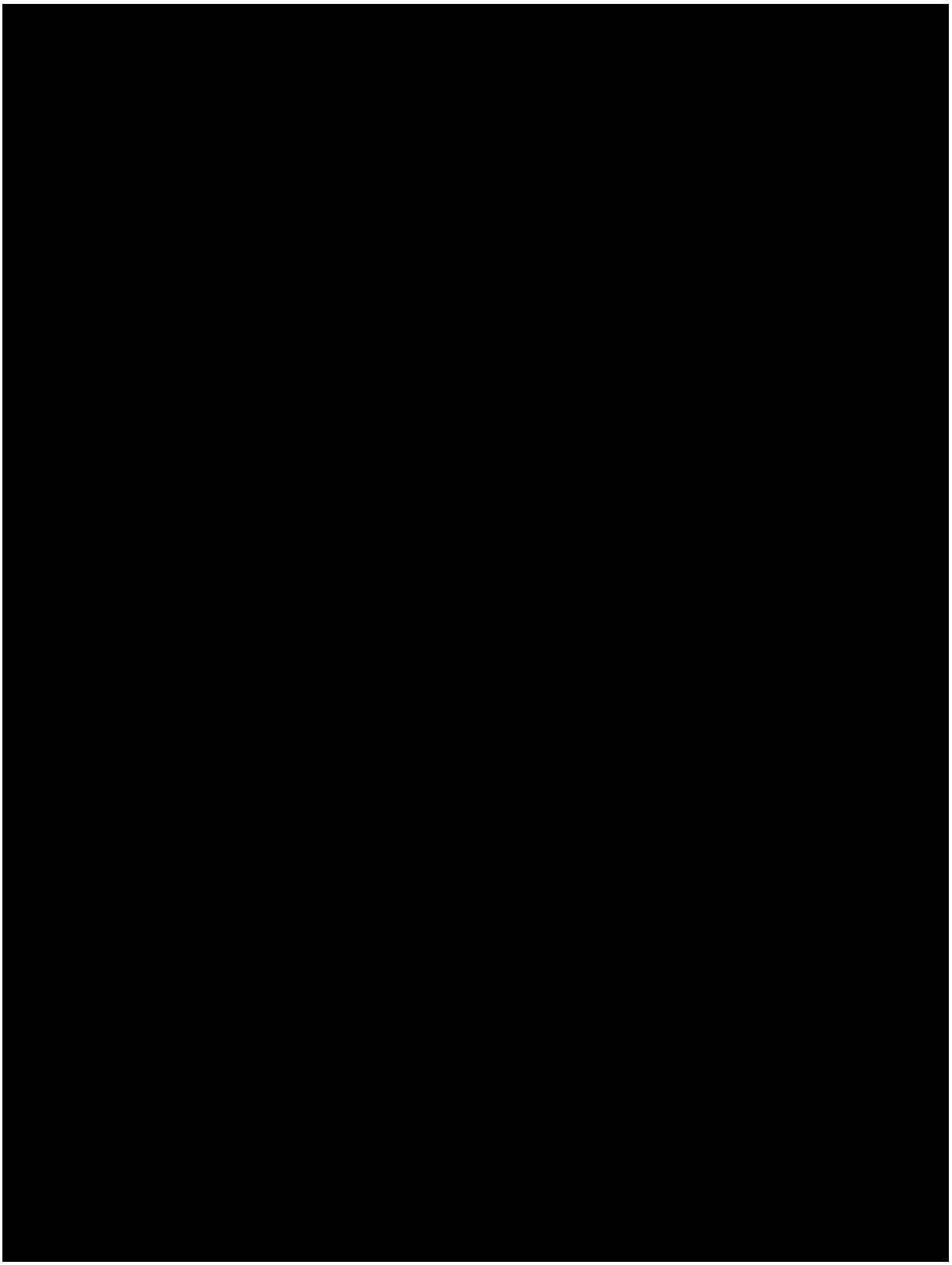


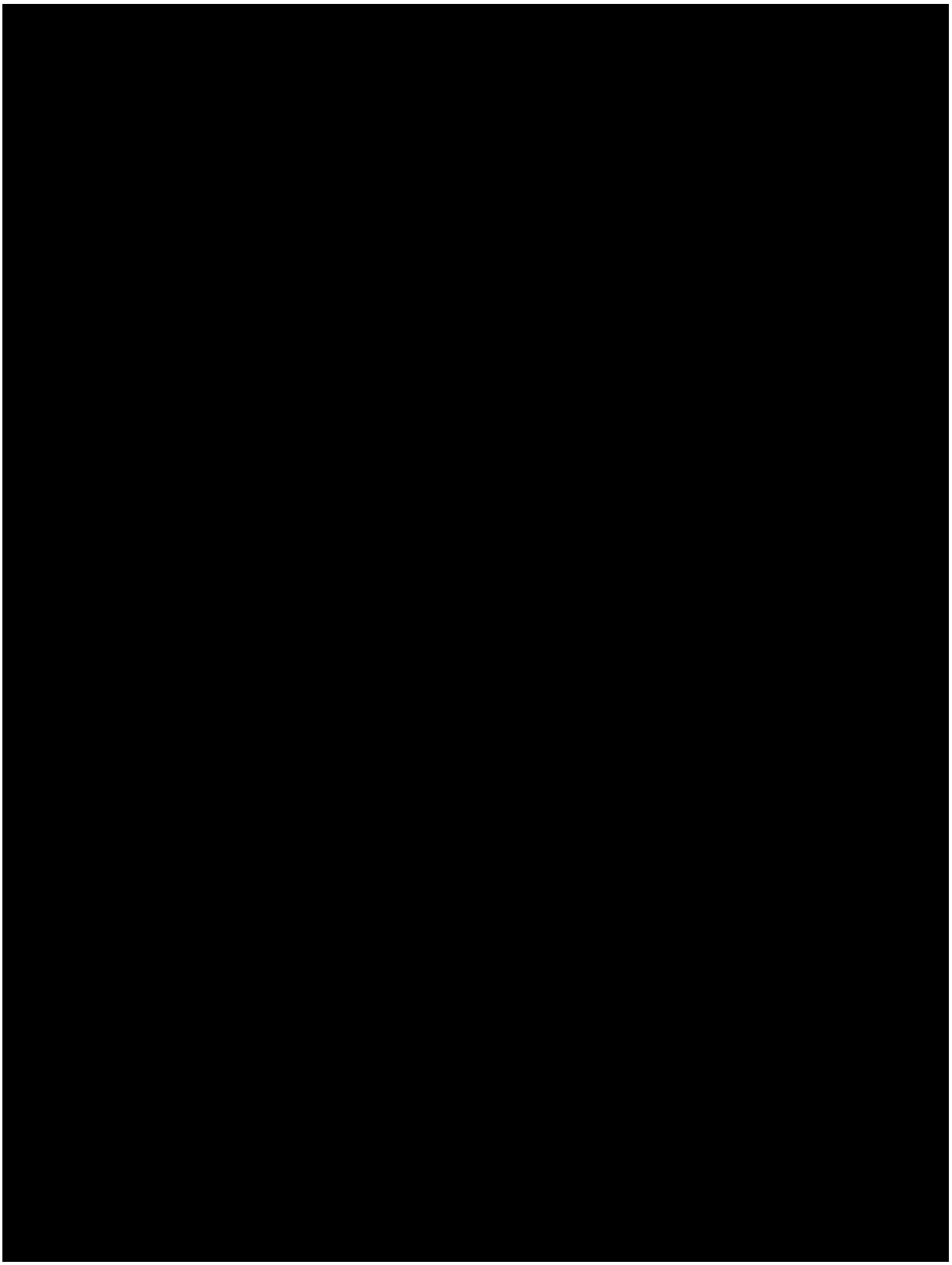


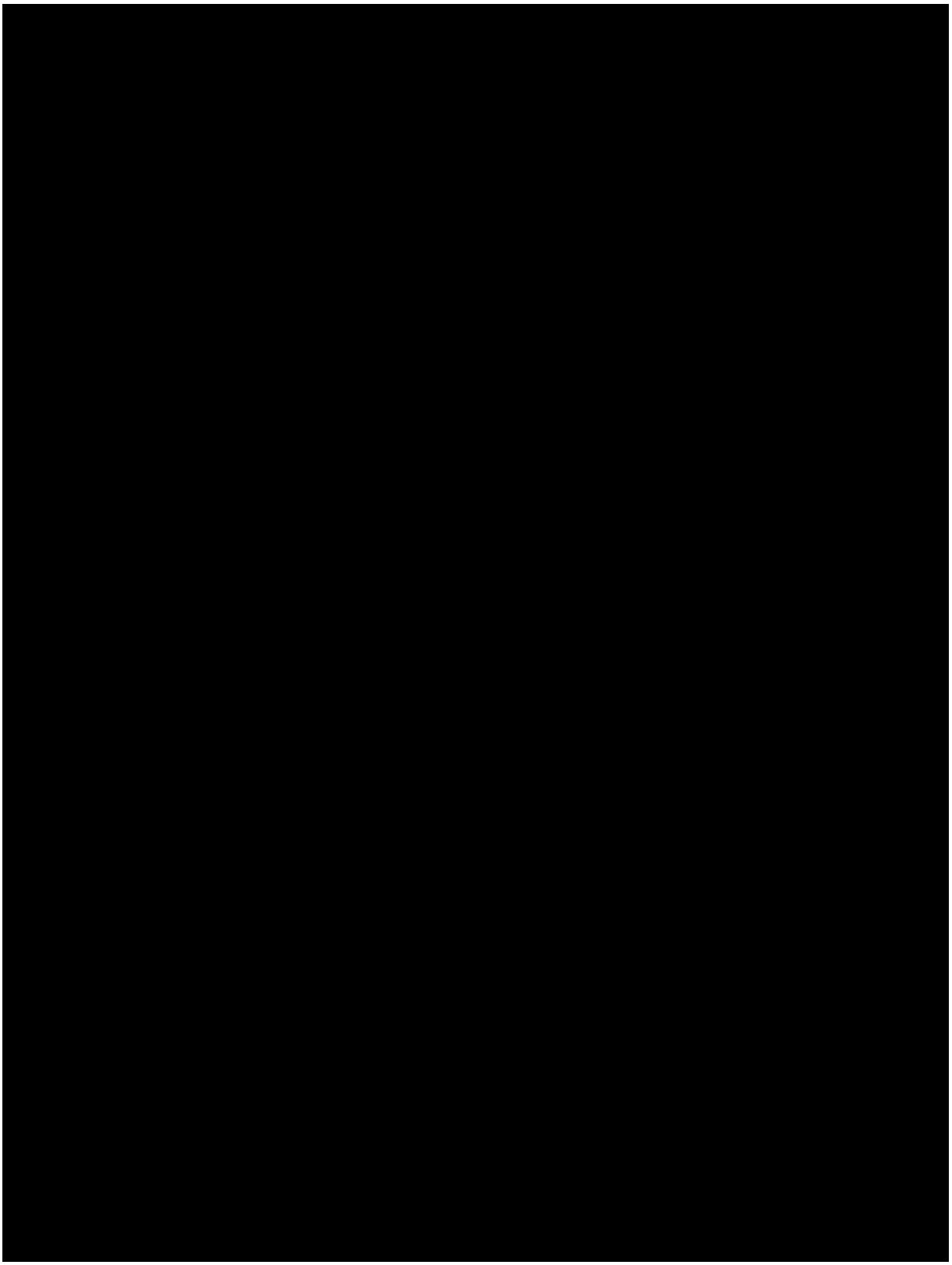












Appendix B: Meta-analysis supplementary files

Figure B1. PUB MED SEARCH STRATEGY

Sensitive/broad search

#11 Search **(Exercise/Broad[filter]) AND (#8)**

#8 Search **#6 AND #7**

#7 Search **#5 OR #6**

#6 Search **#1 OR #2 OR #3 OR #4**

#5 Search **(((((((peak VO2[Text Word]) OR cognitive performance [MeSH Terms]) OR neurocognitive performance [Text Word]) OR executive function [Text Word]) OR memory [Text Word]) OR depression [MeSH Terms]) OR depression[Text Word]) OR memory [MeSH Terms])**

#4 Search **(((exercise[MeSH Terms]) OR exercise therapy [MeSH Terms]) OR aerobic exercise[Text Word]) OR exercise training[Text Word]**

#3 Search **((physical activity [MeSH Terms]) OR physical training [Text Word])**

#2 Search **((((exercise [MeSH Terms]) OR exercise training [Text Word])**

#1 Search **(((((dementia [MeSH Terms]) OR cognitive impairment[Text Word]) OR mild cognitive impairment [Text Word] OR Alzheimer's disease [Text word])**

Table B1. Excluded randomized controlled trials.

Elderly men and women with mild cognitive impairment, Alzheimer's disease, or dementia

Baker et al., 2010 [15]	Incomplete data to allow data pooling analysis
Conradsson 2010 [16]	Outcomes not relevant to this review
Davis et al., 2013 [17]	Non-demented participants
Eggermont 2009b [18]	Outcomes not relevant to this review
Fallah et al., 2013 [19]	Non-demented participants
Frances 1997 [20]	Outcomes not relevant to this review
Holliman 2001 [21]	Outcomes not relevant to this review
Hwang 2010 [22]	Conference Paper
Liu-Ambrose et al., 2012 [23]	Incomplete data to allow data pooling analysis
McMurdo et al., 1994 [24]	Incomplete data to allow data pooling analysis
McMurdo et al., 2000 [25]	Incomplete data to allow data pooling analysis
Nagamatsu et al., 2012 [26]	Incomplete data to allow data pooling analysis
Rolland 2007 [27]	Outcomes not relevant to this review
Santana-Sosa et al., 2008 [28]	Outcomes not relevant to this review
Scherder et al., 2005 [29]	Incomplete data to allow data pooling analysis
Steinberg 2009 [30]	Outcomes not relevant to this review
Van Uffelen et al., 2008 [31]	Incomplete data to allow data pooling analysis
Williams et al., 2008 [32]	Outcomes not relevant to this review
Williamson et al., 2009 [33]	Incomplete data to allow data pooling analysis
Yaguez et al., 2010 [34]	Incomplete data to allow data pooling analysis
Yerokhin et al., 2012 [35]	Control group cohort was healthy

Table B2. Included randomized controlled trials.

Each with an exercise training component in elderly men and women with varying degrees of cognitive impairment and/or Alzheimer's disease

Study	**Intervention**	**Group 1**	**Group 2**	**Outcomes**
Brown et al., 2009 [1]	Resistance & balance training	Flexibility & relaxation training	Control (sedentary)	WAIS-R similarities & arithmetic sub tests
Cheng et al., 2013 [2]	Tai Chi	Mahjong (not included in this analysis)	Control (simple handicraft)	MMSE
Christofoletti 2008 [3]	Physiotherapy	Physiotherapy supervised (intervention group)	Control (Education)	MMSE, memory, clock drawing tests
Dorner et al., 2007 [4]	Resistance & balance training	Control (sedentary)		MMSE
Eggermont 2009a [5]	Walked for 30 min, 5 days a week, for 6 weeks	Control (sedentary)		Verbal fluency (letter 7 Category), digit span (forward & back), delayed and picture recall
Kemoun et al., 2010 [6]	Multi-component training, including aerobic (60% to 70% peak VO_2)	Control (sedentary)		ERFC
Lam et al., 2010 [7]	Tai Chi	Control (stretching & toning)		MMSE, CDR, ADAS-Cog CVFT, delay recall VSF, VSB, Trails A
Lautenschlager et al., 2008 [8]	Walk, strength, or other aerobic exercise of choice	Control (sedentary)		ADAS- cog, CDR-sum of boxes, word list delayed recall

Stevens et al., 2006 [9]	Multi-component exercise accompanied by music	Control (social visits)		Clock drawing test
Suzuki et al., 2012 [10]	Aerobic 60% peak VO_2, strength, postural bal	Control (sedentary)		MMSE, WMS-LM I, LVFT
Van de Winckel et al., 2004 [11]	Music-based, seated, dance therapy	Control (social visits)		MMSE & ADS 6
Varela et al., 2011 [12]	Cycling 40% peak VO_2, 5 min stretching	Cycling 60% peak VO_2 & 5 min stretching	Control (handicrafts, cards, reading, etc.)	MMSE
Venturelli et al., 2011 [13]	Moderate intensity walking	Control (sedentary)		MMSE
Vreugdenhill 2012 [14]	Four months supervised walking	Usual treatment		MMSE & ADAS

Abbreviations: WAIS-R (Wechsler adult intelligent scale- revised), MMSE (Mini mental state exam), ERFC (Rapid evaluation of cognitive function- French version), ADAS-cog (Alzheimer's Disease Assessment Scale- cognitive subscale), DSST (Digit symbol substitution tests), CDR-sum of boxes (Clinical dementia rating scale– sum of boxes), CVFT (Verbal fluency test), VSF (Visual span forward), VSB (Visual span backward), WMS-LM I (Logical Memory subtest of the Wechsler memory scale- revised - immediate story recall), LVFT (Letter verbal fluency test)

References of included and excluded studies

[1] Brown AK, Liu-Ambrose, T, Tate, R, Lord, SR. The effect of group-based exercise on cognitive performance and mood in seniors residing in intermediate care and self-care retirement facilities: a randomised controlled trial. Br J Sports Med. 2009 Aug;43(8):608-14.
[2] Cheng ST, Chow PK, Song YQ, Yu EC, Chan AC, Lee TM, et al. Mental and physical activities delay cognitive decline in older persons with dementia. Am J Geriatr Psychiatry. 2014 Jan;22(1):63-74.
[3] Christofoletti G, Oliani MM, Gobbi S, Stella F, Bucken Gobbi LT, Renato Canineu P. A controlled clinical trial on the effects of motor intervention on balance and cognition in institutionalized elderly patients with dementia. Clin Rehabil. 2008 Jul:22(7):618-26.
[4] Dorner T, Kranz A, Zettl-Wiedner K, Ludwig C, Rieder A, Gisinger C. The effect of structured strength and balance training on cognitive function in frail, cognitive impaired elderly long-term care residents. Aging Clin Exp Res2007 Oct;19(5):400-5.
[5] Eggermont LH, Swaab DF, Hol EM, Scherder EJ. Walking the line: a randomised trial on the effects of a short term walking programme on cognition in dementia. J Neurol Neurosurg Psychiatry. 2009 Jul;80(7):802-4.
[6] Kemoun G, Thibaud M, Roumagne N, Carette P, Albinet C, Toussaint L, et al. Effects of a physical training programme on cognitive function and walking efficiency in elderly persons with dementia. Dement Geriatr Cogn Disord. 2010;29(2):109-14.
[7] Lam LC, Chau RC, Wong BM, Fung AW, Lui VW, Tam CC, et al. Interim follow-up of a randomized controlled trial comparing Chinese style mind body (Tai Chi) and stretching exercises on cognitive function in subjects at risk of progressive cognitive decline. Int J Geriatr Psychiatry. 2011 Jul;26(7):733-40.
[8] Lautenschlager NT, Cox KL, Flicker L, Foster JK, van Bockxmeer FM, Xiao J, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. JAMA. 2008 Sep 3;300(9):1027-37.
[9] Stevens J, Killeen M. A randomised controlled trial testing the impact of exercise on cognitive symptoms and disability of residents with dementia. Contemp Nurse. 2006 Feb-Mar;21(1):32-40.
[10] Suzuki T, Shimada H, Makizako H, Doi T, Yoshida D, Tsutsumimoto K, et al. Effects of multicomponent exercise on cognitive function in older adults with amnestic mild cognitive impairment: a randomized controlled trial. BMC Neurol. 2012 Oct 31;12:128.
[11] van de Winckel A, Feys H, de Weerdt W, Dom R. Cognitive and behavioural effects of music-based exercises in patients with dementia. Clin Rehabil. 2004 May;18(3):253-60.
[12] Varela S, Ayan C, Cancela JM, Martin V. Effects of two different intensities of aerobic exercise on elderly people with mild cognitive impairment: a randomized pilot study. Clin Rehabil. 2012 May;26(5):442-50.
[13] Venturelli M, Scarsini R, Schena F. Six-month walking program changes cognitive and ADL performance in patients with Alzheimer. Am J Alzheimers Dis Other Demen. 2011 Aug;26(5):381-8.
[14] Vreugdenhil A, Cannell J, Davies A, Razay G. A community-based exercise programme to improve functional ability in people with Alzheimer's disease: a randomized controlled trial. Scand J Caring Sci. 2012 Mar;26(1):12-9.
[15] Baker LD, Frank LL, Foster-Schubert K, Green PS, Wilkinson CW, McTiernan A, et al. Effects of aerobic exercise on mild cognitive impairment: a controlled trial. Arch Neurol. 2010 Jan;67(1):71-9.
[16] Conradsson M, Littbrand H, Lindelof N, Gustafson Y, Rosendahl E. Effects of a high-intensity functional exercise programme on depressive symptoms and psychological well-being among older people living in residential care facilities: a cluster-randomized controlled trial. Aging Ment Health. 2010;14(5):565-76.
[17] Davis JC, Bryan S, Marra CA, Sharma D, Chan A, Beattie BL, et al. An economic evaluation of resistance training and aerobic training versus balance and toning exercises in older adults with mild cognitive impairment. PLoS One. 2013;8(5):e63031.
[18] Eggermont LH, Knol DL, Hol EM, Swaab DF, Scherder EJ. Hand motor activity, cognition, mood, and the rest-activity rhythm in dementia: a clustered RCT. Behav Brain Res. 196, 2009 Jan;2:271-8.
[19] Fallah N, Hsu CL, Bolandzadeh N, Davis J, Beattie BL, Graf P, et al. A multistate model of cognitive dynamics in relation to resistance training: the contribution of baseline function. Ann Epidemiol. 2013 Aug;23(8):463-8.
[20] Frances TSJ, Butler FR. The effects of regular exercise on muscle strength and functional abilities of late stage Alzheimer's residents. Am J Alzheimer's Dis. 1997;12(3):122-7.
[21] Holliman DC OU, Forney JP. Developing an interactive physical activity group in a geriatric psychiatry facility. Act Adapt Aging. 2001;26(1):57-69.
[22] Hwang HH CY. The effects of the dance therapy program through rhythmic exercise on cognitive memory performance of the elderly with dementia. Proceedings of the 21st Pan-Asian Congress of Sports and Physical Education. 2010:412-7.

[23] Liu-Ambrose T, Nagamatsu LS, Voss MW, Khan KM, Handy TC. Resistance training and functional plasticity of the aging brain: a 12-month randomized controlled trial. Neurobiol Aging. 2012 Aug;33(8):1690-8.
[24] McMurdo ME, Rennie LM. Improvements in quadriceps strength with regular seated exercise in the institutionalized elderly. Arch Phys Med Rehabil. 1994 May;75(5):600-3.
[25] McMurdo ME, Millar AM, Daly F. A randomized controlled trial of fall prevention strategies in old peoples' homes. Gerontology. 2000 Mar-Apr;46(2):83-7.
[26] Nagamatsu LS, Handy TC, Hsu CL, Voss M, Liu-Ambrose T. Resistance training promotes cognitive and functional brain plasticity in seniors with probable mild cognitive impairment. Arch Intern Med. 1012 Apr 23;172(8):666-8.
[27] Rolland Y, Pillard F, Klapouszczak A, Reynish E, Thomas D, Andrieu S, et al. Exercise program for nursing home residents with Alzheimer's disease: a 1-year randomized, controlled trial. J Am Geriatr Soc. 2007 Feb;55(2):158-65.
[28] Santana-Sosa E, Barriopedro MI, Lopez-Mojares LM, Perez M, Lucia A. Exercise training is beneficial for Alzheimer's patients. Int J Sports Med. 2008 Oct;29(10):845-50.
[29] Scherder EJ, van Paasschen J, Deijen JB, van Der Knokke S, Orlebeke JF, Burgers I, et al. Physical activity and executive functions in the elderly with mild cognitive impairment. Aging Ment Health. 2005 May;9(3):272-80.
[30] Steinberg M, Leoutsakos JM, Podewils LJ, Lyketsos CG. Evaluation of a home-based exercise program in the treatment of Alzheimer's disease: the Maximizing Independence in Dementia (MIND) study. Int J Geriatr Psychiatry. 2009 Jul;24(7):680-5.
[31] van Uffelen JG, Chinapaw MJ, van Mechelen W, Hopman-Rock M. Walking or vitamin B for cognition in older adults with mild cognitive impairment? A randomised controlled trial. Br J Sports Med. 2008 May;42(5):344-51.
[32] Williams CL, Tappen RM. Exercise training for depressed older adults with Alzheimer's disease. Aging Ment Health. 2008 Jan;12(1):72-80.
[33] Williamson JD, Espeland M, Kritchevsky SB, Newman AB, King AC, Pahor M, et al. Changes in cognitive function in a randomized trial of physical activity: results of the lifestyle interventions and independence for elders pilot study. J Gerontol A Biol Sci Med Sci. 2009 Jun;64(6):688-94.
[34] Yaguez L, Shaw KN, Morris R, Matthews D. The effects on cognitive functions of a movement-based intervention in patients with Alzheimer's type dementia: a pilot study. Int J Geriatr Psychiatry. 2011 Feb;26(2):173-81.
[35] Yerokhin V, Anderson-Hanley C, Hogan MJ, Dunnam M, Huber D, Osborne S, et al. Neuropsychological and neurophysiological effects of strengthening exercise for early dementia: a pilot study. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2012;19(3):380-401.

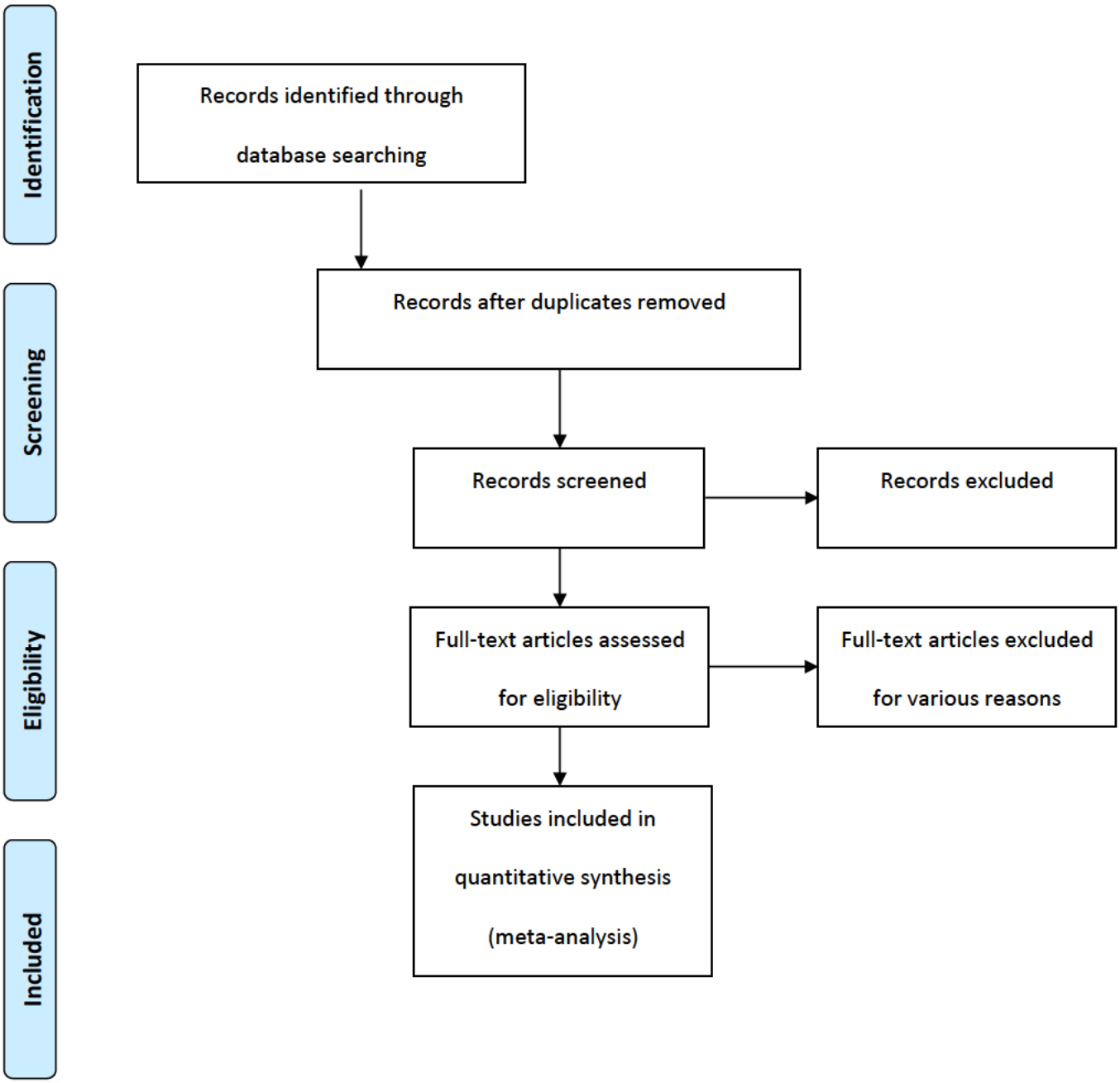


Figure B2. Consort statement.

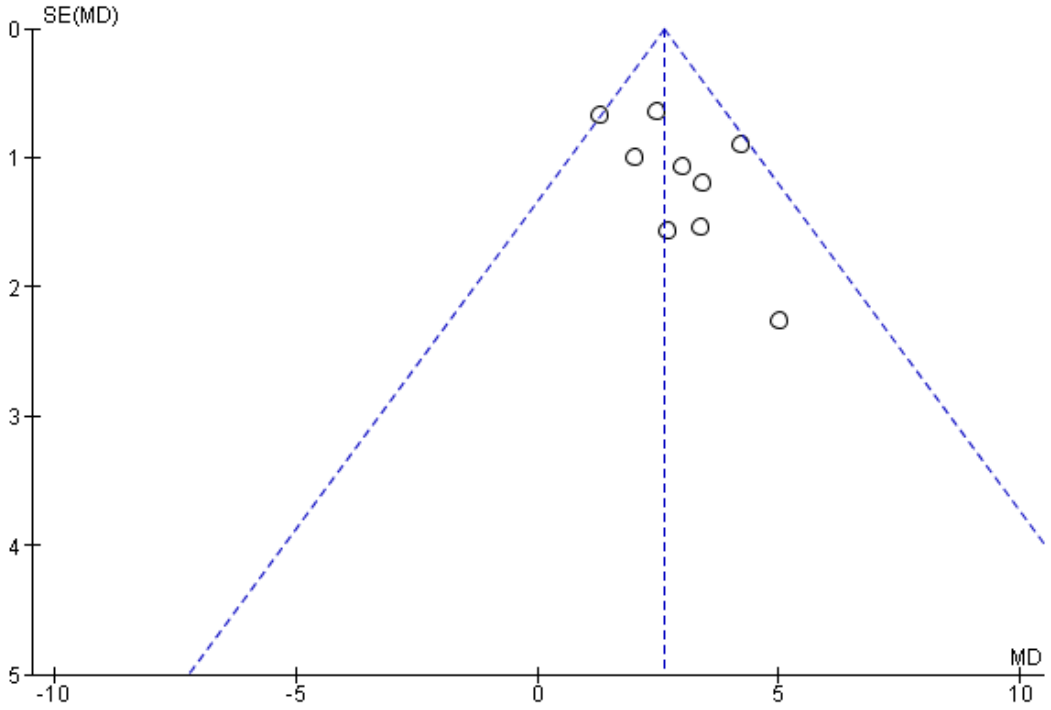


Figure B3. Egger plot for MMSE

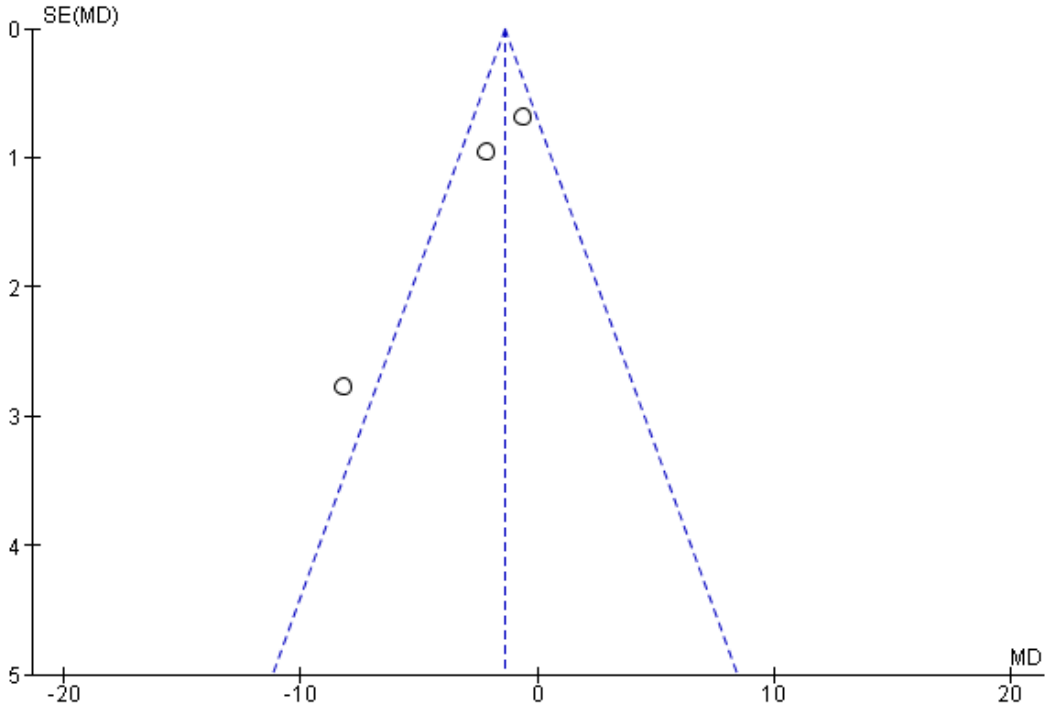


Figure B4. Egger plot for ADAS-cog

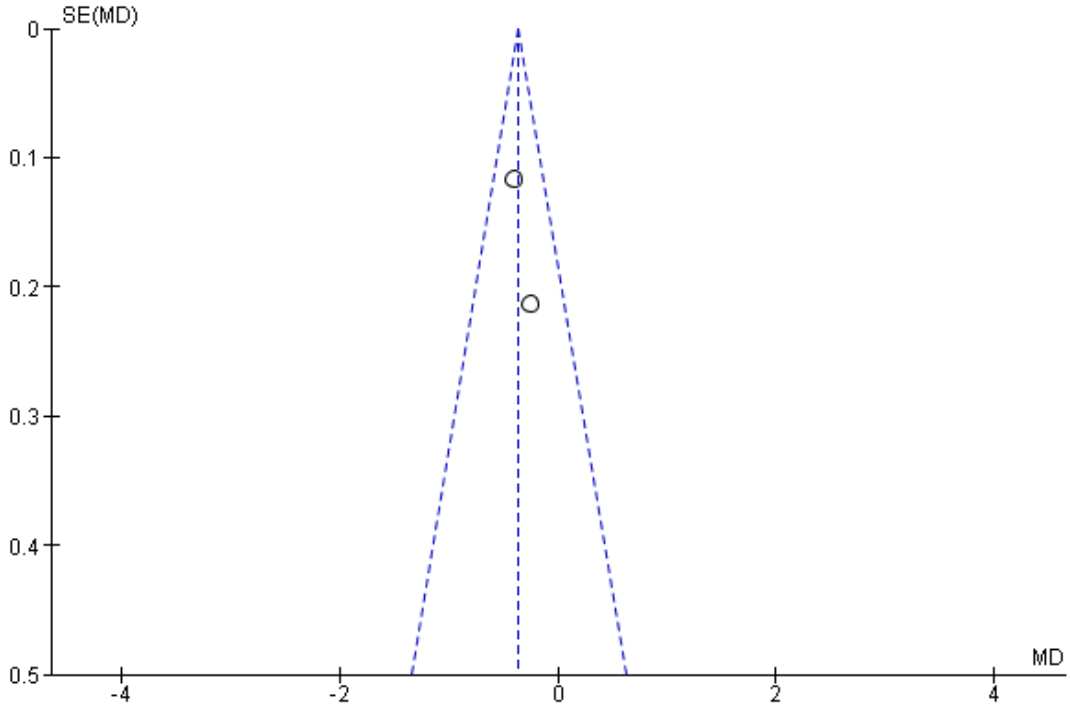


Figure B4. Egger plot for CDR-sum of boxes

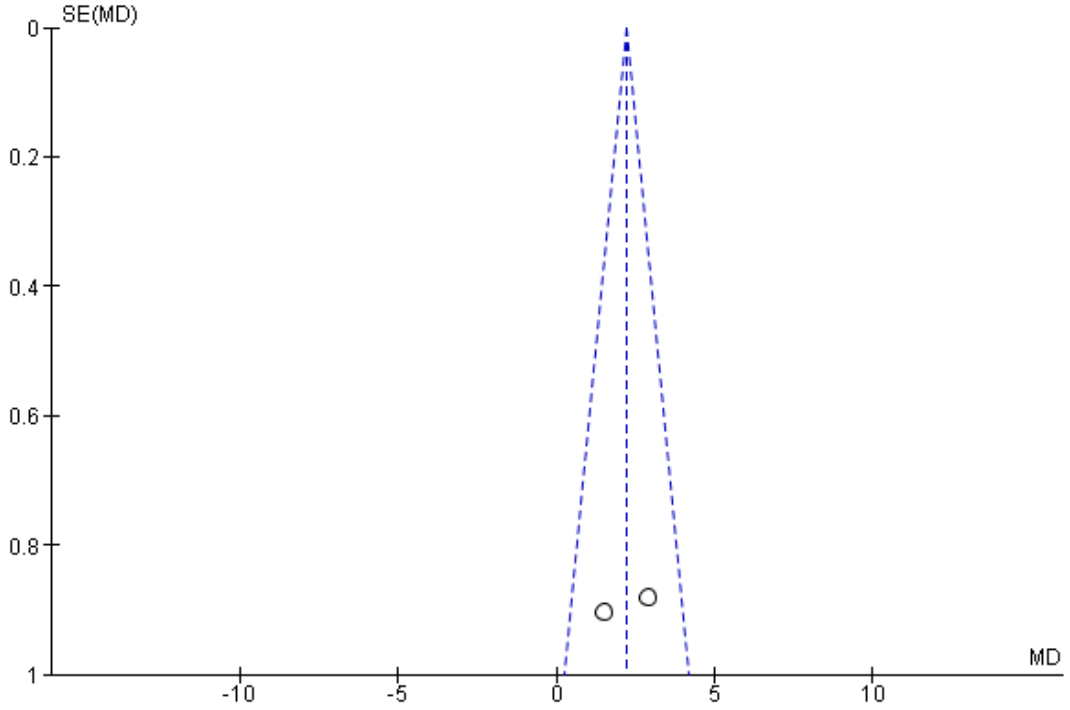


Figure B5. Egger plot for WAIS-R similarities

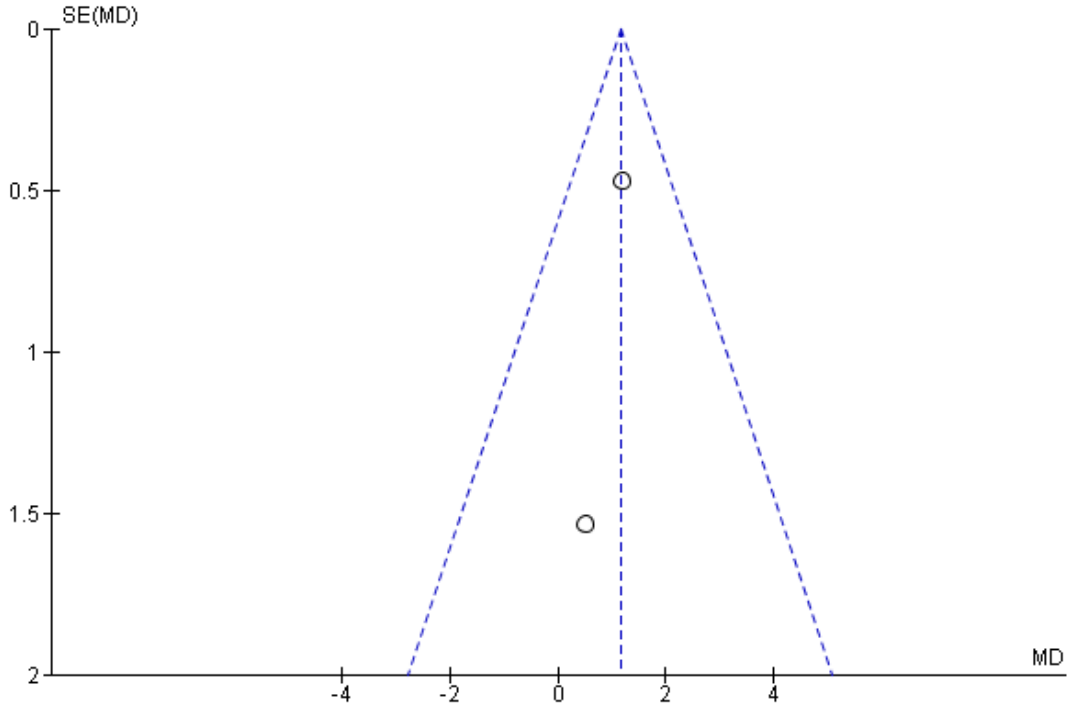


Figure B6. Egger plot for WAIS-R arithmetic

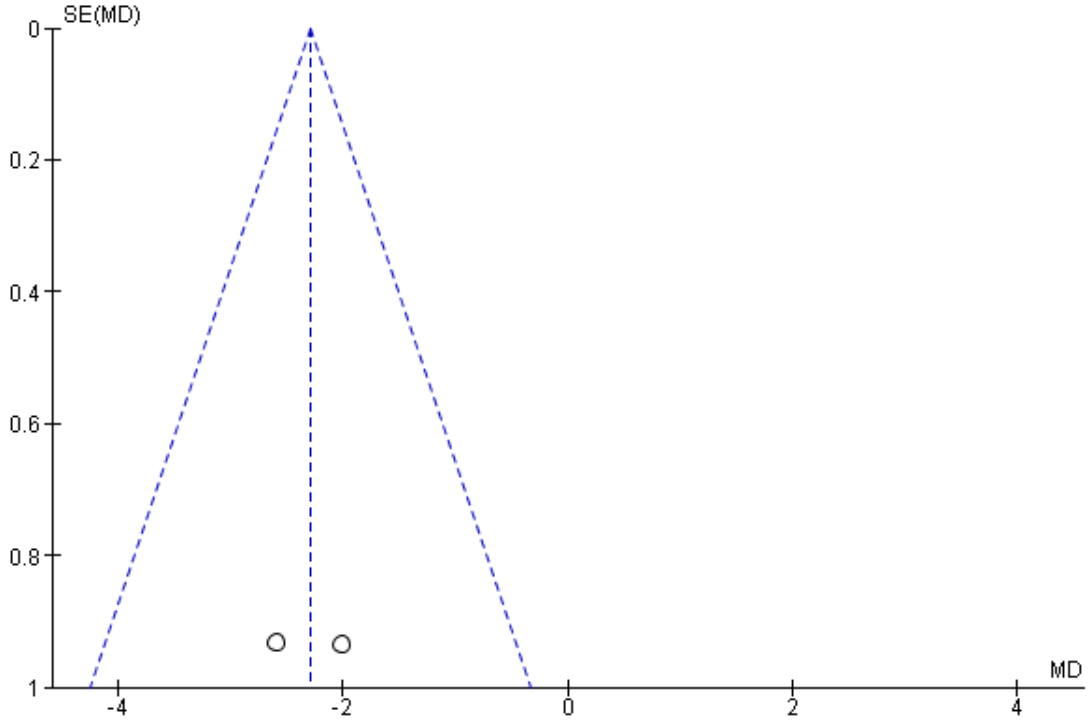


Figure B7. Egger plot for ADS 6 (picture recognition)

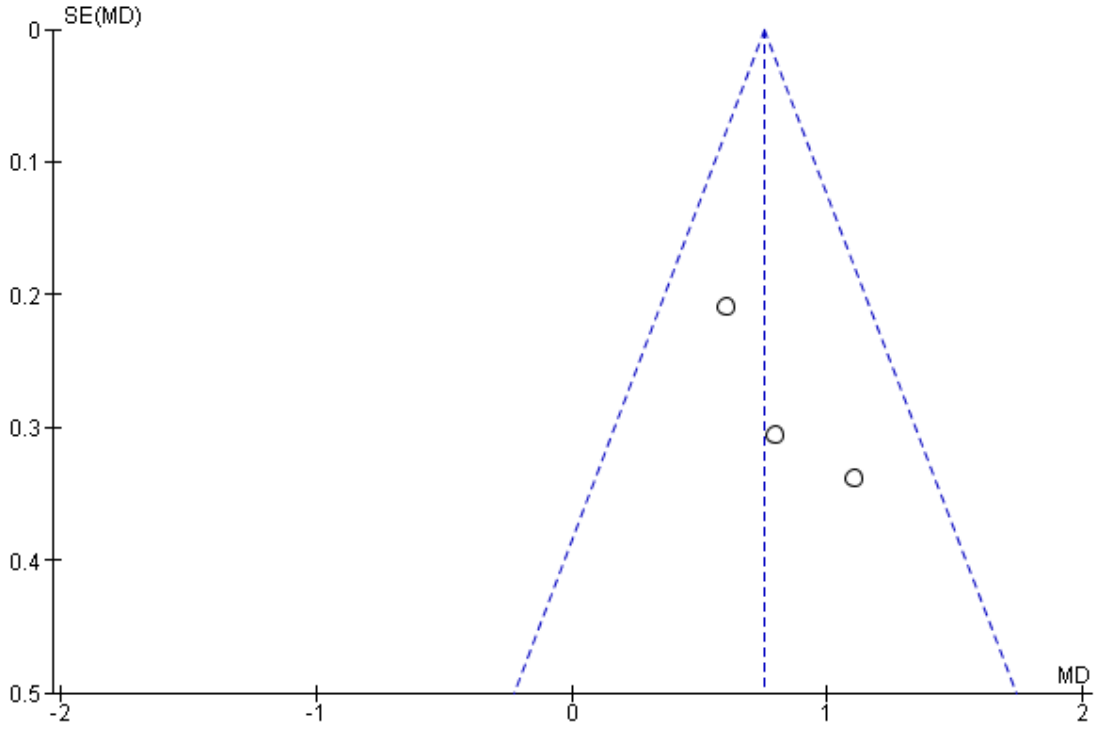
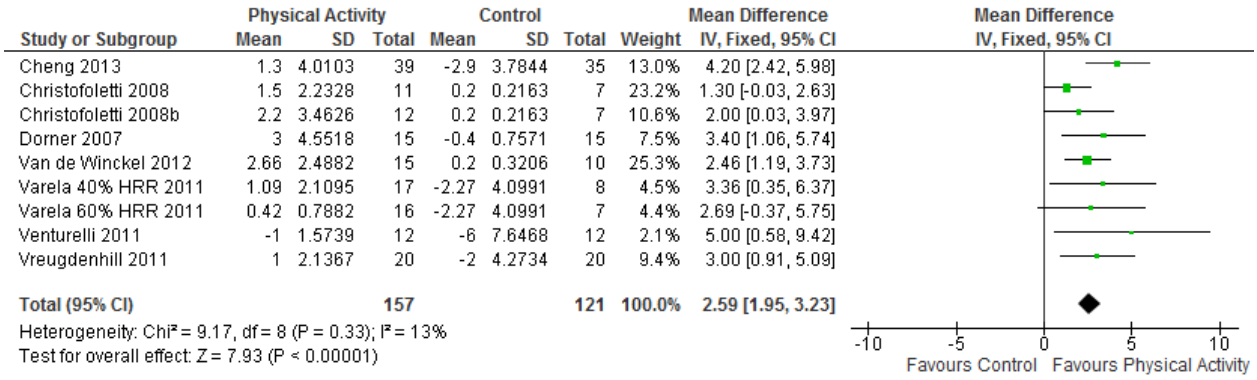


Figure B8. Egger plot for clock drawing test

(a)



(b)

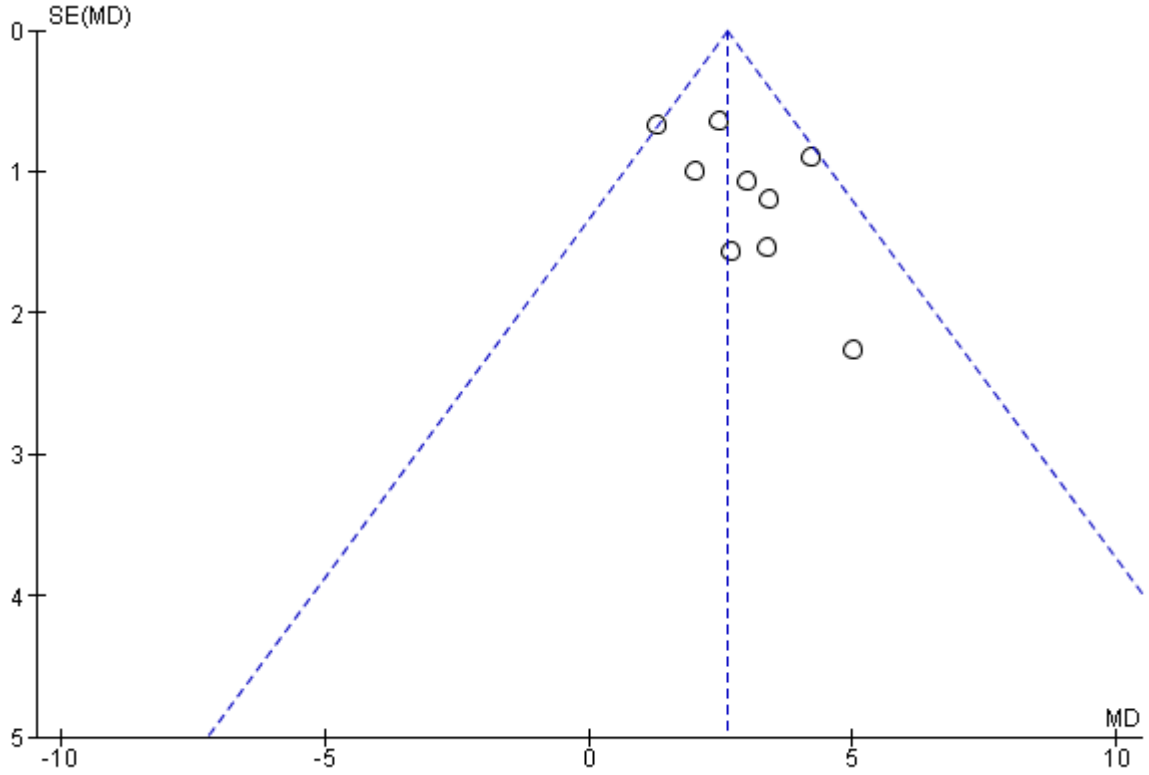


Figure B9. Sensitivity Analysis.

(a) MMSE Sub-Analysis SA1. Reduced heterogeneity of data after removing Lam (2011) and Suzuki (2012) from the analysis. (b) Egger plot sensitivity analysis for the MMSE

Table B3. Modified PEDro scale (maximum score 9).

Assessment of the study quality using a modified PEDro scale (maximum score 9)

Other commonly used tools, e.g., JADAD, are relatively insensitive at detecting the study quality of physical training interventions. We chose the PEDro scale because it is designed for use by physical therapists and is the tool most closely related to the needs of exercise scientists. That said, while the implementation of participant and investigator blinding in physiotherapy studies is sometimes possible, blinding is extremely difficult, even impossible, in most exercise training studies. For this reason, we omitted these items from the PEDro scale because all of the included studies would have scored 0.

COGNITIVE IMPAIRMENT AND DEMENTIA – PHYSICAL ACTIVITY AND COGNITIVE IMPROVEMENT: Quality of the metrics of the included studies

Study name	**Eligibility criteria specified**	**Random allocation of participants**	**Allocation concealed**	**Groups similar at baseline**	**Assessors blinded**	**Outcome measures assessed in 85% of participants**	**Intention to treat analysis**	**Reporting of between group statistical comparison**	**Point measures and measures of variability reported**	**Total Score Out of 9**
Brown 2009 [1]	YES	YES	NO	YES	Unclear	YES	NO	YES	YES	6
Cheng 2013 [2]	YES	YES	NO	YES	Unclear	YES	YES	YES	YES	7
Christofoletti 2008 [3]	YES	YES	NO	NO	YES	YES	YES	YES	YES	6
Dorner et al., 2007 [4]	YES	YES	NO	YES	YES	YES	NO	YES	YES	7

Eggermont 2009a [5]	YES	YES	NO	Unclear	YES	YES	YES	YES	YES	6
Kemoun et al., 2010 [6]	YES	YES	NO	YES	Unclear	YES	NO	YES	YES	6
Lam et al., 2010 [7]	YES	YES	NO	YES	YES	YES	YES	YES	YES	8
Lautenschlager 2008 [8]	YES	YES	NO	YES	YES	YES	YES	YES	YES	8
Stevens et al., 2006 [9]	YES	YES	NO	Unclear	Unclear	YES	NO	YES	YES	5
Suzuki et al., 2012 [10]	YES	YES	NO	YES	YES	YES	YES	YES	YES	8
Van de Winckel 2004 [11]	YES	YES	NO	YES	YES	YES	NO	YES	YES	7
Varela et al., 2011 [12]	YES	YES	NO	YES	YES	YES	YES	NO	YES	7
Venturelli et al., 2011 [13]	YES	YES	NO	YES	Unclear	YES	NO	YES	YES	6
Vreugdenhill 2012 [14]	YES	YES	NO	YES	YES	YES	YES	YES	YES	7

MEDIAN SCORE 7

Appendix C: Information Sheet for Participants

School of Science and Technology
University of New England
Armidale NSW 2351 Australia
Phone: 02 6773 3118 Fax: 02 6773 5011
Email: hos-st@une.edu.au

INFORMATION SHEET for PARTICIPANTS

Physiological responses to isometric resistance training in healthy individuals. A randomized, controlled trial.

We wish to invite you to participate in our research project. The details of the study follow and we hope you will consider being involved. We are conducting this research project at the University of New England. The research is being conducted and led under the supervision of Associate Professor Neil Smart PhD, ESSA Accredited Exercise Physiologist. Neil is the study's lead investigator at UNE and PhD supervisor for Nicole Hess. The project also involves Associate Professor Jim McFarlane, Dr Gudrun Dieberg and Dr Debra Dunstan.

The researchers can be contacted as follows:

1. Associate Professor Neil Smart: nsmart2@une.edu.au Phone 02 6773 4076
2. Nicole Hess: nhess@myune.edu.au Phone 0411 967 053
3. Associate Professor Jim McFarlane: jmcfarla@une.edu.au Phone 02 6773 3201
4. Dr Gudrun Dieberg: gdieberg@une.edu.au Phone 02 6773 2321
5. Dr Debra Dunstan: ddunstan@une.edu.au Phone 02 6773 3764

Participation is entirely voluntary; you may withdraw at any time without any penalty.

Purpose of the study: To investigate the physiological effects of six (6) weeks of isometric hand grip training on healthy individuals.

Potential Benefits: Participants may be likely to temporarily improve their resting heart rate and blood pressure.

Inclusion Criteria

You are eligible to participate if you meet the following criteria: If you are aged between 25 to 75 years, are not hypertensive, have no significant verbal, visual, or motor impairments, are able to respond to visual and verbal commands and able to exercise.

Time Requirements:

- Thirty (30) minutes to provide information and to complete paperwork at a participant screening session.
- Fifteen (15) minutes to collect blood and saliva samples on the first day of isometric exercise.
- Sixteen (16) minutes of isometric exercise training three times a week for eight weeks.
- Five (5) minutes to collect blood during week three of the study.
- Fifteen (15) minutes to collect blood and saliva samples at the conclusion of participation in exercise.
- Fifteen (15) minutes to measure blood pressure and take saliva samples at a follow up session, four (4) weeks after completion of exercise participation.

Clinical evaluation and consent: At a screening session prior to commencement of the isometric exercise program you will be asked to complete a participant history questionnaire, an adult exercise screening questionnaire, and a written consent. If you are unaware of your health status, you will be advised to see your general practitioner.

Study Protocol

Description of the research: You will be asked to complete three isometric exercise sessions per week for six (6) weeks.

Familiarisation: Prior to commencing isometric hand grip training you will be familiarised with the exercise protocol. Each session should run for approximately sixteen (16) to twenty (20) minutes.

Testing: We will measure your blood pressure and heart rate on a regular basis throughout the study, including at follow up. This is not painful or invasive. The other physical tests require a saliva sample, and blood samples which will be collected by a phlebotomist or medical practitioner. Together, these tests will allow us to assess the association between biological and physiological markers.

Cardiovascular measures: To minimise the influence of external variables on cardiovascular measures (blood pressure readings), please refrain from vigorous exercise and alcohol for 24 hours prior to each scheduled blood pressure measurement, caffeine for 12 hours prior and fast for 4 hours prior.

Blood measures: To minimise the influence of external variables on blood measurements, please refrain from vigorous activity 12 hours prior to giving blood and fast for 4 hours prior.

Exercise Intervention: Subjects for both exercise groups will be asked to complete a maximum of six (6) weeks of supervised isometric exercise training, which will consist of three sixteen minute exercise sessions per week. You will be randomly assigned to either group 1 (the intervention group) or group 2 (the control group). Prior to and during the research period you will not be made aware of which group you have been assigned too. Both groups will complete unilateral isometric hand grip exercise for 4 x 2 minute intervals with 2 minute rest in between intervals.

Confidentiality: Your identity as a participant in this research and the information obtained from the study will be kept confidential to the extent permitted by law. However, this research record may be reviewed by the University of New England research ethics committee that oversees all human research at the University of New England. Your information will be stored in a coded (de-identified)

format in a locked filing cabinet at the researcher's office. The data will be kept in the same manner for five (5) years following thesis submission and then destroyed.

Voluntary Participation: You may refuse to participate at any time during the study. Before signing the informed consent form, please do not hesitate to ask any questions regarding any aspect of this study that perhaps is unclear to you.

Counselling in case of adverse events

Should you, the participant, or a relative need to seek counselling because of an adverse event resulting from you participating in this study the following services are available locally:

Lifeline 13 1114
Armidale Community Health (02) 6776 9600

Research Process: The results may also be presented at conferences or in scientific journals without any individual identifying information.

This project has been approved by the Human Research Ethics Committee of the University of New England (Approval No. **HE14-047** Valid to 01/05/2015).

Should you have any complaints concerning the manner in which this research is conducted, please contact the Research Ethics Officer at the following address:

Research Services
University of New England
Armidale, NSW 2351.
Telephone: (02) 6773 3449 Facsimile (02) 6773 3543
Email: ethics@une.edu.au

Thank you for considering this request and we look forward to further contact with you.

Kind Regards

Neil Smart
Associate Professor of Clinical Exercise Physiology
University of New England, NSW 2351

Appendix D: Invitation to Participate

School of Science and Technology
University of New England
Armidale NSW 2351 Australia
Phone: 02 6773 3118 Fax: 02 6773 5011
Email: hos-st@une.edu.au

Invitation to Participate in a Research Study
Physiological responses to isometric resistance training in healthy individuals.
A randomized, controlled trial.

The project has been approved by Human Research Ethics Committee of the University of New England (Approval No. **HE14-047** Valid to 01/05/2015)

We are conducting a **six (6) week study to evaluate the effects of isometric resistance exercise training on heart rate and blood pressure in healthy adults.**

The study is being run by PhD student Miss Nicole Hess under the supervision of her University of New England supervisors Associate Professor Neil Smart, Associate Professor Jim McFarlane, Dr Gudrun Dieberg, and Dr Debra Dunstan.

The study will involve the measurement of blood pressure and heart rate which is neither painful nor invasive. Saliva will be collected on **three (3)** separate occasions and a blood test will be conducted on **three (3)** separate occasions by a phlebotomist or medical practitioner. Participants will be asked to complete a **six (6) week, low intensity, isometric handgrip training program consisting of three sixteen minute sessions per week.**

The identity of all participants in this research and the information obtained from the study will be kept confidential to the extent permitted by law.

We hope that you will consider participating in this study. Please note that your participation is entirely voluntary.

If you are interested, full details of this study will be provided by Associate Professor Neil Smart who can be contacted by email at nsmart2@une.edu.au or by phone on 02 6773 4076, or by Miss Nicole Hess who can be contacted by email at nhess@myune.edu.au or by phone 02 6773 2981.

Kind Regards

Associate Professor Neil Smart
Associate Professor Jim McFarlane
Dr Gudrun Dieberg
Dr Debra Dunstan
Nicole Hess

Appendix E: Patient History

Name:_____Age_____

Date of Birth:_____ Sex: M/F

Home Address:_____

Occupation:_____

Social History

Marital status: □ Single (never married) □ Divorced or widowed □ Married □ Long term live together

Alcohol intake (weekly average consumption): □ Glasses/cans/bottles of Beer

□ Glasses of wine □ Servings of mixed drinks or hard alcohol □ Other

Tobacco use: □ never used □ discontinued use □ Cigarettes per day

Education (check highest level completed): □ high school below year 10 □ high shool year 10 □ completed high school □ TAFE/Technical/Trade school □ Diploma

□ 1-2 years of university □ Bachelor's degree □ post Graduate Degree

□ Professional School

Vocational history

Retired: Y / N Age at retirement (years)_____

Total length of employment (years)_____

Vocation, including type of industry and duration of employment:

1._____

2._____

3._____

4. _____

5. _____

6. _____

Medical history

Have you suffered from or been diagnosed with:

- Stroke? YES/NO
- Epilepsy? YES/NO
- Brain Tumour? YES/NO
- Other neural disorder? YES/NO

[If yes, please specify ……]

- Any motor disorder (eg Parkinson's Disease, Multiple Sclerosis)? YES/NO

[If yes, please specify ……]

- Any developmental disorder (eg ASD, Asperger's Syndrome)? YES/NO

[If yes, please specify ……]

Cardiovascular:

□ High blood pressure (hypertension) □ Low blood pressure (hypotension)

□ Heart Attack (myocardial infarction) □Angina/chest pain □Congestive heart failure

□ Rapid heart rate (tachycardia) □ Slow heart rate (bradycardia)

□ High cholesterol □ Poor blood circulation (cold extremities/ pain in calf when walking)

Other:_____

_____

Current Medications and indications (name/dose/frequency of taking/for how long):

1. _____

2. _____

3. _____

4. _____

5. _____

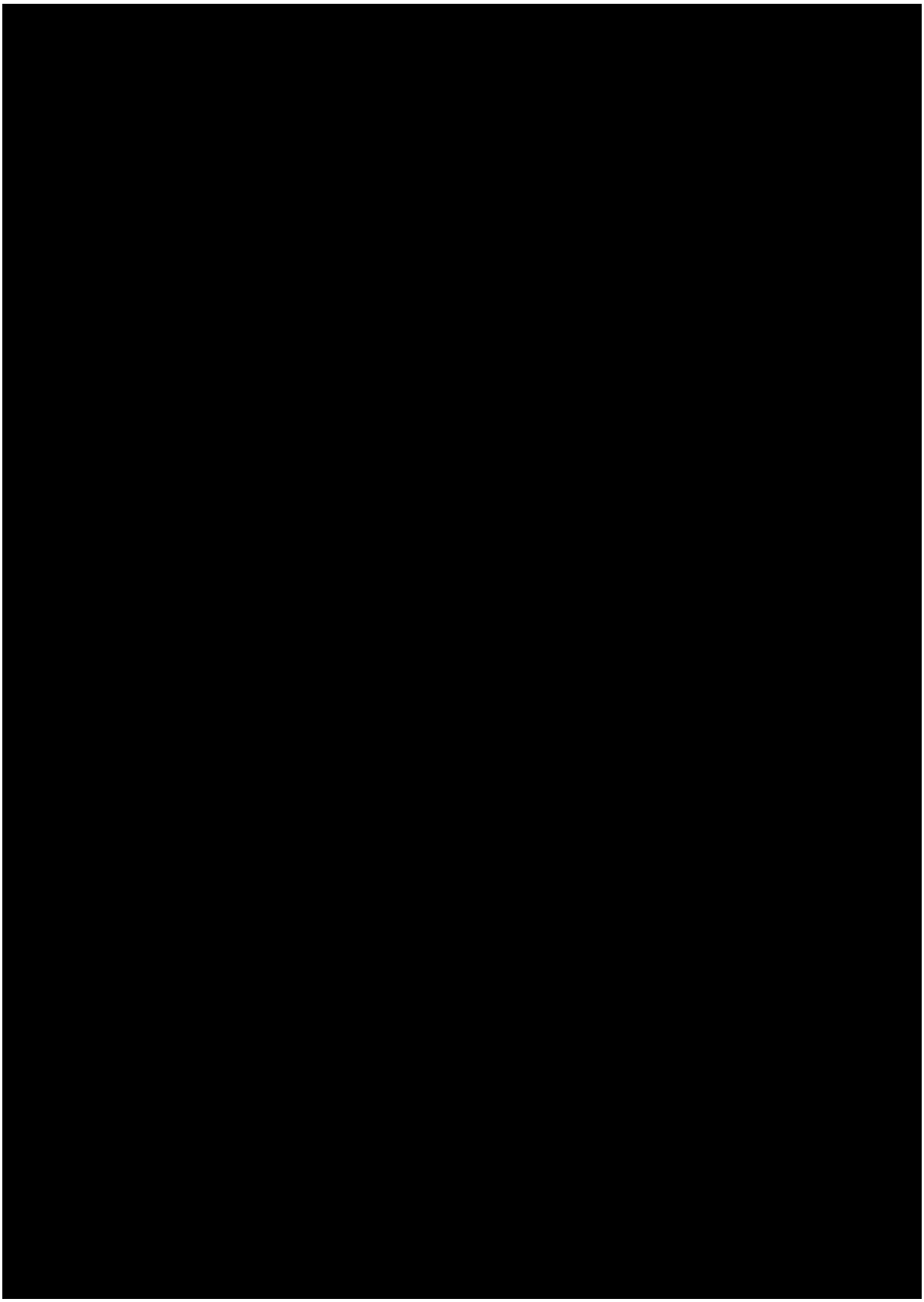
6. _____

7. _____

8. _____

9. _____

Appendix F: Adult Pre-Exercise Screening Tool



Appendix G: Consent Form

School of Science and Technology
University of New England
Armidale NSW 2351 Australia
Phone: 02 6773 3118 Fax: 02 6773 5011
Email: hos-st@une.edu.au

Consent Form for Participants

Protocol Title: Physiological responses to isometric resistance training in healthy individuals. A randomised, controlled trial. HE14-047.

I, ..., have read the information contained in the Information Sheet for Participants and I am satisfied with the answers to all of my questions. Yes/No

I have been made aware of the risks of participating in this research study. Yes/No

I understand that I need to attend a familiarization session about exercise testing and training. Yes/No

I understand that study participation will require me to give saliva samples on three (3) separate occasions. Yes/No

I understand that my saliva samples may be stored until they can be analysed, but immediately after analysis remaining saliva will be discarded. Yes/No

I understand that study participation will require me to give blood samples on three (3) separate occasions. Yes/No

I understand that my blood samples may be stored until they can be analysed, but immediately after analysis remaining blood will be discarded. Yes/No

I understand that study participation will require me to do isometric exercise which should be between 18 and 20 minutes. Each bout is two (2) minutes long, followed by a (2) minute rest period. Yes/No

I understand that I will do three (3) bouts of supervised isometric resistance exercise training per week over a six (6) week period, and give a single blood sample and a single saliva sample four (4) weeks after the isometric resistance training is completed. Yes/No

I understand that my identity will remain confidential and all of the information I provide will be treated anonymously. Yes/No

I understand that the information gathered for the study will be part of a larger patient group data analysis and the groups findings may be presented and published, but my individual information will not be published. Yes/No

I have discussed my study participation with my general practitioner and he/she has agreed to my participation. Yes/No

I have read the above and understand the information contained in the Information Sheet for Participants. I consent to participate in this study and realize that I may withdraw at any time without penalty or change to my medical care. Yes/No

.....	.....
Participant	Date

.....	.....
Researcher	Date

.....	.....
Witness	Date

Appendix H: Invitation to Information Session

School of Science and Technology
University of New England
Armidale NSW 2351 Australia
Phone: 02 6773 3118 Fax: 02 6773 5011
Email: hos-st@une.edu.au

Invitation to attend afternoon tea and information session.

My name is Nicole Hess and I am a PhD student at the University of New England. I am currently investigating age related changes in blood pressure, memory and thought processes. Specifically, the focus of my research is to investigate whether low level hand grip exercises are capable of improving blood pressure, and memory and thought processes in individuals experiencing memory difficulties.

A common complaint of many elderly Australians is the experience of an unreliable memory. Considerable research has linked blood pressure management with improvements in memory function and thought processes. Other research suggests that mild to moderate physical activity may assist with both blood pressure management and memory function.

I am conducting a study, which will be run here at Sunny Cove, to evaluate how effectively low intensity hand grip exercises can improve blood pressure and memory function in individuals experiencing memory difficulties.

If you think that you might be interested in participating in this study or if you are simply interested in learning more about my project then I would like to invite you to attend an information session and afternoon tea to be held at:

Sunny Cove, in the dining area **Wednesday 17th February 2016** at **3pm**

This project has been approved by Human Research Ethics Committee of the University of New England (Approval No. HE14-047 Valid to 30/12/2016).

Kind Regards

Nicole Hess

Appendix I: Invitation to Participate

School of Science and Technology
University of New England
Armidale NSW 2351 Australia
Phone: 02 6773 3118 Fax: 02 6773 5011
Email: hos-st@une.edu.au

Invitation to Participate in a Research Study

Physiological and cognitive responses to isometric resistance training in individuals experiencing memory difficulties.

The project has been approved by Human Research Ethics Committee of the University of New England (Approval No. ***HE14-047*** *Valid to 30/12/2016).*

We are conducting a study to evaluate how effectively isometric resistance exercise training can improve heart rate, blood pressure and cognitive response in individuals experiencing memory difficulties.

The study is being run by PhD student Miss Nicole Hess under the supervision of her University of New England supervisors Associate Professor Neil Smart, Associate Professor Jim McFarlane, Associate Professor Debra Dunstan and Dr Gudrun Dieberg.

We hope that you will consider participating in this study. Please note that your participation is entirely voluntary and that your health care will not be adversely affected in any way if you decide not to participate.

The study will involve the measurement of blood pressure and heart rate which is neither painful nor invasive. Neuropsychological tests will be administered to measure cognitive performance outcomes. Participants will be asked to complete three separate isometric hand grip exercise sessions (low intensity) per week over the course of a six week period.

The identity of all participants in this research and the information obtained from the study will be kept confidential to the extent permitted by law.

Full details of this study will be provided by Associate Professor Neil Smart who can be contacted by email at nsmart2@une.edu.au or by phone on 02 6773 4076, or by Miss Nicole Hess who can be contacted by email at nhess@myune.edu.au or by phone 02 6773 2981.

Kind Regards

Associate Professor Neil Smart
Associate Professor Jim McFarlane
Associate Professor Debra Dunstan
Dr Gudrun Dieberg
Nicole Hess

Appendix J: Information Sheet for Participants

School of Science and Technology
University of New England
Armidale NSW 2351 Australia
Phone: 02 6773 3118 Fax: 02 6773 5011
Email: hos-st@une.edu.au

INFORMATION SHEET for PARTICIPANTS

Physiological and cognitive responses to isometric resistance training in individuals experiencing memory difficulties.

We wish to invite you to participate in our research project. The details of the study follow and we hope you will consider being involved. We are conducting this research project at Sunny Cove. The research is being conducted and led under the supervision of Associate Professor Neil Smart PhD, ESSA Accredited Exercise Physiologist. Neil is the study's lead investigator at UNE and PhD supervisor for Nicole Hess. Associate Professor Debra Dunstan is a clinical psychologist and is involved in the study because of her interest in the area of rural mental health and wellbeing. The project also involves Associate Professor Jim McFarlane because of his involvement in the Centre for Bioactive Discovery in Health & Ageing. Dr Gudrun Dieberg, is the study' administrator, Gudrun is involved in this research project as her teaching and research interests are in the area of human health sciences.

The researchers can be contacted as follows:

6. Associate Professor Neil Smart: nsmart2@une.edu.au Phone 02 6773 4076
7. Associate Professor Debra Dunstan: ddunstan@une.edu.au Phone 02 6773 3764
8. Associate Professor Jim McFarlane: jmcfarla@une.edu.au Phone 02 6773 3201
9. Dr Gudrun Dieberg: gdieberg@une.edu.au Phone 02 6773 2321
10. Nicole Hess: nhess@myune.edu.au Phone 0411 967 053

Participation is entirely voluntary; you may withdraw at any time without any penalty or change to your medical treatment.
Purpose of the study: To investigate the effect of isometric resistance training on physiological and cognitive responses in individuals experiencing difficulties with memory.

Potential Benefits: Participants are likely to temporarily improve their resting blood pressure and cognitive performance outcomes on prescribed neuropsychological tests.

Inclusion Criteria

You are eligible to participate if you meet the following criteria: If you are aged between 55 to 85 years, experience memory difficulties, are a non-smoker, have no significant verbal, visual, or motor impairments', are able to respond to visual and verbal commands and able to exercise.

Clinical evaluation and consent:

You will be asked to complete a medical screening questionnaire before the test which details a comprehensive history, patient medication, and a written consent. If necessary, final medical clearance will be obtained from your medical specialist. If you are unaware of your health status, you will be advised to see your general practitioner.

Testing: Your mental and physical functioning will be assessed with a series of tests. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) will be used to assess your memory, attention, use of language and visual perception abilities. The RBANS involves short quizzes and tests that take about 30 to 40 minutes to complete. The tests will be administered by a provisional psychologist enrolled in the clinical psychology program at the University of New England. We will also measure your blood pressure and heart rate; this is not painful or invasive. Together, these tests will allow us to assess the association between physiological changes and mental activity.

Exercise Intervention: Participants will be asked to complete a maximum of 6 weeks of supervised isometric exercise training, which will consist of three exercise sessions per week. Participants will complete unilateral (one handed) isometric hand grip exercise for 4 x 2 minute intervals with 2 minute rest in between intervals.

Familiarisation: You will be familiarised with the exercise protocol. Each session should be approximately 12 minutes.

Study Protocol

Description of the research: Prior to commencing isometric hand grip training, you will be required to complete the RBANS (as described above under the heading, 'Testing') and your blood pressure will be taken each day for two weeks. After this time, a second round of the RBANS will be administered and you will be asked to complete three separate isometric hand grip exercise sessions each week for 6 weeks. Blood pressure will continue to be monitored twice per week each week throughout the 6 weeks of isometric hand grip exercise. At the end of six weeks your blood pressure will be measured and a third round of the RBANS will be administered and gauged to assess whether any changes in blood pressure and/or cognitive performance are evident after 6 weeks of isometric exercise training.

Follow up: Four weeks after the completion of exercise participation a final set of blood pressure measurements will be taken and a fourth round of the RBANS will be administered.

Time Requirements over 12 weeks:

Two hours for information and completion of paperwork at a participant screening session.

Forty minutes for the administration of a neurocognitive test two weeks prior to commencement of isometric exercise.

Five to Ten minutes of blood pressure measurements each day for ten days prior to the commencement of isometric exercise.

Forty minutes for the administration of a neurocognitive test the day before isometric exercise begins.

Twelve minutes of isometric exercise training three times a week for 6 weeks.
Forty minutes for the administration of a neurocognitive test after completion of exercise participation.

Forty five minutes for the administration of a neurocognitive test and a blood pressure measurement four weeks after completion of exercise participation.

Confidentiality: Your identity as a participant in this research and the information obtained from the study will be kept confidential to the extent permitted by law. However, this research record may be reviewed by the University of New England research ethics committee that oversees all human research at the University of New England. Your information will be stored in a coded (de-identified) format in a locked filing cabinet at the researcher's office. The data will be kept in the same manner for five (5) years following thesis submission and then destroyed.

Voluntary Participation: You may refuse to participate at any time during the study. Before signing the informed consent form, please do not hesitate to ask any questions regarding any aspect of this study that perhaps is unclear to you.

Counselling in case of adverse events

Should you, the participant, or a relative need to seek counselling because of an adverse event resulting from you participating in this study the following services are available locally:

Lifeline 13 1114
Armidale Community Health (02) 6776 9600

Research Process:

The results may also be presented at conferences or in scientific journals without any individual identifying information.

This project has been approved by the Human Research Ethics Committee of the University of New England (Approval No. **HE14-047** Valid to 30/12/2016).

Should you have any complaints concerning the manner in which this research is conducted, please contact the Research Ethics Officer at the following address:

Research Services

University of New England

Armidale, NSW 2351.

Telephone: (02) 6773 3449 Facsimile (02) 6773 3543

Email: ethics@une.edu.au

Thank you for considering this request and we look forward to further contact with you.

Kind Regards

Nicole Hess

BPsych(Hons)

&

Neil Smart

Associate Professor of Clinical Exercise Physiology

University of New England, NSW 2351

Appendix K: Consent Form for Participants

School of Science and Technology
University of New England
Armidale NSW 2351 Australia
Phone: 02 6773 3118 Fax: 02 6773 5011
Email: hos-st@une.edu.au

Consent Form for Participants

Protocol Title: Physiological and cognitive responses to isometric resistance training in individuals experiencing memory difficulties.

I, ..., have read the information contained in the Information Sheet for Participants and I am satisfied with the answers to all of my questions. Yes/No

I have been made aware of the risks of participating in this research study. Yes/No

I understand that I need to attend a familiarization session about exercise testing and training. Yes/No

I understand that study participation will require me to do isometric exercise which should be between 8 and 12 minutes. Each stage is 2 minutes long. Yes/No

I understand that I will do three bouts of supervised isometric resistance exercise per week over a 6 week period, and participate in a final cognitive assessment after the isometric resistance training is completed. Yes/No

I understand that my identity will remain confidential and all of the information I provide will be treated anonymously. Yes/No

I understand that the information gathered for the study will be part of a larger patient group data analysis and the groups findings may be presented and published, but my individual information will not be published. Yes/No

I have discussed my study participation with my general practitioner and he/she has agreed to my participation. Yes/No

I have read the above and understand the information contained in the Information Sheet for Participants. I consent to participate in this study and realize that I may withdraw at any time without penalty or change to my medical care. Yes/No

…… ……

Participant Date

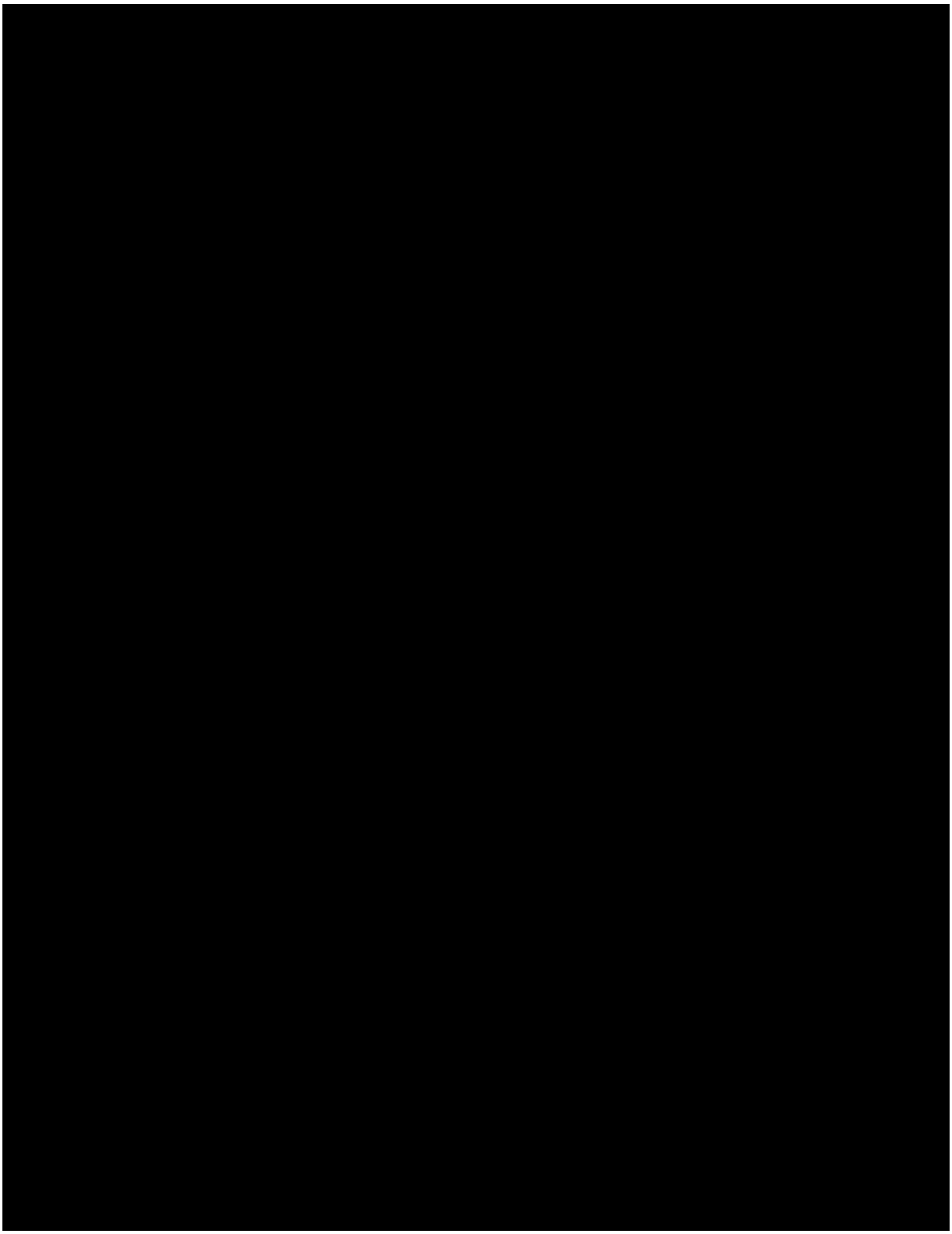
…… ……

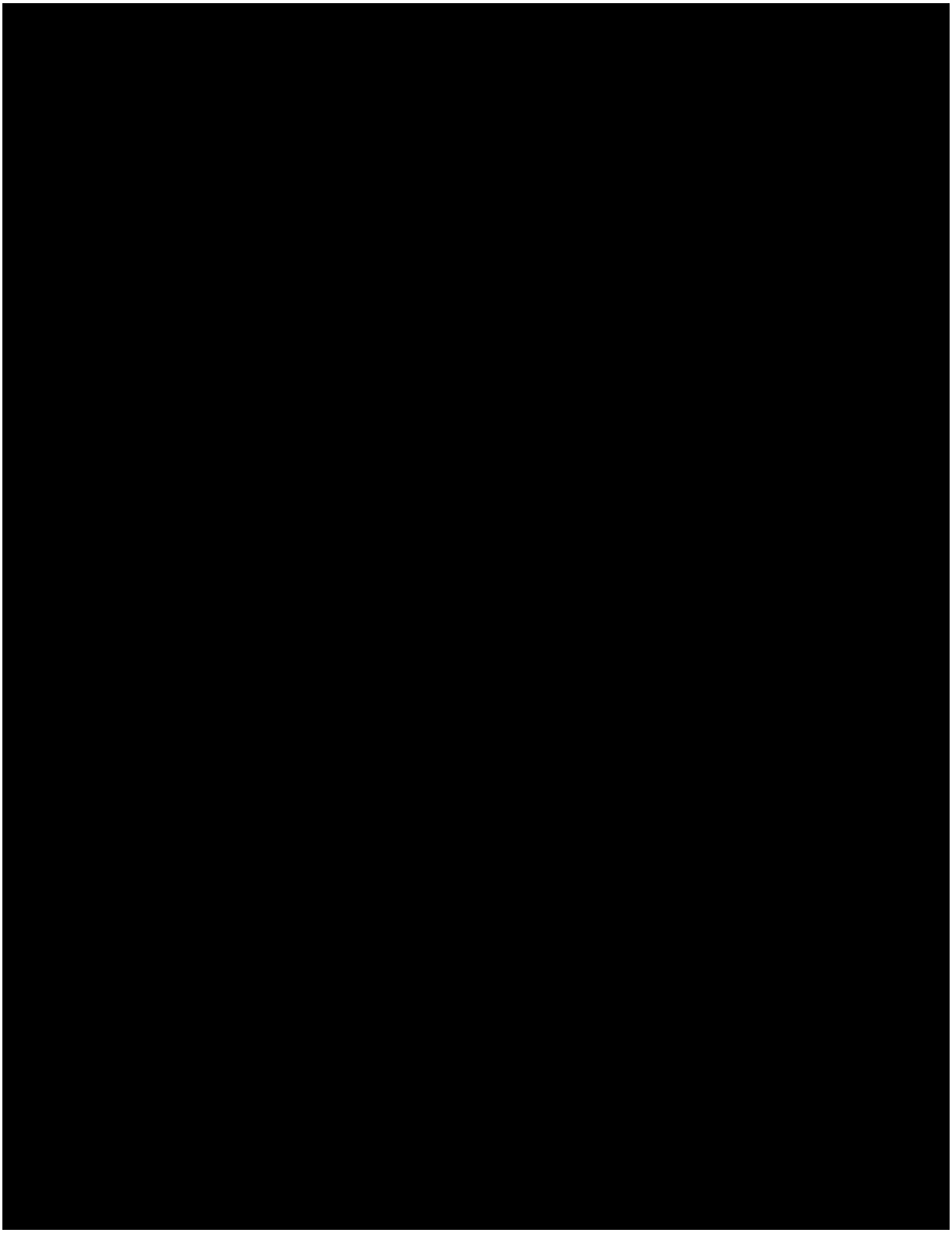
Researcher Date

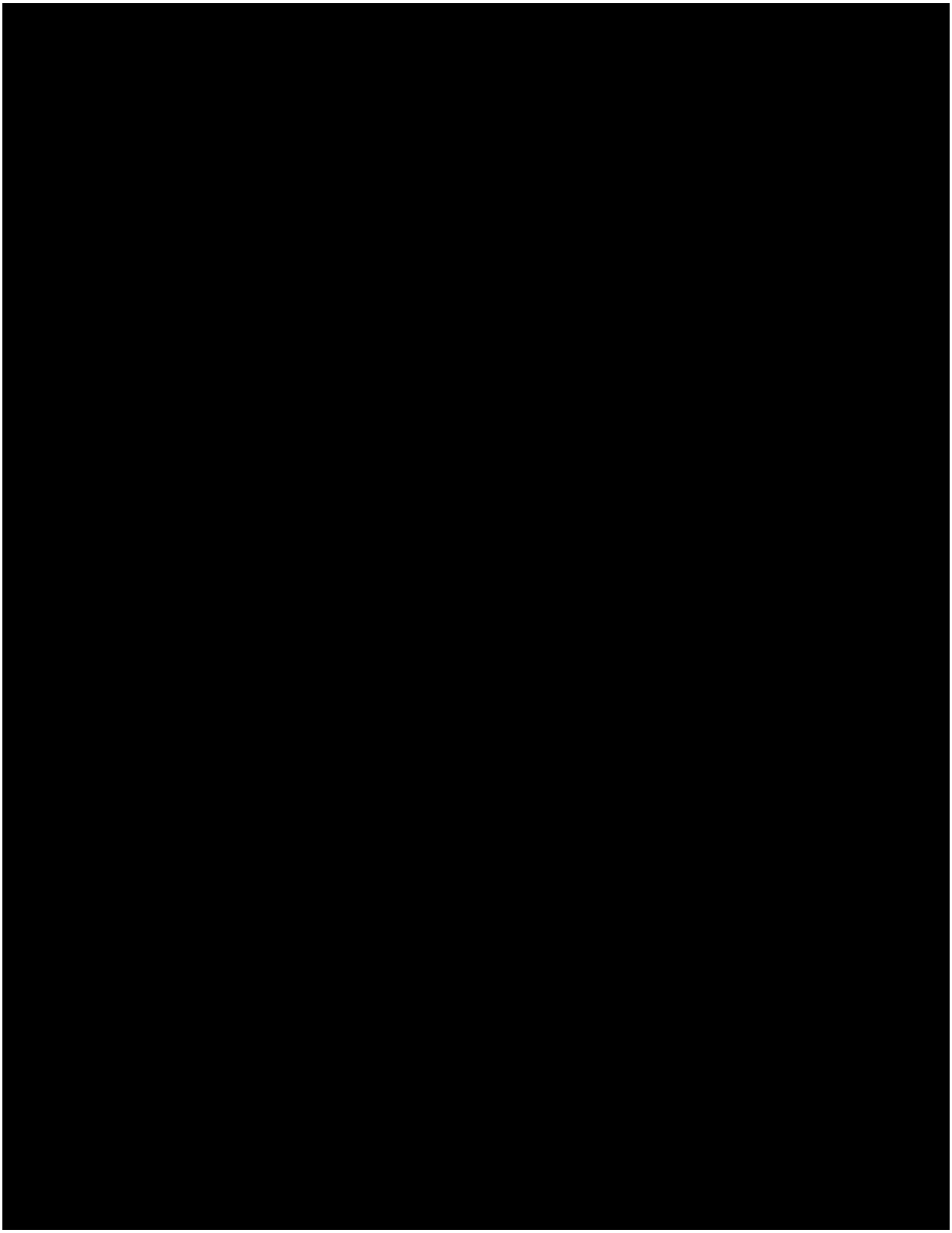
…… ……

Witness Date

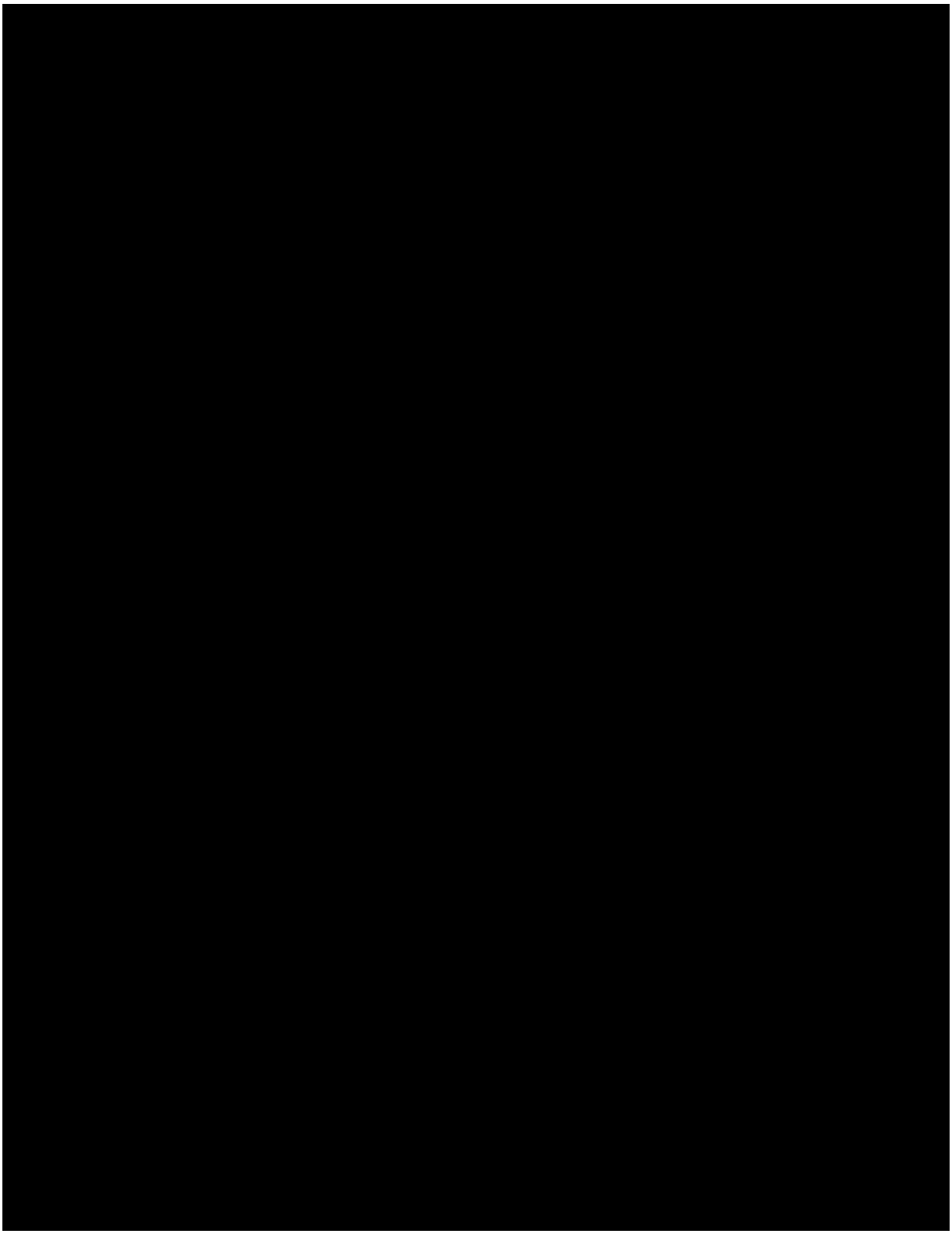
Appendix L: Mini-Mental State Examination

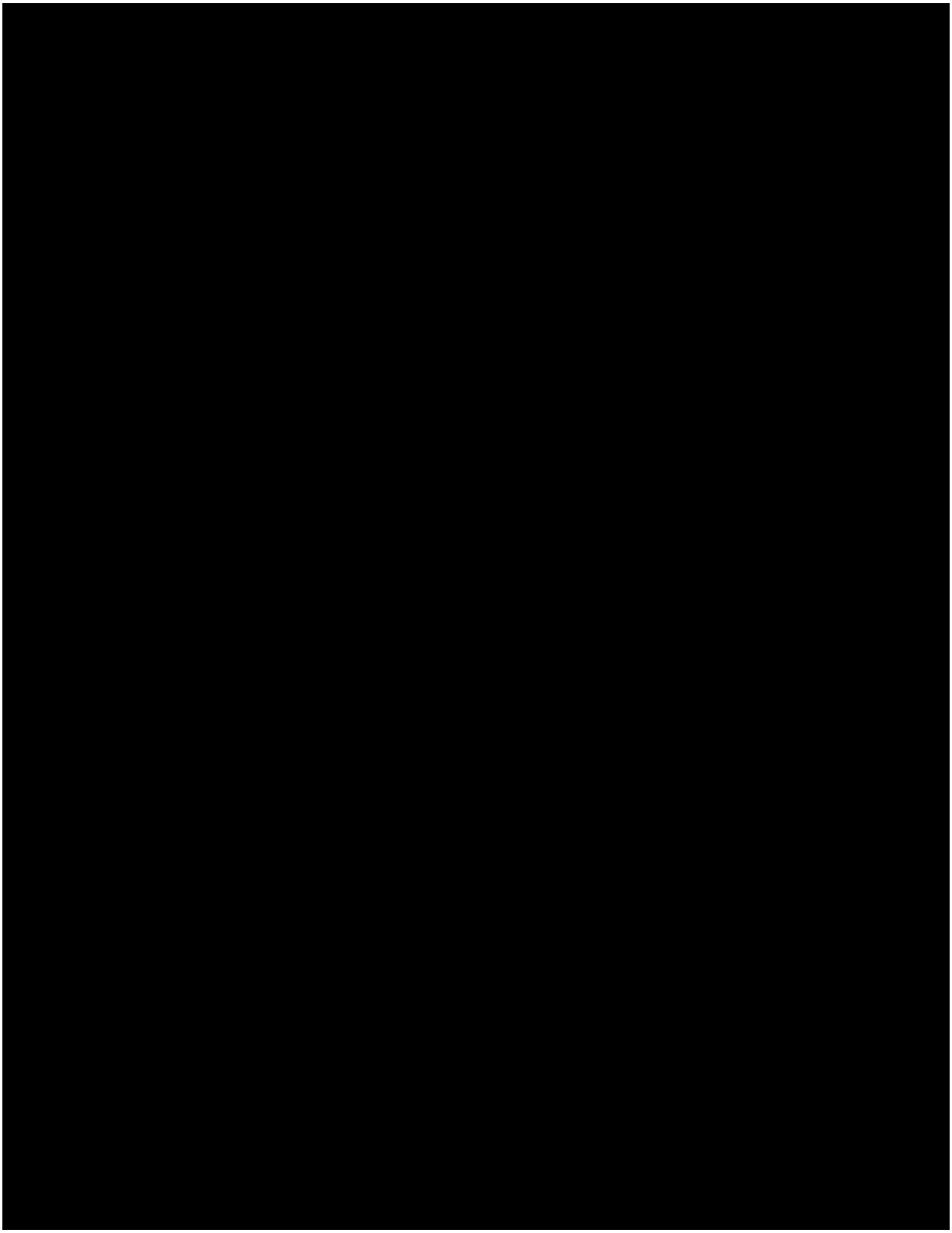






Appendix M: Geriatric Depression Scale





Appendix N: Repeatable Battery for the Assessment of Neurological Status