Preface

This master thesis was part of a two year program of Master of Science in Neuroscience at the Norwegian University of Science and Technology, Norway. The work was performed at the MR-centre at St. Olav's University Hospital, Trondheim, Norway.

I would like to thank my supervisors Asta Håberg and Tor Ivar Hansen for guidance and encouragement during the process of writing this thesis. I would like to thank my colleagues and friends, Elise Haferstrom and Hanne Nikkels, for good help along the way. Finally, I would like to give special thanks to my always loving and supportive mother who has encouraged me throughout my years of education.

Trondheim, May 2014

Stine Bjøralt

Abstract

Background: Numerous studies have reported on the positive influence of superior physical health on the preservation of cognitive functions as we age. For example, several exercise interventions of varying lengths aiming at increasing cardiorespiratory fitness in elderly populations have shown better preservation of brain structures and associated cognitive functions. Other health factors commonly known to affect cognition in old age are the metabolic syndrome (MetS) and various cardiovascular risk factors.

Aim: We wanted to look at older adults' cardiorespiratory fitness ($VO2_{peak}$), the prevalence of metabolic syndrome (MetS) and risk for cerebro-cardiovascular disease in relation to performance on a battery of neuropsychological tests.

Method: A cross-sectional design was employed including 105 healthy older adults (mean age 74 years). Cardiorespiratory fitness was assessed by graded maximal exercise testing, MetS was classified according to previous definitions, and cerebro-cardiovascular disease was calculated using the atherosclerotic cardiovascular risk estimator developed by the American Heart Association and the American College of Cardiology. Cognitive performance was assessed using the web-based neuropsychological test battery, Memoro.

Results: Individuals with higher $VO2_{peak}$ had faster processing speed, and there was a significant relationship between these two factors, where higher $VO2_{peak}$ predicted better processing speed, and trends showed that this was true for executive functions as well. Having MetS or high risk of developing cerebro-cardiovascular disease within the next 10 years did not seem to affect performance on cognitive tests, although trends show that having more MetS factors may contribute to better performance on cognitive tests.

Conclusion: Speed of processing, and possibly executive functions are more sensitive to cardiorespiratory fitness compared to other measures of cognitive functions. Additionally, MetS may have a cognitively protective role after a certain age, whereas cerebro-cardiovascular disease did not seem to affect cognition in this population of older adults.

Contents

1 Introduction

With the current increase of the ageing population, the interest in interventions that aim at promoting well-being and extending physical health increases. This is to allow maintenance of quality of life and independence for as long as possible. There is much evidence pointing at lifestyle as an important factor, where research shows that leading a physically and active lifestyle may help preserve age-related deterioration and decrease the risk of disease. Studies show that physical activity also has a positive influence on cognitive functions as we age, as physical activity and exercise in particular has been postulated to protect against deterioration of brain tissue and cognitive functions (Erickson et al., 2010).

Normally ageing individuals suffer from similar cognitive decline as individuals with dementia, though to a lesser degree. This includes impairment of episodic memory and problems with finding words, navigating, problem solving and basic everyday functioning (Bondi et al., 2008). Sensory and motor areas in addition to most of the subcortical structures, are left relatively spared (Karantzoulis & Galvin, 2011). As of today no medical intervention has proven successful in curing or postponing ongoing deterioration of cognitive functions (Ahlskog, Geda, Graff-Radford, & Petersen, 2011), and research suggests that cognitive decline is a result of genetic and environmental risk factors that are particularly affected by lifestyle. Intervention studies aiming to increase cardiorespiratory fitness in older adults have shown that various cognitive functions improve (Erickson et al., 2011) and certain brain structures are better preserved as a result of exercise (Colcombe et al., 2006). Better cardiorespiratory fitness has also been associated with lower prevalence of cardiovascular risk factors (Aspenes et al., 2011), which in turn have been linked to decline in cognitive functions with age (Stampfer, 2006).

To better understand how physical health and cardiorespiratory fitness influences cognitive functions in ageing, it is necessary to first understand how the brain changes with age and how this affects the various cognitive abilities. This will be outlined in the following sections and includes a short overview of the effect of ageing on executive functions, processing speed and memory. The thesis will then go on to describe the role of other health related factors on cognition such as cardiorespiratory fitness as measured by $VO2_{peak}$, the metabolic syndrome (MetS) and cerebro-cardiovascular disease.

1.1 The ageing brain

Atrophy of the brain can be seen in normal ageing as well as in pathological ageing. One study found an annual rate of 2.1% cerebral volume loss in healthy ageing subjects over a period of 4.4 years (Tang, Whitman, Lopez, & Baloh, 2001). This loss of volume is more likely to occur due to lower

synaptic densities than loss of neurons (Terry, 2000), though this could vary from one brain region to another (Uylings & de Brabander, 2002). Volume loss is therefore not uniform across the brain, where frontal and parietal lobes show more atrophy than temporal and occipital lobes (Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003). Resnick et al. (2003) longitudinally investigated whether cerebral volume loss occurred mostly due to atrophy of gray matter, white matter or equal volumes of both, and they found that both gray and white matter decayed over a 4 year period, but that non-significant trends showed that white matter decayed more than gray matter (Resnick et al., 2003). Salat et al. (1999) found support for this trend, and more research is going into the specific role of white matter in cognitive impairment (Back et al., 2011).

In white matter tissue, the level of myelin decreases as a result of age. This can happen due to oxidative stress as free radicals are known to be particularly damaging to myelin (Back et al., 2011). Furthermore, the number of myelinated fibre tracts decreases (Sullivan & Pfefferbaum, 2003) and incidents of white matter hyperintensities (WMH) increase with age (Salat, Kaye, & Janowsky, 1999). WMH are lesions to white matter thought to occur due to ischemic insults. This is relevant for cognitive functions for the reason that lower white matter integrity results in decreased cognitive function (Salat et al., 1999; Sasson, Doniger, Pasternak, Tarrasch, & Assaf, 2012). As a result of cerebral volume loss, cerebrospinal fluid (CSF)-filled spaces increase. One study found that the sulci and ventricles increase by nearly 3% each year in men between the ages of 70-82 years and that this increase accelerated with age (Sullivan, Pfefferbaum, Adalsteinsson, Swan, & Carmelli, 2002). Blood supply to the brain also deteriorates with age; arteries narrow and harden which results in reduced and less compliant blood flow. This gives rise to small vessel disease which in turn may lead to impaired cognition (Iadecola, 2013). There are other risk factors for vascular impairment that can also have a negative effect on cognition: high blood pressure, diabetes, obesity and leading a sedentary lifestyle can also reduce cerebral blood flow (Knopman & Roberts, 2010). These latter risk factors also increase with age.

1.2 Ageing and Cognition

Age is by far the biggest risk factor for developing cognitive impairment and dementia (Bondi et al., 2008). Dementia is a serious neurodegenerative disease that involves cognitive decline in previously unimpaired persons, to a degree beyond what is expected due to normal ageing. Dementia is often preceded by mild cognitive impairment (MCI), which displays as cognitive impairment to a degree that is not serious enough to classify as dementia (Petersen, 2004). The Norwegian Directorate of Health has estimated that ~71 000 individuals and approximately 80% of people living in nursing homes suffer from some type of dementia in Norway (Helsedirektoratet, 2011). With the predicted

demographic change in age distribution in Norway, The Norwegian Directorate of Health expects more than 135 000 people to suffer from dementia in 2040.

There are several types of dementia where the most common are Alzheimer's disease (AD), vascular dementia (VaD), frontal lobe dementia, and dementia with Lewy-bodies. Among these, AD is the most prevalent in the Western world and it is pathologically characterized by atrophy of the brain, loss of synapses, accumulation of amyloid-β in the cortex and neurofibrillary tangles (Karantzoulis & Galvin, 2011). Nevertheless, most individuals with dementia rarely have one clear form of either dementia-type, but rather have mixed pathologies that represent various combinations of several distinct pathological processes (Fotuhi, Hachinski, & Whitehouse, 2009).

Neuropsychological testing can give indications as to which areas of the brain may be implicated in cognitive impairment, both normal and pathological, as different tests are sensitive to functioning of different brain regions. The first neuropsychological symptoms of ageing typically implicate processing speed, executive functioning and learning and memory (Bondi et al., 2008). Numerous brain areas work in concert to carry out these specific tasks (Bennett & Madden, 2013), and they should therefore not be investigated in isolation. Even so, the cognitive functions will be described separately in the following section.

1.2.1 Processing speed

The speed at which people process information is affected by age (Bryan & Luszcz, 1996). However, since other cognitive domains such as executive functions and working memory taps into processing speed (Cepeda, Blackwell, & Munakata, 2013), it is hard to declare whether it decays directly due to age or due to secondary factors (Brown, Brockmole, Gow, & Deary, 2012). Processing speed has been found to depend greatly on the integrity of white matter (Kerchner et al., 2012). Particularly, the breakdown of white matter fibre bundle integrity has been associated with slower processing speed (Ystad et al., 2011), where degeneration of axonal integrity due to loss of myelin in white matter and/or other types of axonal damage was found to interrupt the connection between relevant brain structures and consequently result in the observed reductions in speed of processing (Burgmans et al., 2011).

Comparison tests are typically used to assess processing speed. A more accurate measurement of processing speed is thought to be achieved when participants are asked to perform simple speeded comparison tasks, such as deciding whether two numbers or two figures are identical or not. This is because demands on other cognitive domains might be placed in addition to processing speed when participants are asked to perform more complex tasks such as solving arithmetic problems or answer questions based on comprehension, (Salthouse & Babcock, 1991).

1.2.2 Executive functions, working memory and attention

Executive functions and working memory are mainly responsible for mental manipulation of information, problem solving and cue-directed behaviour (Weintraub, Wicklund, & Salmon, 2012). Working memory is restricted in its capability, but allows retention and mental manipulation of information from a limited number of items during a short period of time (Baddeley, 2003). Age-related reductions in frontal lobe functioning and attention, collectively known as the central executive function, can result in impaired working memory abilities (Brown et al., 2012). Executive functions have been correlated with white matter integrity, especially in middle cerebral and posterior brain regions (Kennedy & Raz, 2009). Kennedy and Raz (2009) concluded that executive functions rely on the integrity of widely dispersed networks of connections in white matter tissue, and that the fronto-parietal network is of particular importance.

Digit span backwards (DSB) measures executive functions, attention and working memory (Clark et al., 2011). In the normal forward digit span test, older adults perform equally well as younger adults for the reason that classical forward tasks taps into the typically spared short-term memory (Hedden & Gabrieli, 2004). Oppositely, when people are asked to mentally manipulate the numbers to repeat in a backward fashion, older adults perform worse than younger adults. This is because the DSB mainly taps into executive functions and working memory which are cognitive domains usually implicated in age-related cognitive decline (Bryan & Luszcz, 1996). A combination of executive function tests, including DSB, allowed discrimination between frontotemporal dementia and healthy older adults, as well discrimination between two different types of frontotemporal dementia (Hornberger, Piguet, Kipps, & Hodges, 2008). In fact, Horbnerger et al. (2008) found that DSB alone correctly classified 82% of patients with the behavioural variant of frontotemporal dementia.

The Tower of London is another test that assesses executive functions. This test measures the ability to plan and solve problems as well as the ability to inhibit inappropriate moves or break rules. The task therefore demands continuous self-monitoring (Rainville, Lepage, Gauthier, Kergoat, & Belleville, 2012). Performance on this test has been found to decrease with age (Zook, Welsh, & Ewing, 2006). Rainville et al. (2012) found that individuals with MCI broke more rules compared to healthy age-matched controls. Furthermore, Rainville et al. (2012) found that individuals with a type of MCI likely of progressing to AD had more rule breaking incidents due to triggers compared to individuals with a stable form of MCI that was not likely to develop into AD. These triggers were lures that invited participants to make incorrect moves.

1.2.3 Memory

Memory is typically divided into two major categories: conscious recollection of facts and events (declarative memory) and memory for learning which cannot be expressed with words (non-declarative). Declarative memory can be further divided into memory for facts (semantic knowledge) and memory for events (episodic memory) (Figure 1). Both verbal and spatial memory are part of episodic memory. In ageing, declarative memory is most affected. Decline in episodic memory performance specifically is one of the first signs of old age. In contrast, non-declarative memory appears more or less unaffected as we age (Kessels, Boekhorst, & Postma, 2005).

Declarative and non-declarative memory are also classified as long-term and short-term memory. The most important structures for long-term abilities are the hippocampus and its adjacent structures such as the entorhinal, perirhinal and parahippocampal cortices (Squire & Zola, 1996). Lesion studies show that damage to these structures can result in anterograde amnesia, which are problems storing new memories. The grade and severity of amnesia depends on size, shape and location of the lesion. It is believed that new memories are formed and consolidated in the hippocampus and eventually stored in the neocortex via an interplay between neocortical sites and the medial temporal lobe (MTL) structures (Squire & Alvarez, 1995). After a memory has been stored in the neocortex, retrieval and activation is independent of the hippocampus. Meanwhile, short-term memory refers to the type of memory that lasts for a very limited amount of time, typically seconds to hours (Baddeley, 2003). These types of memories can also be consolidated and eventually turned into long-term memory (Baddeley, 2003).

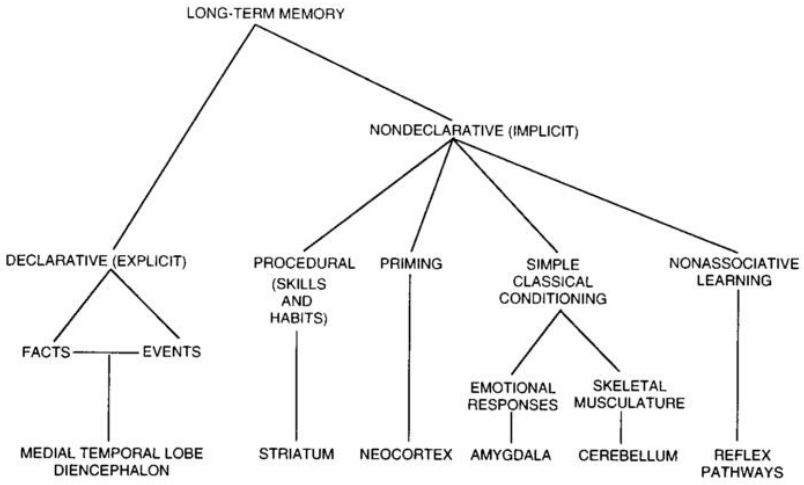

Figure 1: Division of memory (Squire & Zola, 1996).

One neuropsychological test to assess episodic memory is the California Verbal Learning Test (CVLT-II) (Beck, Gagneux-Zurbriggen, Berres, Taylor, & Monsch, 2012). It measures an individual's ability to encode and store new verbal information, both in relation to short-term and long-term. Damage to structures related to episodic memory, such as the hippocampus and the entorhinal cortex, are

therefore assessed by the CVLT-II (Beck et al., 2012). According to Beck et al. (2012), these structures are the first to experience age-related deterioration in AD.

Another important aspect of memory is spatial memory, and it refers to the ability of binding an object to a location. Humans use this ability to navigate in space, and it is thought to comprise of three mechanisms; object processing, spatial-location processing and object-to-location binding (Postma, Kessels, & van Asselen, 2008). Single objects can be identified from the surroundings, or in other words; a spatial location point codes the position for an object of interest (Postma et al., 2008). The temporal lobes, particularly the right hemisphere, is thought to encode the distinctiveness of the object, while spatial-location processing is thought to be supported by the right posterior parietal cortex, also including the prefrontal and hippocampal areas. Finally, the hippocampal formation seems most important for binding of the object to its location (Postma et al., 2008). Spatial memory also consists of a long-term and short-term component. One study showed that that the binding between the memory for an object and its location was impaired when adding 3 seconds to the retention interval (Pertzov, Dong, Peich, & Husain, 2012). The result was an increased likelihood of misplacing objects. The authors hypothesised that the phenomenon occurred due to failure of binding the two memories together rather than failure to recall either the object or the location. They believed that the increase in retention time contributed to rapid short-term forgetting, as shown by increased misplacing of objects, and that the link between the two memories diminish over time instead of the memories themselves. Object-to-location binding abilities decrease with age (Kessels et al., 2005).

To test spatial memory, various paradigms for object-location have been developed. These typically allow participants a certain amount of time to encode a set of objects and their location, before the objects are moved away from their original location. Participants are required to place the objects back in their correct location (Alexander, Packard, & Peterson, 2002; Milner, Johnsrude, & Crane, 1997).

1.2.4 Pattern separation

Pattern separation is the ability to differentiate between new yet related information from previously stored memories. In other words, it is the ability to reduce the overlap between two representations (Kirwan & Stark, 2007). In this way, interference between two memories is avoided. The process of pattern separation is thought to occur when partial or obscured cues in the environment ignite similar (pattern completion) or dissimilar (pattern separation) neuronal patterns. Pattern completion is thought to be supported by the CA1 subfields of the hippocampus whereas pattern separation is thought to be supported by the dentate gyrus and CA3 subfields (Bakker,

Kirwan, Miller, & Stark, 2008). In animal models, there appears to be a shift from pattern separation towards pattern completion, where larger disparity between similar stimuli were needed for separation to occur in older animals (Wilson, Gallagher, Eichenbaum, & Tanila, 2006). This impairment of pattern separation was also found in older humans (Yassa et al., 2011).

Tests of pattern separation are not traditionally included in neuropsychological testing. Instead, they are used for scientific purposes, and pattern separation paradigms are often based on human fMRI studies such as the one by Kirwan and Stark (2007). The aims of these studies are to reveal the role of MTL structures in learning and memory performances.

1.3 Physical Health and Cognition

The World Health Organisation (WHO) defines health as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity" (WHO, 1948). There are several ways to measure health and three measurements were chosen for this study based on their previously shown effects on cognition: 1) cardiorespiratory fitness as measured by $VO2_{peak}$ 2) the metabolic syndrome (MetS) and; 3) cerebro-cardiovascular disease, measured in the present study as the risk for developing atherosclerotic cardiovascular disease (ASCVD) within the next 10 years. The effect of these measurements on cognition will be discussed in the following sections.

1.3.1 Cardiorespiratory fitness and cognition

The gold standard for measuring an individual's cardiorespiratory fitness is maximum oxygen uptake, referred to as $VO2_{max}$ (Aspenes et al., 2011). Higher values indicate better cardiorespiratory fitness. As people age, frailty increases, thus making maximum exercise testing difficult in older adults (Church et al., 2008). Individuals who are not able to meet the criteria of $VO2_{max}$ are given the suboptimal measure $VO2_{peak}$, and this has been proven a valid substitute for $VO2_{max}$ (Day, Rossiter, Coats, Skasick, & Whipp, 2003).

A rapidly growing body of literature suggests that physical exercise aiming at increasing an individual's level of cardiorespiratory fitness may play a protective role on cognition and brain health as we age. By carrying out a one-year exercise intervention in a healthy group of elderly participants, Erickson et al. (2011) found that the normal rate of 1.4% annual decrease of hippocampal volume was reduced (Erickson et al., 2011). Instead, the participants' hippocampal volume increased with 2%, thus resetting 1-2 years of age-related deterioration. The effect was seen selectively in the anterior hippocampus, indicating that the positive effects of increased cardiorespiratory fitness was not spread equally throughout the brain but affected some areas more than others. As a consequence of this selectivity, cognitive functions such as spatial memory improved. The control group experienced hippocampal volume decline as expected.

Executive functions and working memory are other higher order cognitive abilities that have been shown to specifically improve with higher levels of cardiorespiratory fitness (Colcombe & Kramer, 2003). As these abilities are associated with frontal lobe functioning, one can assume that these areas benefit most from increased cardiorespiratory fitness. These exercise induced changes in the brain have also been found in patients already diagnosed with AD, as Burns et al. (2008) found that increased levels of cardiorespiratory fitness led to reduced global atrophy in AD. Erikson et al. (2010) found that a minimum level of physical activity, as measured by blocks walked every day, was needed for a positive association between physical activity and lager volumes of grey matter to be seen 9 years later (Erickson et al., 2010). Walking more than this distance did not increase cognitive functions.

Ideas based on cortical disconnection theories suggest that information processing abilities such as perception, attention and memory are made possible in the brain due to the cooperative and simultaneous processing of several brain regions. Disruption of these connections between key brain areas may lead to deterioration of cognitive functions (Bennett & Madden, 2013). The breakdown of white matter integrity seems central especially in the decline of executive functions and processing speed abilities (Ystad et al., 2011). Consistent with these findings, Voss et al. (2010) showed that cortical connections in healthy seniors were strengthened after a 6 month aerobic training intervention, and that this was associated with better executive functions (Voss et al., 2010).

In an animal model, neurogenesis in the dentate gyrus of the hippocampus was found in response to voluntary exercise in a running wheel. This led to increased long term potentiation, the cellular mechanism for learning and memory, and was taken as evidence for enhanced learning (Farmer et al., 2004). Based on these findings, Pereira et al (2005) investigated whether similar processes occur in the human brain, and the authors found that higher levels of fitness was associated with increased cerebral blood volume in the human dentate gyrus (Pereira et al., 2007). This in turn correlated with improved performance on a modified version of the Rey Auditory Verbal learning test which assesses declarative memory. The authors took this as possible evidence for human neurogenesis, as increased cerebral blood volume has been shown to correlate with neurogenesis in animal models.

1.3.2 Metabolic syndrome and cognition

MetS is a cluster of interconnected factors, and people with the syndrome are at increased risk of developing coronary heart disease (CHD), cardiovascular atherosclerotic disease (CVD) and diabetes type 2 (Kassi, Pervanidou, Kaltsas, & Chrousos, 2011) among others. There are various definitions of the syndrome, however high blood pressure, antihypertensive treatment, elevated or lowered lipid parameters and presence of diabetes and obesity are often included (Brumpton et al., 2013). These

many factors, their varying degree of severity and their estimated possible contribution to MetS make the syndrome heterogeneous, and its prevalence varies across gender, age and ethnicity (Panza et al., 2010).

Many of the MetS factors have independently been associated with higher risk of cognitive decline, two will be described here. For example, diabetes was linked to decreased cognitive performance and increased risk of developing cognitive impairment (Yaffe, Blackwell, et al., 2004), and it was found to specifically result in slower speed of processing and lowered mental flexibility (Brands, Biessels, de Haan, Kappelle, & Kessels, 2005). Diabetes has also been associated with larger ventricles which in turn are associated with impaired cognition in the elderly (Knopman, Mosley, Catellier, & Sharrett, 2005). It was thought that diabetes caused reduced cerebral perfusion and microinfarction resulting in loss of brain volume and increased ventricular sizes (Fein et al., 2000), however inflammation has also been linked to brain atrophy (Knopman et al., 2005).

Obesity, especially abdominal obesity, is another MetS factor that has been correlated with smaller hippocampi, and the findings were consistent with the hypothesis that obesity is associated with cognitive decline (Jagust, Harvey, Mungas, & Haan, 2005). More adipose tissue leads to higher risk of insulin resistance, diabetes, hypertension, dyslipidaemia, CVD and numerous other diseases (Poirier et al., 2006). It is thought that increased levels of inflammation due to adipokines and cytokines released particularly from adipose tissue, circulate in the body and via several steps result in difficulties regulating insulin levels (Luchsinger, 2008). There are conflicting findings in regard to obesity and age, however, obesity in middle-age has consistently been found to associate with increased risk of developing dementia. The findings are more conflicting in regard to older adults (Luchsinger, 2008). Even though several of the MetS factors have independently been linked to cognitive impairment, the combination of all risk factors appears greater than its individual constituents (Yaffe et al., 2007).

High levels of inflammation increase the risk for developing diabetes and atherosclerosis, and this can in turn present as the adverse effects of MetS. In fact, level of inflammation can help distinguish individuals at high risk of developing adverse effects from those who have low risk (Yaffe, Kanaya, et al., 2004). This is important because level of inflammation is associated with cognitive impairment, and is in fact a central factor in the neuropathology of AD and VaD (Yaffe et al., 2003). Yaffe et al. (2003) found that older participants with MetS showed an increased risk of developing cognitive impairment over a 4 year period compared to older participants without the syndrome, and that the effect was particularly pronounced for individuals with higher levels of inflammation compared to those with lower levels. Inflammation is often characterised by plasma concentrations of C-reactive

protein (CRP) and interleukin-6 (IL-6). Higher levels of these factors have been linked to more rapid cognitive declines (Yaffe et al., 2003) and greater risk of developing diabetes and atherosclerosis (Pradhan, Manson, Rifai, Buring, & Ridker, 2001; Ridker, Buring, Shih, Matias, & Hennekens, 1998). It is evident that there is an important etiological overlap between MetS and AD and VaD, where inflammation may play an important role.

Numerous pathological factors interact and have relative importance in both MetS and dementia, making it difficult to find a causal link between the two. Indeed, some studies report an association between MetS and cognition, whereas others do not. This can indicate that certain variations of MetS may lead to specific types of cognitive impairment. Roberts et al. (2010) found that older adults with MetS in combination with high levels of inflammation had increased likelihood of developing a non-amnestic subtype of MCI but not the amnestic subtype (Roberts et al., 2010). The authors found no overall association between MetS and MCI, and they hypothesised that disagreement of which components and respective cut-off values to use when defining MetS, in addition to varying ways of assessing and defining cognitive impairment could result in the inconsistent findings.

Some researchers have found age to be an important factor with regard to MetS and cognition. One study reported that MetS had no association with lower performance on cognitive tests in individuals older than 85 years (van den Berg, Biessels, de Craen, Gussekloo, & Westendorp, 2007). In fact, impairment of cognitive functions slowed down as age increased in individuals with MetS. The authors believed that the phenomenon was affected by high non-fasting glucose levels, high BMI and high blood pressure. To complicate matters further, one study found that MetS did not predict cognitive performance in healthy older subjects, but that it predicted better cognitive performance and reduced cognitive deterioration in individuals with AD (Watts, Loskutova, Burns, & Johnson, 2013). Other studies have also reported that those over the age of 75 years diagnosed with MetS may have lowered risk of developing AD compared to persons under 75 years of age (Forti et al., 2010) and that the presence of MetS was associated with better performance on cognitive tests (Laudisio et al., 2008).

Even though MetS appears to have a protective role against cognitive impairment after a critical age, diabetes type 2 in very old individuals has also been linked to dementia. A clear link between type 2 diabetes and AD and VaD in men with a mean age of 77 years was found in the Honolulu Aging Study, (Peila, Rodriguez, & Launer, 2002). This association was strongest for those with the apoliprotein (APOE) ε4 allele, the most important gene associated with AD. Diabetes type 2 has also been linked with atrophy of the hippocampus and amygdala in older persons with a mean age of 77, once again supporting the link between diabetes type 2 and AD regardless of age (den Heijer et al., 2003). The

authors suspected that specific effects from metabolic impairments resulting from diabetes type 2 were involved.

1.3.3 Cerebro-cardiovascular disease and cognition

Atherosclerosis is an inflammatory disease and involves accumulation of lipids that may result in injured arteries. This can in turn lead to endothelial dysfunction which impairs the adhesiveness and permeability of the endothelium, effectively hardening and reducing the flexibility of arteries (Ross, 1999). As a result, blood flow to the brain is altered and ischemic strokes may occur (Iadecola, 2013). Having experienced a stroke at any given time in life puts an individual at higher risk of cognitive impairment compared to age-matched individuals who have not experienced a stroke (Knopman et al., 2001).

Risk factors for cerebrovascular disease, particularly due to small vessel disease, includes glucose intolerance, diabetes mellitus, hypertension, dyslipidaemia and obesity, and these in turn overlap with risk factors for AD and VaD (Knopman & Roberts, 2010) (Figure 2). Higher risk of developing cerebrovascular disease has been associated with impaired cognition in individuals over 50 years of age (Llewellyn et al., 2008). The risk factors have independently been linked to cognitive deterioration. For example, midlife hypertension has been associated with cognitive impairment and dementia (Tzourio, Dufouil, Ducimetiere, & Alperovitch, 1999). In particular, a strong connection between hypertension and AD and VaD has been found (Launer et al., 2010). Hypertension has also been linked to atrophy of the hippocampus (den Heijer et al., 2005) and increases in WMH, which in turn correlated with impaired cognition, specifically memory and processing speed (Knopman et al., 2005). In a longitudinal study of middle-aged individuals, hypertension at baseline was correlated with cognitive decline after a 6 year period (Knopman et al., 2001).

Total cholesterol and high-density lipoprotein (HDL) cholesterol are good indicators of CVD risk (Di Angelantonio et al., 2012). These, along with implications in controlling its homeostasis, have been associated with the

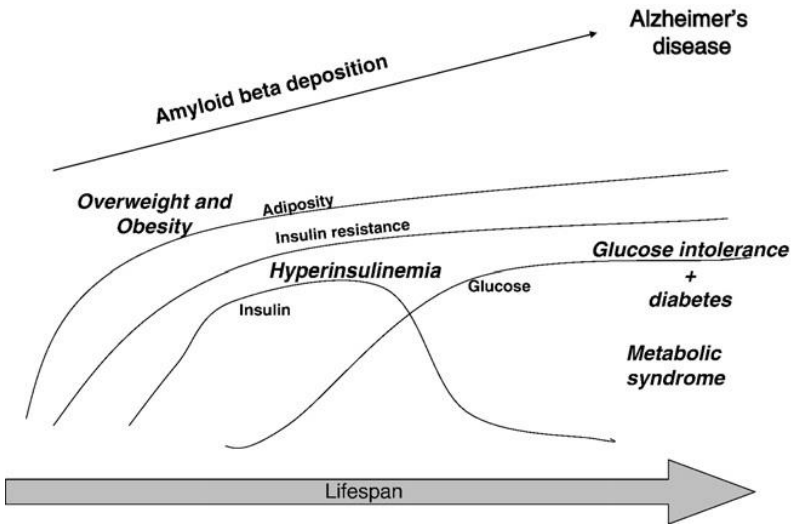

Figure 2: A possible link between obesity and AD. Obesity may lead to hyperinsulinemia, glucose intolerance, diabetes and MetS. This is turn is thought to affect levels of aggregated Aβ in the brain, possibly triggering the development of AD (Luchsinger, 2008). Other CVD-factors may also play important roles.

development of AD (Di Paolo & Kim, 2011). Furthermore, APOE is a low-density lipoprotein that carries cholesterol in the blood, and the gene that codes this protein, the ε4 allele, is overrepresented in AD (Bondi et al., 2008). It is suspected that APOE is involved in the aggregation of Aβ and neurofibrillary tangles in the brain, both of which are hallmarks of AD (Bondi, Salmon, Galasko, Thomas, & Thal, 1999). Bondi et al. (1999) found that the presence of APOE ε4 not only had an effect in demented individuals, but that it also had an effect in non-demented older adults. In this study, non-demented older adults with APOE ε4 were found to perform worse than non-demented older adults without APOE ε4 on tests of episodic memory.

Diabetes and obesity are also factors related to cerebro-cardiovascular disease that have been linked to impaired cognition. These will not be further discussed here as they are described under "Metabolic syndrome and cognition".

1.4 Aims of study

In the present study, we aimed at investigating the relationship between old age, physical health and performance on neuropsychological tests. The focus of this master's thesis is therefore the impact of health, as measured by $VO2_{peak}$, MetS and cerebro-cardiovascular disease, as measures by risk of developing ASCVD within the next ten years, and cognitive performance. Cognitive performance was measured by verbal memory (VM), the tower test (TT), processing speed (PrSp), pattern separation (PaSe), images in grid (IiG) and digit span backwards (DSB) using a web based test battery, Memoro. The participants were dichotomised into groups, and we were particularly interested in comparing participants in the extreme range of the physical health values to investigate whether there were any differences in their cognitive performance. We also wanted to look at the associations between the various continuous measures of physical health and the cognitive measurements using regression models. To do so, we implemented physical and cognitive testing in 105 healthy older adults.

The aims in this study were to investigate

- If there are differences in cognitive performance between participants with the highest $VO2_{peak}$ measurements and those with the lowest $VO2_{peak}$ measurements.
- The general relationship between $VO2_{peak}$ and the various cognitive measurements.
- If there are differences in cognitive performance between participants classified as having MetS and those not classified as having MetS.
- If participants with several risk factors contributing to the MetS classification perform worse on cognitive tests compared to those with fewer risk factors.
- The relationship between number of factors contributing to the MetS classification and cognitive performance.

- If there is relationship between inflammation (as measured by CRP) and cognitive performance.
- If those participants at high risk of developing ASCVD perform differently on cognitive tests compared to those with lower risk of developing ASCVD.
- The relationship between risk of ASCVD and cognitive performance.

2 Materials and Method

2.1 Participants

All individuals residing independently in Trondheim County, Norway, and born 1936 – 1942 (n= 6964) received an invitation letter by post to take part in the "Generation 100" study (G100). This study is a clinical randomized trial of the effect of aerobic exercise on cardiovascular health and mortality over three years in a general population. Those who accepted the invitation to G100 were further invited to participate in various substudies including the current study; Generation 100 and cognitive abilities (G100-Cog).

Inclusion criteria for G100 were the ability to walk continuously for 1km and satisfying a number of health requirements to ensure that all participants had the physical fitness required to take part in aerobic training over three years. Exclusion criteria included inability to perform the intervention activities, medical conditions such as ongoing cancer, untreated hypertension, symptomatic valve disease, hypertrophic cardiomyopathy, unstable angina, dementia or any other type of physical condition associated with health risk if participating in the study. Individuals who were already participating in other research programs were also excluded. Data collection including clinical measurements, blood sample collection, questionnaires and physical assessment described below, was carried out at St. Olav's Hospital, Trondheim, from August 2012 to August 2013.

1565 of those who accepted the invitation to participate in G100 and satisfied the criteria for participation were invited to participate in G100-Cog. Those who accepted this invitation completed a web-based neuropsychological test battery, Memoro, developed by the Trondheim fMRI group (Haferstrom, 2013; Pinzka, 2010) and a test of olfactory identification abilities. Norwegian as first language was preferred. In addition, brain MRI at 3T was performed. Participants with pacemakers, other non-MRI compatible implanted objects or other MRI contraindications were excluded.

This master thesis focuses on the cognitive test results combined with the physical measurements from the G100 data collection. G100 (2012/381b) and G100-Cog (2012/849) were approved by the regional ethical committee and adhered to the Helsinki convention. All G100-Cog participants gave written informed consent. Participation was voluntary and participants were informed that they could withdraw their participation at any time without consequences.

2.2 Clinical evaluation, blood samples, questionnaires and assessment of cardiorespiratory fitness

Participants arrived for clinical and physical assessment at the research unit at St Olav's University Hospital. The clinical measurements including blood pressure was measured two times on each arm by using Philips IntelliVue MP50 (Philips medizin systeme, Boeblingen, Germany). A third measurement was taken if the difference between the two systolic blood pressure measurements were of more than 10 mmHg.

Waist circumference was measured using a measuring tape fitted approximately 2 cm above the navel (for procedure, see http://www.myhealthywaist.org/evaluating-cmr/clinical-tools/waist-circumference-measurement-guidelines/index.html).

Height was measured using a simple wall mounted stadiometer (KWS Medical Supplies, Washington, USA).

Body composition; minerals, body fat, visceral fat, muscle mass and weight was measured with a bioelectrical impedance analyser (Inbody 720, BIOSPACE, Seoul, Korea). Participants were asked to remove their socks and stand barefoot on the steel plates of the InBody apparatus while holding one handle in each hand for approximately 60 second.

Fasting blood samples were taken for measurements of C-reactive protein (CRP), glycosylated hemoglobin (HbA1c), high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, total cholesterol, triglycerides and glucose. All participants filled in a questionnaire concerning participants' previous and current medical health as well as previous and current level of physical activity. The questionnaire also included medical family history.

In total the clinical measurements, blood sampling and questionnaires were completed in approximately 60 minutes.

Cardiorespiratory fitness was determined by $VO2_{max}$/$VO2_{peak}$ using graded maximal exercise testing on a motor-driven treadmill or an ergometer bicycle. Only three G100-Cog participants used the ergometer bicycle, and the protocol for this was similar to treadmill testing. Borg's scale (described under "Normative values") was assessed at the beginning of the test, once during the test, and after completion. $VO2_{max}$ was characterised by reaching a respiratory exchange ratio (RER) of ≥ 1.05, a Borg's scale of ≥ 17 and not having increased more than 2ml in VO2 during the last 30 seconds despite increasing workload. If these criteria were not met, participants were described as having reached $VO2_{peak}$.

Participants warmed up by walking at normal speed for 5-10 minutes. Gas analyser (Oxycon Pro, Erich Jaeger, Hoechberg, Germany/Cortex MetaMax II, Leipzig, Germany), face mask (Hans Rudholph, Germany), heart rate monitor (Polar Electro Oy, Kempele, Finland), and blood pressure apparatus (Tango+, SunTech Medical Instruments, Morrisville, North Carolina, USA), was fitted on the participant before inclination was increased and warm-up continued for additional 4-5 minutes. After ending the warm up, inclination was increased by 2% following an individual protocol until the test ended. Speed was also increased if necessary. Blood pressure was registered several times during the test. Participants were strongly encouraged to continue until they reached a RER value above 1.05 or until oxygen consumption reached a plateau, at which point the participant was close to exhaustion and signalled to stop. After stopping the treadmill, participants were instructed to stand still for one minute while blood pressure, Borg's scale, and RER were assessed one last time. Lastly, blood samples were taken for measurements of lactate levels.

Cardiorespiratory fitness testing was completed in approximately 45 minutes.

2.2.1 Normative values

BMI values below 25 is considered normal whereas BMI values above 25 is considered a risk factor for various obesity-related diseases such as hypertension, diabetes and high blood cholesterol (NOEIE Panel, 1998). However, it has been argued that BMI gives an inaccurate measure as muscle mass can highly skew the measurements, giving either false positive or false negative values. Waist circumference has therefore been argued to be a more accurate measure for obesity-related risks than BMI, especially in relation to the older population (Janssen, Katzmarzyk, & Ross, 2004). A waist circumference of ≥ 102 cm for men and ≥ 88 cm for women is considered a risk factor for obesity-related diseases.

The Borg scale is a measure of perceived exertion and comprises a 20 point self-report questionnaire (Borg, 1982). The scale is used to define the validity of an aerobic fitness test, as it is considered a good indicator of physical strain. It is also often used as criteria to determine whether the test subject has reached $VO2_{max}$ or $VO2_{peak}$. A maximum fitness tests is usually considered valid if the test subject reaches a Borg score of ≥ 17 (Edvardsen et al., 2013).

Normative values for $VO2_{peak}$ changes with age, and one study using a similar research group as the current found that a normal $VO2_{peak}$ value for women above the age 70 was 27 mL/kg/min, whereas it was 34 mL/kg/min for men (Aspenes et al., 2011). Furthermore, women who reported low physical activity had an average $VO2_{peak}$ of 24.7 mL/kg/min whereas women who reported high levels of physical activity had 29.0 mL/kg/min. For men, those who reported low levels of physical activity had

an average $VO2_{peak}$ of 30.2 mL/kg/min, whereas those who reported high levels of physical activity had an average $VO2_{peak}$ of 37.5 mL/kg/min.

2.3 Classification of individuals with the metabolic syndrome and calculation of cerebro-cardiovascular risk scores.

The metabolic syndrome was classified according to the definition used in a study based on a similar study population (Brumpton et al., 2013): waist circumference ≥ 88cm for women and ≥ 102 cm for men; triglycerides ≥ 1.7 mmol/L; HDL cholesterol < 1.3 mmol/L in women and < 1.0 mmol/L in men; systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or use of antihypertensive treatment; glucose ≥ 5.6 mmol/L (4 hours since the last meal) and self-reported diabetes. The presence of ≥ 3 of these factors led to a participant being classified as having the metabolic syndrome.

Cerebro-cardiovascular disease was calculated using the ASCVD risk estimator developed by The American Heart Association and the American College of Cardiology (Goff et al., 2013). This estimator utilises age, sex, race, total cholesterol, HDL cholesterol, systolic blood pressure, treatment for hypertension, diabetes and smoking and it provides an estimate of developing ASCVD within the next 10-year as well as lifetime ASCVD risk. The upper/lower value accepted by the calculator was used in cases where a participant's blood measurement exceeded the accepted value.

2.4 Web based cognitive assessment

Participants either completed the cognitive assessment via the Internet in their own homes or on a computer located at the MR-centre. Participants who completed the test at home received an email with username and password attached in a PDF, as well as a link to the neuropsychological test battery. Instructions on how to log on and to use the system was also attached in the PDF. Participants who completed the tests at the MR-centre were assisted when logging onto the web-based neuropsychological test battery as well as given brief verbal instructions on how to progress through the system. These participants were seated in a quiet room alone during testing. Instructions on how to carry out the individual cognitive tests and questionnaires were given verbally via a headset and were identical for all participants regardless of whether they completed the test at home or at the MR-centre.

The test started with two introductory questionnaires where the first concerned participants' sleep and alertness (Appendix 1) and the second questionnaire concerned the computer in use as well as location of the test (Appendix 2). These questionnaires were given to familiarise the participants with the system. The rest of the test-battery included six cognitive tests and three questionnaires. The full

battery lasted for approximately 1 hour and 15 minutes depending on the duration of breaks and time to complete each test.

The order and type of tests included in the test-battery are presented in Table 1. All tests were implemented according to the manual given for each neuropsychological test and modified to allow for web-based computer testing. Scoring was done automatically by the web-based computer program, except when otherwise stated.

Table 1. Order and types of tests and questionnaires in the web-based neuropsychological test battery, Memoro.

Test	Cognitive domain	Brain structures involved
Verbal memory	Declarative + episodic memory	MTL
Tower of London	Executive function + working memory	Frontal lobes
Processing speed	Executive function	Global brain structures
Verbal memory (recall & recognition)	Declarative + episodic memory	MTL
Pattern separation	Pattern separation	CA3/dentate gyrus
BREAK		
Images in grid	Spatial location memory	MTL
HAD	Questionnaire	
Digit span backwards	Executive function + working memory	Frontal lobes
Everyday memory	Questionnaire	
General memory	Questionnaire	

MTL: Medial Temporal Lobe; HAD: Hospital Anxiety and Depression scale

2.4.1 Questionnaires

Hospital Anxiety and Depression: This self-reported questionnaire measures the frequency of anxiety and depression during the last week (Herrmann, 1997). The version used in this study was a 14 item version given on a 4-point Likert scale where 0 represented “not at all” and 3 represented “very often”. Seven of the items concerns anxiety (HAD-A) and seven items concerns depression (HAD-D).

Everyday Memory: This questionnaire measures everyday memory. It is a 22 item questionnaire concerning failure to remember everyday occurrences (Royle & Lincoln, 2008), such as “forgetting something you were told yesterday or a few days ago”. In addition to these 22 items, there are six bogus items added to judge participant’s response validity. This gives a total of 28 items. Responses are given in absolute terms on a 9-point Likert scale, such as “about once per week” or “more than once per week”.

General Memory: This self-report questionnaire was developed to measure participants’ memory over the past 30 years. Participants were asked three questions comparing their present memory to what it were five years ago, 15 years ago and 30 years ago. Responses are given on a 5-point Likert scale where 1 corresponds to “much worse” and 5 corresponds to “much better”.

These questionnaires will not be further discussed in the current work.

2.4.2 Cognitive tests

Verbal Memory Test: This web-based test of VM is similar to the CVLT-II test, except that the words differ and the main list was presented four times, not five times. The four categories used in the test were furniture, fruits, vehicles and animals. There were four trials, each with a total of 16 words that were presented in a random fashion. The same 16 words (word list 1) were presented in all four trials. Participants were presented with a distraction list as the fifth trial. The distraction list had a new set of 16 words (word list 2) from the categories; furniture, body parts, fruits and animals. At the end of each of the five trials, participants were asked to type in each word they remembered (see Figure 3). Finally, participants were asked to type in the words they could remember from word list 1 one more time. This was the immediate free recall test.

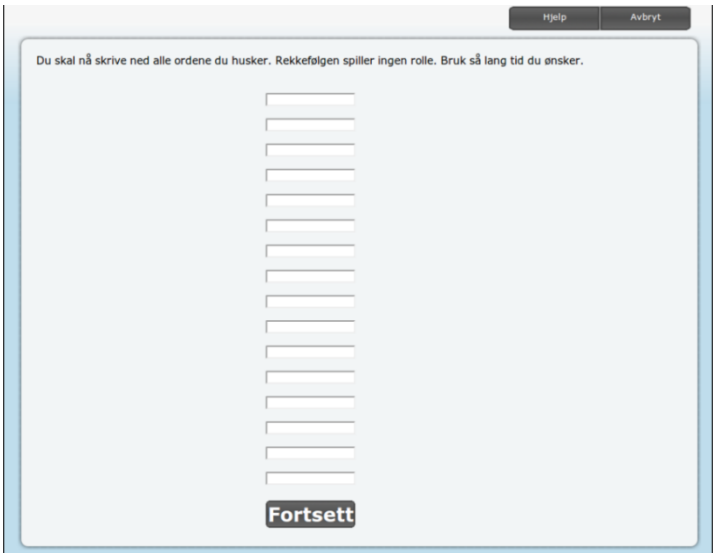

Figure 3: Memory version of VM.

After the immediate free recall test, participants performed other nonverbal tests for approximately 20 minutes before once again being asked to type in all the words they could remember from word list 1. This was the delayed free recall test. They were also presented with all the words from both word lists in a random fashion and asked to decide whether they had heard the particular word in word list 1 or word list 2. This was the forced recognition test and it will not be further mentioned in this thesis. Participants were not informed whether their responses were correct or incorrect.

All written responses were scored by the Memoro system except for those in which participants had responded incorrectly. These incorrect responses were manually evaluated as correct or incorrect before the final score was demined. This was because words that were frequently misheard, misspelled or sounded phonologically similar to another word were registered as an incorrect response by the Memoro system. A word that was clearly meant as a correct response was manually changed from incorrect to correct. Examples are “lomme” instead of “plomme”, “farge” instead of “ferge” or “kayak” instead of “kajakk”.Two separate scores were included in the analyses; the immediate free recall test, VM (imm.rec), and the delayed free recall test, VM (late.rec). The maximum score was 16 for both tests.

Tower Test: This web-based tower test is a modified version of Shallice's tower of Hanoi (Shallice, 1982). It is designed to measure executive functions which are thought to be supported by the frontal lobes (Rainville et al., 2012). Participants were required to copy a pattern of discs on towers with as few moves as possible. Participants were also instructed to obey a set of rules; one could only move one disc at a time and one could only move the top disc. The first peg could fit one disc, the second peg could fit two discs and the last could fit three discs. Participants used the PC-mouse to drag discs from one peg to another (see Figure 4). There were a total number of 15 trials where the first trial required only one move to complete. The test became progressively more difficult by demanding more moves to complete the trial. The most difficult task required 5 moves. Trials were discontinued if participants made more than 20 consecutive moves without completing the required pattern. The total score was counted by each participant's moves (correct + incorrect) divided by the optimal number of moves given the trial they reached before the test discontinued. This number was divided by the average time the participant used to click.

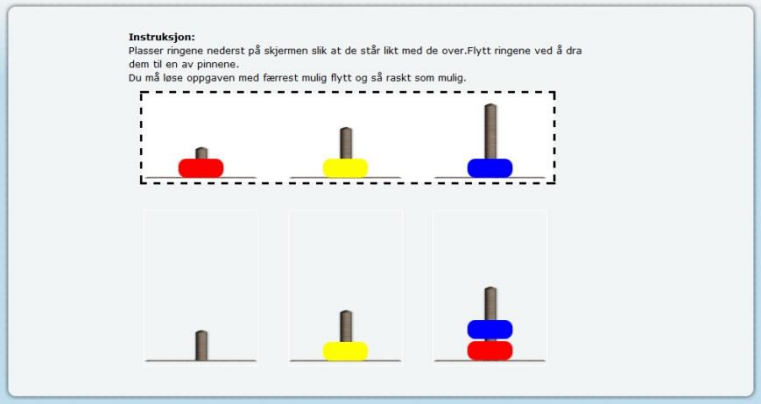

Figure 4: Memoro version of TT.

Processing Speed: The test of processing speed was a web-based version of the "Number comparison test" and the "Letter comparison test", both developed by Salthouse and Babcock. (Salthouse & Babcock, 1991). Participants were asked to decide whether two images were identical or dissimilar. They were instructed to do so as quickly as possible. 30 seconds were given to compare the similarity of as many images as possible in one trial; although a maximum of 24 images could be seen in each trial. The test moved on to the next trial of comparisons if participants did not respond within the given timeframe of 30s. The test consisted of six trials in total; three of which involved numbers and three of which involved simple figures. The test became increasingly more difficult from trial to trial. The participant responded to identical images by pressing the "F" key for dissimilar ("forskjellig") and by pressing the "L" key ("like") for identical (see Figure 5). The total score was the number of correct comparisons, and the maximum score was 144.

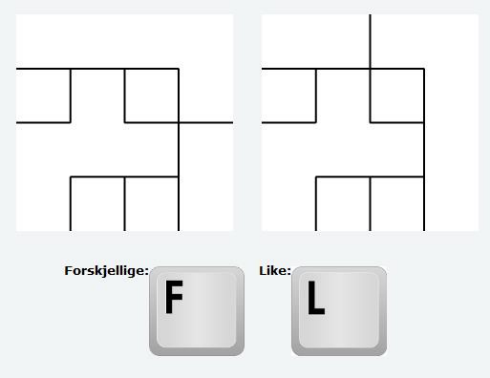

Figure 5: Memoro version of PrSp.

Pattern Separation: This test measures participants' ability to discern pictures that are novel from photos that are similar. This function is thought to be supported by the CA3/dentate gyrus of the hippocampus (Yassa et al., 2011). Participants viewed 108 consecutive images of everyday objects for as long as they needed. For each image, participants were asked to decide whether the image was new, if they had seen the exact same image before, or whether the image was similar to another image they had seen earlier in the same test. There were 16 identical images, 16 images were similar to another previously shown image, and 76 images were new. Participants gave their response by using the PC-mouse to click on the appropriate alternative (see Figure 6). There was no time limit in the test. The total score was the number of correct judgements, and the maximum score was 108.

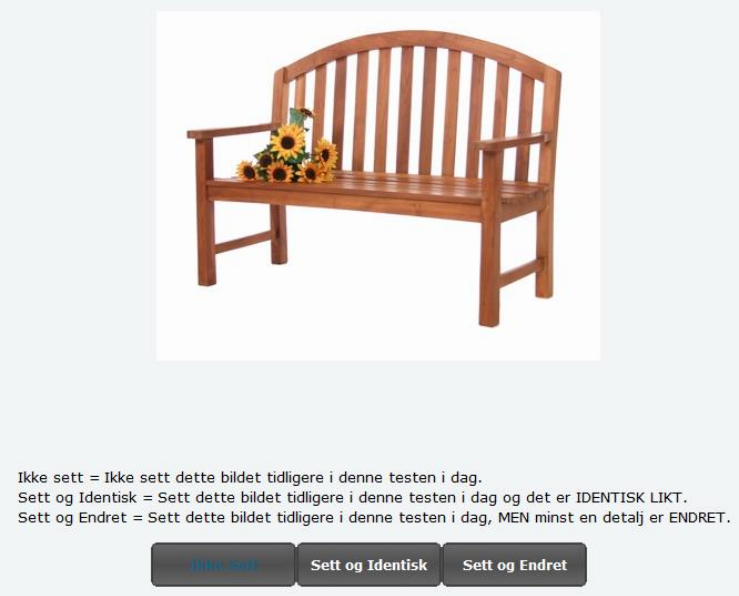

Figure 6: Memoro version of PaSe.

Images in Grid: Binding an object to a specific location is part of spatial memory. In this web-based test, similar to the Silverman and Eals Location Memory test used in another study (Alexander et al., 2002), the participants were shown 18 items to be remembered. Each item was located in one of 36 squares in a 6x6 grid. Life-like objects were used. Objects were presented in their correct locations for 90 seconds (see Figure 7) before they were removed from the grid. Immediately after, the participants were required to place the images back in their original position using the PC-mouse to drag the images from the side of the screen. The images could be moved from location to location until the participant was satisfied. There was no time limit to this part of the test, and the total score was the number of correctly placed images. The maximum score in this test was 18.

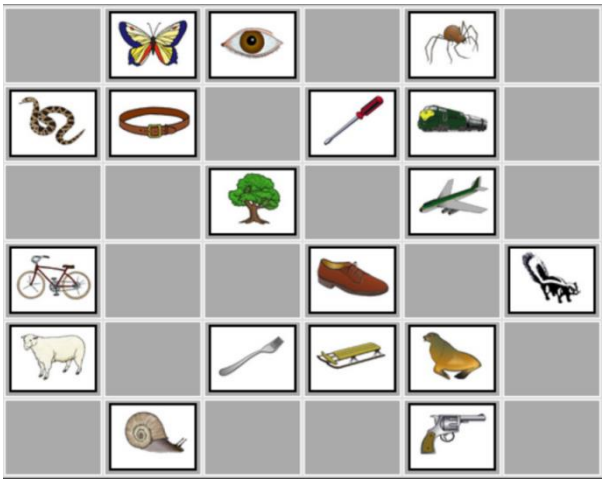

Figure 7: Memoro version of IiG.

Digit Span Backwards: In this test of executive functions and working memory based on the WMS-III Technical Manual digit span backwards test (Psychological Corporation, 2002), digits between one and nine were presented to the participant. Participants were asked to type the same digits, but in a reversed order, into a box that appeared after presentation (see Figure 8). For example, if the participant saw the digits 917, the correct response would be 719. The first and easiest trial contained two digits. The test became progressively more difficult in every other trial by adding one more digit to be repeated. The hardest trial comprised 8 digits. The test was discontinued if more than 3 consecutive errors were made. The participants were unaware of this criterion. The total score was the number of correct responses, with a maximum score of 18.

Figure 8: Memoro version of DSB.

2.4.3 Age, gender and education

With the invitation to participate in the G100 study, participants also received a questionnaire assessing the various inclusion and exclusion criteria for the G100 study. This questionnaire included age, gender, ethnicity, educational level and so on.

Education was divided into four levels as by Statistics Norway (Satistics Norway, 2013), although slightly modified to ensure approximately equal distribution of participants at each level. The 1st level corresponded to 1-7 years of education, 2nd level corresponded to 10 years of education, 3rd level corresponded to 13 years of education and the 4th level corresponded to more than 13 years of education.

2.5 Analysis

All data was collected from the Memoro database and prepared for analyses using IBM SPSS Statistics 20. Values are given as mean ± SD and range, except where otherwise stated. Parametric tests were chosen for most of the analyses as the data was normally distributed as judged by histograms and Q-Q plots. However, non-parametric tests were chosen for ordinal data, as one cannot assume equal degree of difference between ranks or levels. Log transformation was performed on one variable to reduce skewness. All values were considered significant if $p \leq 0.05$, and all tests were two tailed.

Independent t-tests were used to look for differences between men and women with regard to age and performance of cognitive tests, whereas Mann-Whitney *U* tests were used to look for differences between men and women with regard to education. To assess gender differences with regard to MetS and ASCVD, Pearson's Chi Square and independent t-tests were used, respectively.

Pearson's r correlation was used to look for correlations between age and cognitive performance, whereas the correlations between education and cognitive performance were assessed using Spearman's Rho correlation. Spearman's Rho was used in these latter tests as education was ranked into four different levels.

For analyses of cardiorespiratory fitness data, the G100-Gog group were dichotomised into two $VO2_{peak}$ groups; those who were 1 SD above (n = 16) the mean $VO2_{peak}$ measurement and those that were 1 SD below (n = 16) the mean $VO2_{peak}$ measurement. The SD for $VO2_{peak}$ was calculated separately for men and women to account for known gender-differences in $VO2_{peak}$ measurements. Independent t-tests were used to see if the high $VO2_{peak}$ group and low $VO2_{peak}$ group performed differently on the various cognitive tests. Regression analyses with $VO2_{peak}$ as a continuous variable, correcting for gender, was performed to investigate its relationship with cognitive performance.

For the analyses of MetS data, participants were also dichotomised into two groups; those with MetS (n = 41) and those without MetS (n = 63). Independent t-tests were used to look for differences in the cognitive performance of these two groups. To investigate the difference in number of MetS factors and cognitive performance, participants were divided into those with 0 MetS factors (n = 10) and those with 4 MetS factors (n = 11). Independent t-tests were used to look for differences. Regression analyses with number of MetS factors as a continuous variable was also performed to investigate its relationship with cognitive performance. This was done to see if number of MetS factors could predict the performance on cognitive tests. Regression analyses with CRP as continuous variable were also used to investigate the relationship between inflammation and cognitive performance. Lastly, as obesity is part of the classification of MetS, regression analyses were used to look at the relationship between cognitive performance and waist (corrected for gender) and BMI.

Cerebro-cardiovascular disease data was calculated using the ASCVD risk estimator. The G100-Cog group were dichotomised into two groups; those who had an ASCVD risk score of 1SD above the average ASCVD risk (n = 18) and those who were 1SD below the average ASCVD risk (n = 17). Independent t-tests were used to investigate if the low ASCVD risk group performed differently compared to the high ASCVD risk group on the various cognitive tests. Regression analyses were performed with risk for ASCVD as a continuous variable, where the relationship between risk for ASCVD and the various cognitive tests were examined. Lastly, as hypertension is part of the ASCVD

calculation, independent t-tests were used to look for differences between participants with and without hypertension.

3 Results

3.1 Participants

3.1.1 Physical demographics

109 participants were interested in participating in G100-Cog. However, three participants withdrew their consent and one did not complete the cognitive test battery. An additional participant was excluded due to previous brain surgery and radiation therapy, resulting in 105 participants to be included in the analyses. Participants were approximately equally distributed between gender, and the age range varied from 72-78 years. Education ranged from levels 1-4 (see "Methods and materials" for more details). Table 2 gives an overview of physical measurements from the G100-Cog group. There were no statistical difference in relation to age and education between men and women.

Three participants were excluded from the $VO2_{peak}$ analyses; two of these were scheduled for bypass surgery and could therefore not reach their true $VO2_{peak}$ measurement and one had unilateral recurrence nerve damage with vocal cord paresis. Therefore, 101 (51 women) were included in the $VO2_{peak}$ analyses. 65.3% participants reached $VO2_{max}$ whereas 34.7% participants reached $VO2_{peak}$. Three participants completed the VO2 test using ergometer bicycle.

One participant did not complete the physical measurements and could therefore not be included in the MetS or ASCVD analyses, leaving 104 participants (52 women) in these analyses. 52.9% of the G100-Cog group were hypertensive, as classified by average systolic blood pressure ≥ 140 mmHg and/or use of antihypertensive treatment.

Table 2 shows that both men and women were classified as overweight based on the average BMI, and there were three men and five women considered morbidly obese while one man was considered severely obese. One woman was considered underweight. The average waist circumference for women was classified as "at risk for obesity-related diseases", (89.0 ± 10.4), whereas the average waist circumference for men were classified as "not at risk" (97.8 ± 9.0). Based on the mean systolic and diastolic blood pressure for both groups, men and women were classified as having pre-high systolic blood pressure and ideal diastolic blood pressure. Men and women had similar Borg's scale scores and the median of these scores was consistent with satisfactory cardiorespiratory testing in both genders. However, the range shows that not all participants reached a satisfactory Borg's scale. The average $VO2_{peak}$ measurement for both genders was close to normal (27.5 ± 5.0 and 33.1 ± 6.4 respectively) (see "Normative values" for more details). However, based on previous findings from Aspenes et al. (2011), the range shows that at least one man and one woman

had $VO2_{peak}$ measurements that corresponded to low levels of physical activity and one man and one woman has measurements corresponded to high levels of physical activity.

Table 2. Overview of morphometric, clinical and physical measurements for men and women in the G100-Cog group. N shows (men/women).

	N	Men	Women	All
Age (years)	(52/52)	74.2 ± 1.8 [72-78]	73.9 ± 1.7 [72-78]	74.0 ± 1.8 [72-78]
Education (level)*	(51/52)	3.0 [1-4]	3.0 [1-4]	3.0 [1-4]
BMI (Kg/m^2)	(52/52)	26.1 ± 2.8 [21.0-35.3]	25.6 ± 3.6 [18.3-34.7]	25.9 ± 3.2 [18.3-35.3]
Waist (cm)	(52/52)	97.8 ± 9.0 [75.0-124.5]	89.0 ± 10.4 [69-110.2]	93.4 ± 10.7 [69-124.5]
Systolic BP (mmHg)	(52/52)	133.6 ± 16.2 [97-170]	137.5 ± 18.6 [101-181]	135.6 ± 17.5 [97-181]
Diastolic BP (mmHg)	(52/52)	76.4 ± 8.3 [57-96]	74.3 ± 8.8 [52-96]	75.3 ± 8.5 [52-96]
Borg's Scale*	(50/49)	18 [13-20]	17 [13-20]	18 [13-20]
VO2 (mL/ (kg·min)	(50/51)	33.1 ± 6.4 [20.3-48.5]	27.5 ± 5.0 [18.8-39.5]	30.3 ± 6.3 [18.8-48.5]

BMI: Body mass index; BP: Blood pressure; VO2: Maximal oxygen consumption. *values are reported as median [min-max].

An overview of the results from the blood samples in the G100-Cog group can be found in Table 3. The reference values are listed according to St. Olav's Hospital's recommendations (St. Olav's Hospital, 2014). The various measurements were within the reference values for both men and women. There was a statistically significant difference between genders in relation to the incidence of MetS, as shown by Pearson's Chi Square test, ($c^2(1, n = 104) = 6.8$, $p = 0.009$). The percentage of participants with MetS based on MetS scores was within previously published prevalence rates for participants >50yrs (45% - 69.1%) (Saad, Cardoso, Martins, Velarde, & Cruz Filho, 2014). This was true for both genders. There was also a statistically significant difference between men and women in relation to ASCVD risk, as shown by independent t-tests; men had significantly higher risk for ASCVD than women ($t(102) = 4.314$, $p = 0.000$). Four participants reported that they were diabetics and eight participants were smokers.

Table 3. Overview of result of blood sample analyses, incidence of MetS and estimated risk scores for ASCVD for men and women participating in G100-Cog.

	Men (52)	Women (52)	All (104)	Reference value
CRP (mg/L)	2.0 ± 3.6 [0.2-20.1]	1.9 ± 2.6 [0.2-18.9]	2.0 ± 3.1 [0.2-20.1]	< 5
HbA1c (%)	5.6 ± 0.4 [5.1-7.2]	5.6 ± 0.3 [5.0-6.7]	5.6 ± 0.3 [5.0-7.2]	4.3 – 5.6
HDL (mmol/L)	1.8 ± 0.6 [0.8-3.7]	1.9 ± 0.6 [1.1-4.5]	1.8 ± 0.6 [0.8-4.5]	0.80 – 2.10 / 1.0 - 2.7
LDL (mmol/L)	3.2 ± 1.0 [0.0-5.2]	3.5 ± 1.3 [0.0-5.7]	3.3 ± 1.2 [0.0-5.7]	2.0 – 5.3
Cholesterol (mmol/L)	5.6 ± 0.9 [3.1-7.3]	6.1 ± 1.0 [3.7-8.2]	5.8 ± 1.0 [3.1-8.2]	3.9 – 7.8
Triglycerides (mmol/L)	1.0 ± 0.5 [0.4-2.7]	1.0 ± 0.4 [0.4-2.2]	1.0 ± 0.5 [0.4-2.7]	0.45 – 2.60
Glucose (mmol/L)	5.5 ± 0.7 [4.2-8.3]	5.6 ± 0.6 [4.2-7.8]	5.6 ± 0.7 [4.2-8.3]	4.0 – 6.0
MetS	n = 14 (26.9%)	n = 27 (51.9%)	n = 41 (39.4%)	
ASCVD	25.1 ± 6.6 [13.2-43.8]	19.4 ± 6.9 [9.2-39.2]	22.3 ± 7.2 [9.2-43.8]	
Diabetes	n = 3 (2.9%)	n = 1 (1%)	n = 4 (3.8)	
Smokers	n = 3 (2.9%)	n = 5 (4.8 %)	n = 8 (7.7%)	

CRP: C-reactive protein; HbA1c: glycosylated haemoglobin; HDL: high-density lipoprotein cholesterol; LDL: Low-density lipoprotein cholesterol; MetS: Metabolic syndrome; ASCVD: Atherosclerotic cardiovascular disease. ASCVD and MetS were calculated from blood measures and clinical data (for more details see "Materials and Methods").

Groups based on $VO2_{peak}$ were divided according to ± 1 SD of the mean $VO2_{peak}$ value calculated separately for men and women. Those who were 1 SD above the mean were classified as having high $VO2_{peak}$ and those who were 1 SD below the mean was classified as having low $VO2_{peak}$. Table 4 gives an overview of the different demographic data, clinical measurements and different scores for the high and low $VO2_{peak}$ groups. There was an equal distribution between gender in the two groups, and no statistically significant differences between the groups in relation to age. However, the high $VO2_{peak}$ group had significantly higher education than the low $VO2_{peak}$ group as shown by Mann-Whitney *U* test (*U* = 62.5, p = 0.009). Furthermore, the low $VO2_{peak}$ group was considered overweight, whereas the high $VO2_{peak}$ group is considered normal based on BMI. The groups did not differ with regard to systolic or diastolic blood pressure, nor did they differ with regard to Borg's scale. The Pearson's Chi-Square test showed that 43.8% of the participants in the low $VO2_{peak}$ group were classified as having MetS (n = 7) compared to 31.2% of the participants in the high $VO2_{peak}$ group (n = 5). The difference was not statistically significant. The groups differed slightly in risk for ASCVD; however this was not statistically significant.

Table 4. Overview of morphometric, clinical and physical measurements results in the dichotomised high and low $VO2_{peak}$ groups in G100-Cog.

	High VO2peak (n = 16)	Low VO2peak (n = 16)
Gender (M/W)	8 / 8	7/ 9
Age (years)	74.0 ± 2.0 [72-78]	74.6 ± 2.0 [72-78]
Education (level)*	4.0 [1-4]	2.0 [2-4]
BMI (Kg/m^2)	23.4 ± 1.8 [20.9-28.1]	27.1 ± 4.3 [18.3-35.3]
Waist (cm)	86.6 ± 7.7 [76.0-99.8]	98.0 ± 16.7 [72.0-124.5]
Systolic BP (mmHg)	138.1 ± 21.2 [106-174]	137.6 ± 14.4 [103-159]
Diastolic BP (mmHg)	73.7 ± 8.3 [59-94]	76.2 ± 11.3 [52-90]
Borg's Scale*	18 [13-20]	17 [13-19]
VO2 (L/min)	39.4 ± 4.6 [32.5-48.5]	21.9 ± 2.2 [18.8-26.7]
MetS	n = 5 (31.2%)	n = 7 (43.8%)
ASCVD	22.7 ± 9.8 [10.1-43.8]	25.0 ± 7.6 [14.9-39.2]

M/W: Men / Women; BMI: Body mass index; BP: Blood pressure; VO2: Maximal oxygen consumption; MetS: Metabolic syndrome; ASCVD: Atherosclerotic cardiovascular disease. *values are reported as median [min-max].

3.1.2 Cognitive demographics

81% of the participants completed the neuropsychological test battery in their homes, whereas 19% completed the tests at the MR-centre. Table 5 shows the cognitive scores for all G100-Cog participants. Independent t-tests showed that women performed significantly better than men on VM (imm.rec), while men performed significantly better than women on PrSp. Men also showed trends of performing better than women on the DSB test; however this was not statistically significant.

Table 5. Descriptive statistics for the cognitive test results from all G100-Cog participants. N shows (men/women).

Test	N	Men	Women	All	p-value
VM (imm.rec)	(42/46)	11.1 ± 2.7 [6-15]	12.3 ± 2.0 [8-16]	11.7 ± 2.4 [6-16]	**.024**
VM (late.rec)	(40/45)	12.1 ± 2.6 [7-16]	12.5 ± 2.2 [7-16]	12.3 ± 2.4 [7-16]	.397
TT	(27/39)	0.28 ± 0.12 [0.07-0.50]	0.25 ± 0.11 [0.02-0.48]	0.26 ± 0.11 [0.02-0.40]	.315
PrSp	(51/50)	45.0 ± 12.1 [23-77]	40.4 ± 11.2 [20-79]	42.7 ± 11.8 [20-79]	**.050**
PaSe	(47/44)	90.3 ± 5.9 [74-99]	90.0 ± 5.1 [77-98]	90.2 ± 5.5 [74-99]	.797
IiG	(51/49)	7.3 ± 3.1 [2-13]	7.5 ± 4.1 [1-17]	7.4 ± 3.6 [1-17]	.809
DSB	(51/45)	8.0 ± 2.6 [4-16]	7.1 ± 2.4 [2-11]	7.6 ± 2.5 [2-16]	.060

VM (imm.rec): Verbal Memory Immediate Recall; VM (late.rec): Verbal Memory Late Recall; TT: Tower Test; PrSp: Processing Speed; PaSe: Pattern Separation; IiG: Images in Grid; DSB: Digit Span Backwards. The p-value shows the difference between genders on the various cognitive tests.

Pearson's correlations were also performed to look for correlations between age and cognitive performance, where it was found that age correlated with TT (p = 0.032). A summary of the correlations between education and the various cognitive tests, using Spearman's Rho correlations, can be found in Table 6. Education correlated significantly with both subtests of VM (imm.rec: *r* = 0.395, p = 0.000 and late.rec: *r* = 0.340, p = 0.002) and with IiG (r = 0.301, p = 0.002). This means that in all cases; more education was positively associated with better performance on these tests.

Table 6. Overview of correlations between education and cognitive tests for all G100-Cog participants.

Test	N	Correlation	p-value
Education vs VM (imm.rec)	88	.395	**.000**
Education vs VM (late.rec)	85	.340	**.002**
Education vs TT	66	.221	.075
Education vs PrSp	101	.188	.060
Education vs PaSe	91	.150	.159
Education vs IiG	100	.301	**.002**
Education vs DSB	96	.125	.226

VM (imm.rec): Verbal Memory Immediate Recall; VM (late.rec): Verbal Memory Late Recall; TT: Tower Test; PrSp: Processing Speed; PaSe: Pattern Separation; IiG: Images in Grid; DSB: Digit Span Backwards. TT was not corrected for age as there was no correlation between age and education.

3.2 Cardiorespiratory fitness and cognition

Table 7 shows descriptive statistics and the results from comparing the cognitive performance of the high versus low $VO2_{peak}$ group. The high $VO2_{peak}$ group had significantly higher PrSp than the low

$VO2_{peak}$ group (t (29) = 3.025, p = 0.005) with a Cohen's *d* of 1.1, indicating a strong effect size. There was no statistical difference in performance between the high and low $VO2_{peak}$ groups on any of the other cognitive tests. However, trends show that those in the high $VO2_{peak}$ group performed better than those in the low $VO2_{peak}$ group on the TT and that those in the low $VO2_{peak}$ group performed better than those in the high $VO2_{peak}$ group on VM (late.rec). A test of sample size showed that only 24 participants would be needed in each group for the TT to reach significance, whereas 47 participants would be required for VM (late.rec) to reach significance. Cohen's *d* was 0.686 and -0.428, indicating large and medium effect sizes, respectively. This will be further debated in the discussion.

Table 7. Overview of descriptive statistics and comparison of cognitive performance in the high and low $VO2_{peak}$ groups. N shows (high $_{VO2peak}$/low $VO2_{peak}$).

Test	N	High VO2 peak	Low VO2 peak	P-value
VM (imm.rec)	(14/13)	11.9 ± 2.0 [8-15]	11.9 ± 2.3 [7-15]	.995
VM (late.rec)	(14/12)	12.4 ± 2.2 [9-16]	13.3 ± 2.0 [8-16]	.285
TT	(11/10)	0.26 ± 0.12 [0.02-0.42]	0.19 ± 0.08 [0.07-0.33]	.190
PrSp	(16/15)	48.6 ± 12.4 [31-77]	36.0 ± 10.7 [20-51]	**.005**
PaSe	(16/14)	91.3 ± 3.7 [84-97]	90.5 ± 4.3 [83-96]	.610
IiG	(16/15)	8.1 ± 3.3 [3-13]	6.7 ± 4.0 [1-14].	.298
DSB	(16/13)	8.0 ± 2.0 [3-11]	7.6 ± 3.5 [2-16]	.717

VM (imm.rec): Verbal Memory Immediate Recall; VM (late.rec): Verbal Memory Late Recall; TT: Tower Test; PrSp: Processing Speed; PaSe: Pattern Separation; IiG: Images in Grid; DSB: Digit Span Backwards.

When performing linear regression analyses, gender was added as covariate. In the TT analysis, age was also added as covariate. The results are displayed in Table 8. There was a statistically significant relationship between $VO2_{peak}$ and PrSp, where both gender and $VO2_{peak}$ combined significantly predicted performance on the PrSp test, F (94) = 5.724, p = 0.005. After correction for gender, this association remained significant (p = 0.01), and showed that there was an increase of 0.283 comparisons for every SD increase in $VO2_{peak}$.

Table 8. Linear regression analyses of $VO2_{peak}$ as a continuous variable and the various cognitive measures, corrected for gender.

Test	N	Standardised β	P-value	R^2
VM (imm.rec)	84	.048	.684	.062
VM (late.rec)	81	-.014	.909	.006
TT	65	.120	.402	.099
PrSp	97	.283	**.010**	.109
PaSe	93	.101	.383	.014
IiG	96	.034	.769	.001
DSB	92	.060	.594	.048

VM (imm.rec): Verbal Memory Immediate Recall; VM (late.rec): Verbal Memory Late Recall; TT: Tower Test; PrSp: Processing Speed; PaSe: Pattern Separation; IiG: Images in Grid; DSB: Digit Span Backwards. Standardised β represents the increase in test score for every SD increase in VO2. R^2 represents the overall model fit.

3.3 Metabolic syndrome and cognition

Results from comparing the performance on the various cognitive tests of participants with and without MetS are shown in Table 9. There were no statistically significant differences between those classified as having MetS and those classified as not having MetS. A calculation of sample size for VM (late.rec) and TT show that even though trends based on averages indicate that individuals classified as having MetS tend to perform better than those without MetS, it would take groups of ~500 and ~1500 participants, respectively, to demonstrate significance. Calculations of effect size shows a Cohen's *d* of 0.128 and 0.079, respectively, indicating small effect sizes for both. This will be further debated in the discussion.

Table 9. Overview of descriptive statistics and comparison of cognitive performance in those with and without MetS. N shows (with MetS/without MetS).

Test	N	With MetS	Without Mets	P-value
VM (imm.rec)	(36/52)	11.9 ± 2.2 [6-15]	11.6 ± 2.6 [6-16]	.645
VM (late.rec)	(34/51)	12.5 ± 2.4 [7-16]	12.2 ± 2.3 [7-16]	.478
TT	(31/35)	0.27 ± 0.14 [0.07-0.50]	0.26 ± 0.11 [0.02-0.45]	.660
PrSp	(40/61)	42.1 ± 13.7 [20-79]	43.1 ± 10.5 [20-63]	.698
PaSe	(37/54)	89.5 ± 5.5 [77-99]	90.6 ± 5.4 [74-98]	.361
IiG	(38/62)	7.5 ± 4.0 [1-17]	7.4 ± 3.4 [2-14]	.908
DSB	(37/59)	7.3 ± 2.4 [3-12]	7.8 ± 2.6 [2-16]	.427

VM (imm.rec): Verbal Memory Immediate Recall; VM (late.rec): Verbal Memory Late Recall; TT: Tower Test; PrSp: Processing Speed; PaSe: Pattern Separation; IiG: Images in Grid; DSB: Digit Span Backwards.

Table 10 shows the results from comparing participants with 0 MetS factors with participants who had 4 MetS factors. There were no statistically significant differences between these two groups. Sample size was calculated for VM (imm.rec) and IiG to illustrate that even though trends based on averages show that those with 4 MetS factors performed better than those without any MetS factors, it would take 307 and 25 participants, respectively, in each group for these trends to become significant. The effect size was -0.173 and -0.615 respectively, indicating a small effect size for VM (imm.rec) and a large effect size for IiG. This will be further debated in the discussion.

Table 10. Overview of descriptive statistics and comparison of cognitive performance in those with 0 MetS factors and those with 4 MetS factors. N shows (with 0 MetS factors/with 4 MetS factors).

Test	N	With 0 MetS factors	With 4 Mets factors	P-value
VM (imm.rec)	(7/10)	11.9 ± 2.5 [8-14]	12.3 ± 2.1 [9-15]	.701
VM (late.rec)	(7/10)	12.9 ± 2.0 [10-15]	12.5 ± 3.0 [7-16]	.788
TT	(5/7)	0.28 ± 0.14 [0.11-0.45]	0.27 ± 0.11 [0.11-0.42]	.929
PrSp	(10/11)	41.5 ± 10.9 [23-60]	42.6 ± 17.3 [20-77]	.861
PaSe	(9/10)	89.8 ± 2.8 [85-93]	90.0 ± 3.8 [84-97]	.887
IiG	(10/10)	5.3 ± 2.4 [2-11]	6.9 ± 2.8 [2-11]	.188
DSB	(9/11)	6.7 ± 2.3 [3-10]	7.2 ± 2.9 [3-12]	.670

VM (imm.rec): Verbal Memory Immediate Recall; VM (late.rec): Verbal Memory Late Recall; TT: Tower Test; PrSp: Processing Speed; PaSe: Pattern Separation; IiG: Images in Grid; DSB: Digit Span Backwards.

The regression analyses between the number of factors contributing to the classification of MetS and performance of the cognitive tests are displayed in Table 11. The TT analysis was corrected for age. As can be seen, the number of factors contributing to the MetS classification did not reveal any statistically significant relationships. This means that the number of factors contributing to the MetS classification did not predict participants' performance on the various cognitive tests.

Table 11. Regression analyses with number of MetS factors as continuous variable and cognitive performance.

Test	N	R	R^2	P-value
VM (imm.rec)	88	.106	.011	.327
VM (late.rec)	85	.076	.006	.487
TT	66	-.004*	.070	.973
PrSp	101	.015	.000	.882
PaSe	91	.020	.000	.851
IiG	100	.082	.007	.418
DSB	96	.019	.000	.854

VM (imm.rec): Verbal Memory Immediate Recall; VM (late.rec): Verbal Memory Late Recall; TT: Tower Test; PrSp: Processing Speed; PaSe: Pattern Separation; IiG: Images in Grid; DSB: Digit Span Backwards. *Shows standardised β value which refers to the increase in TT-score for every SD increase in MetS factors.

Table 12 shows the regression analyses with CRP as a continuous variable and cognitive performance. CRP was log transformed to reduce skewness and the TT analysis was corrected for age. There were no statistically significant relationship between CRP and cognitive performance.

Table 12. Regression analyses with CRP as continuous variable and cognitive performance.

Test	N	R	R^2	P-value
VM (imm.rec)	88	.042	.002	.697
VM (late.rec)	85	.082	.007	.455
TT	66	-.112*	.082	.360
PrSp	101	.156	.024	.120
PaSe	91	.117	.031	.093
IiG	100	.032	.001	.750
DSB	96	.057	.003	.584

VM (imm.rec): Verbal Memory Immediate Recall; VM (late.rec): Verbal Memory Late Recall; TT: Tower Test; PrSp: Processing Speed; PaSe: Pattern Separation; IiG: Images in Grid; DSB: Digit Span Backwards. *Shows standardised β value, which refers to the increase in TT-score for every SD increase in CRP.

As waist was used in classifying MetS, its relationship with cognitive performance was also investigated. Gender was corrected for, and the results are displayed in Table 13. TT analyses were also corrected for age. BMI was also included in Table 13 as there has been some dispute with regards to whether waist or BMI best explains obesity-related risk-factors. As shown, there was no statistically significant linear relationship between waist or BMI and performance on the cognitive tests.

Table 13. Linear regression between cognitive performance and waist (corrected for gender) and BMI as continuous variables.

	Waist					BMI			
Test	**N**	**Standardised β**	**p-value**	**R^2**	**Test**	**N**	**R**	**R^2**	**p-value**
VM (imm.rec)	88	.075	.520	.064	VM (imm.rec)	88	.008	.000	.941
VM (late.rec)	85	-.008	.946	.009	VM (late.rec)	85	.083	.007	.449
TT	66	-.099	.469	.096	TT	66	-.155*	.093	.210
PrSp	101	-.017	.877	.038	PrSp	101	.031	.001	.758
PaSe	91	-.107	.355	.010	PaSe	91	.145	.021	.170
IiG	100	.066	.559	.004	IiG	100	.052	.003	.610
DSB	96	-.083	.458	.043	DSB	96	.025	.001	.810

VM (imm.rec): Verbal Memory Immediate Recall; VM (late.rec): Verbal Memory Late Recall; TT: Tower Test; PrSp: Processing Speed; PaSe: Pattern Separation; IiG: Images in Grid; DSB: Digit Span Backwards. Standardised β represents the increase in test score for every SD increase in waist. R^2 represents the overall model fit. *Shows standardised β value, which refers to the increase in TT score for every SD increase in BMI.

3.4 Cerebro-cardiovascular disease and cognition

Table 14 gives the results of comparing those classified as at high risk of developing ASCVD with those classified as at low risk for developing ASCVD. As shown, VM (imm.rec) showed trends of difference between the two groups, where those in the low risk for ASCVD group tended to perform better than those in the high risk for ASCVD group. Cohen's *d* was -0.667, indicating a large effect size; however this did not reach statistical significance. A calculation of sample size shows that it would only take 21 participants in each group for this trend to reach significance. None of the other cognitive tests showed significant statistical differences. The mean response of the two groups showed trends that participants in the high risk group performed better than participants in the low risk group on DSB and PaSe with a Cohen's *d* of 0.574 and 0.181 respectively, indicating a large effect size for DSB and a low effect size for PaSe. Calculations of sample size show that it would take 31 and 271 participants,respectively for these trends to reach significance. This will be further debated in the discussion.

Table 14. Overview of descriptive statistics and comparison of cognitive performance in the high and low ASCVD risk groups. N shows (high ASCVD risk/low ASCVD risk).

Test	N	High ASCVD risk	Low ASCVD risk	P-value
VM (imm.rec)	(15/15)	11.1 ± 2.6 [7-15]	12.7 ± 1.6 [10-15]	.061
VM (late.rec)	(15/15)	12.3 ± 2.8 [7-16]	12.7 ± 1.9 [9-15]	.649
TT	(13/10)	0.27 ± 0.11 [0.07-0.45]	0.29 ± 0.12 [0.02-0.45]	.644
PrSp	(18/16)	43.9 ± 11.2 [26-77]	44.0 ± 9.9 [27-63]	.988
PaSe	(16/15)	91.6 ± 4.7 [78-97]	90.8 ± 4.1 [84-98]	.610
IiG	(18/16)	7.7 ± 3.1 [2-13]	8.3 ± 3.7 [3-14].	.614
DSB	(18/16)	8.7 ± 3.2 [5-16]	7.1 ± 2.3 [3-10]	.110

VM (imm.rec): Verbal Memory Immediate Recall; VM (late.rec): Verbal Memory Late Recall; TT: Tower Test; PrSp: Processing Speed; PaSe: Pattern Separation; IiG: Images in Grid; DSB: Digit Span Backwards.

Table 15 shows the regression analyses of risk for ASCVD and performance on the various cognitive tests. The TT analysis was corrected for age. There were no statistically significant findings; however

risk for ASCVD showed trends of explaining some of the variance in the performance on DSB. On average, the DSB score increased by 0.186 for every SD increase in risk for ASCVD score.

Table 15. Linear regression analyses with ASCVD as continuous variable and cognitive functions.

Test	N	R	R^2	P-value
VM (imm.rec)	88	.127	.016	.239
VM (late.rec)	85	.022	.000	.840
TT	66	.267*	.042	.757
PrSp	101	.019	.000	.848
PaSe	96	.025	.001	.818
IiG	100	.098	.010	.334
DSB	96	.186	.035	.069

VM (imm.rec): Verbal Memory Immediate Recall; VM (late.rec): Verbal Memory Late Recall; TT: Tower Test; PrSp: Processing Speed; PaSe: Pattern Separation; IiG: Images in Grid; DSB: Digit Span Backwards. *Shows standardised β value, which refers to the increase in TT-score for every SD increase in ASCVD score.

As hypertension was used in calculations of risk for ASCVD, investigations of differences between participants with and without hypertension were included. Table 16 shows that there was no statistically significant difference between participants with and without hypertension. Trends based on averages shows that those with hypertension perform better on DSB compared to normotensive participants, and that normotensive participants perform better on PrSp compared to those with hypertension. A test of sample size shows that 148 and 1030 participants would be required in each group, respectively, for these trends to reach significance. A calculation of effect size shows a Cohen's *d* of 0.240 and -0.093 respectively, indicating small effect sizes for both. This will be further debated in the discussion.

Table 16. Overview of descriptive statistics and comparison of participants with and without hypertension. N shows (hypertensive/normotensive).

Test	N	Hypertensive	Normotensive	P-value
VM (imm.rec)	(49/39)	11.9 ± 2.4 [6-15]	11.5 ± 2.5 [6-16]	.546
VM (late.rec)	(47/38)	12.4 ± 2.5 [7-16]	12.2 ± 2.2 [8-16]	.671
TT	(19/48)	0.26 ± 0.13 [0.02-0.50]	0.26 ± 0.10 [0.07-0.45]	.921
PrSp	(54/47)	42.2 ± 12.6 [20-79]	43.3 ± 11.0 [20-65]	.622
PaSe	(47/44)	90.1 ± 4.9 [77-98]	90.3 ± 6.0 [74-99]	.841
IiG	(52/48)	7.5 ± 3.8 [1-17]	7.4 ± 3.4 [2-13]	.905
DSB	(50/46)	7.9 ± 2.4 [3-15]	7.3 ± 2.6 [2-16]	.263

VM (imm.rec): Verbal Memory Immediate Recall; VM (late.rec): Verbal Memory Late Recall; TT: Tower Test; PrSp: Processing Speed; PaSe: Pattern Separation; IiG: Images in Grid; DSB: Digit Span Backwards.

4 Discussion

This study showed that better physical health, as measured by $VO2_{peak}$, affect specific aspects of cognition in older adults. Trends showed that MetS and ASCVD could also affect specific aspects, but we were unable to statistically confirm these trends due to small sample size. Not all aspects of cognition are influenced by physical health in the same way, as some domains are more affected than others. With regard to $VO2_{peak}$, this study showed that older adults with higher $VO2_{peak}$ made significantly more comparisons on the PrSp test compared to older adults with lower $VO2_{peak}$. There was also a statistically significant linear relationship between $VO2_{peak}$ and PrSp, where higher $VO2_{peak}$ predicted higher scores on the PrSp test. Having MetS did not appear to affect cognition in any statistically significant way in this elderly population, nor did level of inflammation, as measured with CRP. Having high risk of developing ASCVD within the next 10 years did not appear to affect cognitive performance; however regression analyses showed trends where the risk for ASCVD was significantly associated with DSB. Here, higher risk of ASCVD predicted higher scores on the DSB test.

4.1 Study population

The morphometric measurements and blood pressure recordings were slightly elevated for more than a few participants in the current study, but the average $VO2_{peak}$ measurements were within the normal range for both men and women. The study population was healthy with regard to blood samples, as all mean values were within their respective reference values. There was a low incidence of smokers and diabetics. Taken together, these clinical and physical data indicate that the current study population was of good health. It would be interesting to compare G100-Cog with G100 to see if G100-Cog is representative of the entire G100 group. However, this is beyond the scope of this thesis.

The current study population was equally distributed between men and women. When looking at differences between genders in relation to cognitive performance, we found a significant effect on VM (imm.rec) and PrSp. Here, women performed better than men on VM (imm.rec) and men performed better than women on the PrSp test. It has previously been shown that women tend to perform better than men on verbal tests (Roivainen, 2011) across life (Camarata & Woodcock, 2006), however the literature on gender differences with regard to tasks of processing speed is more inconsistent (Majeres, 1983). Camarata and Woodcock (2006) reported in a large sample spanning the ages of 2 to over 90 years of age that men performed worse than women on tasks of processing speed, except during the ages 50-79 years; in this age-period, men tended to have a slight advantage. Our findings can only support the trend of men performing better than women between the ages 72-78 years. Nevertheless, another study showed that women were better at clerical-types of

processing speed tasks, such as matching digits. This gender difference was reduced when the task involved geometric shapes (Majeres, 1983). Majeres (1983) concluded that gender differences in tasks of processing speed greatly depend on the type of tasks given, and this could help explain the inconsistent findings in the literature. We found no differences in performance between genders on any of the other cognitive tests.

The G100-Cog group was evenly divided with regard to age, spanning ages from 72 – 78 years. With regard to cognitive functions, research shows that there is typically a negative correlation between age and cognitive functions (Bryan & Luszcz, 1996; Kessels et al., 2005; Lamar, Resnick, & Zonderman, 2003). However, these studies typically use a wider age-range than the current study, and we did therefore not expect to find similar negative correlations. Nonetheless, the TT correlated with age. It has been postulated that performance on tests of executive functions that include planning and problem solving deteriorate more than other cognitive functions as a result of age. In one study, individuals in their 70s and 80s were found to perform significantly worse than individuals in their 20s and 30s on the Tower of Hanoi test and on verbal tests (Davis & Klebe, 2001). Participants in this study were tested again after 6.6 years, and the results showed that the older individuals performed significantly worse on the Tower of Hanoi test but not on the verbal tests compared to their original performance. Younger participants' performance on both the Tower of Hanoi and on the verbal test remained the same during this 6.6 year period. The findings led the authors to believe that non-declarative and/or problem solving abilities suffer more as a result of age compared to declarative abilities. This could explain why only performance on the TT test and not performance on any of the other cognitive tests correlated with age in the present study.

64.4% of the study population had attained higher education, meaning 13 years or more of schooling. Education correlated significantly with performance on some of the cognitive tests, where higher levels of education led to higher scores on both subtests of the VM and on the IiG test. Other studies have also found a positive correlation between higher education and cognition and/or better preservation of cognition (Christensen et al., 1997; Lamar et al., 2003). For example, one study found that lower levels of education was associated with greater declines on the mini mental state examination and on verbal tests among others, but that it had no effect on the symbol letter modalities test, the episodic memory test or choice reaction time (Christensen et al., 1997). There were no correlations between performance and education on any of the other cognitive tests, which is in agreement with previous reports.

4.2 Cardiorespiratory fitness and cognition

When comparing the high $VO2_{peak}$ group with the low $VO2_{peak}$ group, we found that there was a statistically significant difference in PrSp. Those with high $VO2_{peak}$ made significantly more comparisons on the PrSp test than those with low $VO2_{peak}$. Cohen's *d* was 1.1, indicating a very large effect size. The linear regression analysis with corrections for gender showed that there was a statistically significant relationship between $VO2_{peak}$ and PrSp, where there was an increase of 0.283 comparisons on the PrSp task for every SD increase in $VO2_{peak}$. We did not find any other statistically significant results for the other cognitive tests and $VO2_{peak}$.

There is a wealth of research reporting that fitness training in older individuals can increase cognitive performance, where executive functions, reaction time and spatial cognition were most positively affected (Colcombe & Kramer, 2003). We also found evidence that higher levels of fitness, as shown by $VO2_{peak}$, was associated with faster processing speed. Cortical disconnection theories propose that information processing abilities in humans such as perception, attention and memory are possible due to the joint processing of several brain regions. Disruption of the connection between these brain structures can lead to the breakdown of cognitive abilities (Bennett & Madden, 2013). Breakdown of white matter fibre bundle integrity seems important particularly in the deterioration of executive functions and processing speed abilities, as diffusion tensor derived parameters have shown an association between these fibre bundles and the specific cognitive functions (Ystad et al., 2011). Others have found that deterioration of processing speed, but not episodic memory, visuospatial ability or fluency was caused by reductions in the integrity of white matter (Salami, Eriksson, Nilsson, & Nyberg, 2012). In older individuals, a link between white matter integrity and processing speed specifically was reported, where degeneration of axonal integrity via loss of myelin in white matter and/or other types of axonal damage was found to interrupt the connection between relevant brain structures, and result in reduced speed of information processing (Burgmans et al., 2011). Trends showed that this might be true for executive functions as well. Relating these findings to our study, it could be argued that higher values of $VO2_{peak}$ leads to better preservation of white matter tissue and integrity of related fibre tracts in the brain, which in turn specifically leads to better speed of processing. We also found trends that this might be true for executive functions as well, which is consistent with the literature mentioned above. This would mean that speed of processing, and possibly executive functions, are more sensitive to cardiorespiratory fitness compared to other measures of cognitive functions used in the present study.

Better physical fitness is associated with better cardiovascular function, which in turn is associated with better efficiency of blood delivery to the brain. With the delivery of blood come also the delivery of oxygen and other nutrients (Bunce & Murden, 2006) that may lead to better brain tissue

integrity and healthier endothelial functions (Iadecola, 2013). Superior physical fitness is thought to attenuate some of the age-related deterioration in cognitive functions by the higher levels of available nutrients in the brain. Blood supply to the brain is carefully regulated, meaning that all necessary nutrients are available at all times regardless of the activities the person is currently undertaking (Iadecola, 2004). $VO2_{peak}$ measures an individual's ability to take up oxygen during maximal fitness training, or during heavy-workload situations, nevertheless, it is unlikely that higher $VO2_{peak}$ leads to faster speed of processing due to an immediate increase in oxygen whenever an individual is performing a task that requires immediate delivery of oxygen. Given the information previously presented, it is more likely to assume that individuals with higher $VO2_{peak}$, as acquired over a prolonged period of continuously healthy and active living, leads to a superiorly sustained supply of nutrients to the brain. This can lead to positive long-term effects by allowing better preservation of brain tissue and structural integrity, thus resulting in better performance on cognitive tests. Oppositely, individuals with lower $VO2_{peak}$, as acquired over a prolonged period of continuously leading an unhealthy and sedentary lifestyle, may lead to an insufficient supply of nutrients to the brain, possibly leading to negative structural alterations that effectively may result in poorer performance on cognitive tests.

We did not find that level of $VO2_{peak}$ significantly affected any of the other cognitive domains in this study. Although many studies do find that other cognitive faculties are positively affected by higher cardiorespiratory fitness as measured by $VO2_{peak}$, others find that they are not. A meta-analysis of 11 relevant studies with regard to physical activity and enhanced fitness concluded that faculties such as motor function, cognitive speed, delayed memory functions and auditory and visual attention were most beneficially affected by interventions aimed at improving aerobic fitness. However, the authors concluded that most of the comparisons resulted in non-significant findings (Angevaren, Aufdemkampe, Verhaar, Aleman, & Vanhees, 2008). The authors suspected that this was due to methodical differences. For example, it is possible that more than a few of the intervention studies used in the meta-analysis show short-term cognitive improvements, meaning that cognitive gains based on increases in aerobic fitness declines after a certain period post-intervention. Few studies look at the long-term effects of these interventions. Opposite to this, our study reflects the long-term and possibly stable effect of the relationship between $VO2_{peak}$ and cognition, as this relationship is represented by the true habitual living pattern of the participants in our study, and is therefore more likely to represent a true phenomenon in an ageing population. Furthermore, Angevaren et al. (2008) suspected that various physiological processes occur at different times across the lifespan, making it difficult to draw conclusions on its effects on cognition from one group of research participants to another.

4.3 Metabolic syndrome and cognition

We found no statistically significant difference on cognitive performance between individuals with and without MetS, nor were there any statistically significant differences between those with zero MetS factors and those with four MetS factors. However, in the latter analyses there were 10 or fewer participants in each of the groups making it hard to detect statically significant differences. Nevertheless, trends showed that participants with four MetS factors performed better on more than a few of the cognitive tests compared to participants without any MetS factors. For instance, on the IiG test this trend had a Cohen's *d* of -0.615, indicating a large effect size and calculations of sample size showed that this trend would reach significance if we had 25 participants in each group. The regression analyses showed no statistically significant relationship between number of MetS factors or level of inflammation and performance on the cognitive tests. As waist circumference was part of the criteria for MetS, we investigated whether waist/BMI could explain any of the variance in performance on the cognitive tests. We did not find any statistically significant relationships.

MetS is a cluster of factors that include high waist circumference, elevated or lowered lipid parameters, high systolic/diastolic blood pressure, use of antihypertensive treatment, heightened glucose levels and the presence of diabetes (Brumpton et al., 2013). Three or more of these factors classifies as MetS, and individuals with the syndrome are at much higher risk of developing CHD, CVD and diabetes type 2 (Kassi et al., 2011); all of which have independently been associated with deterioration of cognitive functions (Stampfer, 2006). We did not detect any differences between individuals with and without MetS, nor did we find any differences between those classified as having several MetS risk factors and those classified as not having any MetS factors. Conversely, we did find trends showing that those with several MetS factors performed better on cognitive tests compared to those without any factors.

Our findings are both consistent and contrasting in light of previous research. Contrasting, as one study in elderly Latinos found that the joint influence of MetS on cognitive functions were greater than its single components (Yaffe et al., 2007), but also consistent, as Roberts et al. (2010) found no overall association between MetS and MCI. In fact, one study found that the presence of MetS was associated with better performance on cognitive tests (Laudisio et al., 2008). The average age of their study population was 79 years and the trend was found in women over the age of 80. The phenomenon was hypothesised to occur due to abdominal obesity and lower levels of HDL. The authors concluded that individuals with MetS might be spared of other more important risk factors contributing to cognitive decline, such as malnutrition. Indeed, obesity and dyslipidaemia have been linked to greater survival rates and cognitive functions in the oldest old (Karlamangla, Singer, Reuben, & Seeman, 2004). Additionally, another study found that MetS might have a protective role

with regard to cognition in the very old, as the age-related reduction in cognitive abilities in participants with MetS between the ages of 85 to 90 was found to slow down (van den Berg et al., 2007). The effect was mostly due to glucose, BMI and moderately due to blood pressure.

In relation to inflammation, Roberts et al. (2010) stressed the importance of distinguishing MetS with high levels of inflammation and MetS without or low levels of inflammation, as this was found to directly relate to different types of MCI (Roberts et al., 2010). In fact, inflammation is a central factor in the neuropathology of AD (Yaffe et al., 2003). We did not find a significant relationship between inflammation as measured by CRP and performance on cognitive tests.

Our study population had a mean age of 74 years and were relatively healthy with regards to the risk factors mentioned above. This makes it somewhat unlikely that our study population had reached the possible critical age at which point MetS may have a protective role; however, this cannot be ruled out as a possibility.

4.4 Cerebro-cardiovascular disease and cognition

There were no statistically significant differences between those at high risk of developing ASCVD and those at low risk. However, trends showed that those with low risk performed better on the VM (imm.rec), with a large effect size as shown by Cohen's *d* = -0.667. It would take 21 participants in each group for this trend to become a significant group difference, while we had only 15 in each group. Oppositely, for DSB trends showed that those in the high risk group performed better than those with low risk, with an effect size of 0.574, also indicating a large effect size. It would take 31 participants for this trend to become significant, whereas we had 18 vs 16. This trend was also found in the linear regression analysis, where the DSB score increased by 0.186 for every SD increase in risk of ASCVD score. This trend was not significant. As systolic blood pressure as well as use of antihypertensive treatment was part of the factors for calculating the ASCVD score, we looked at differences between hypertensive and normotensive participants on cognitive performance; however, we found no statistically significant differences.

Atherosclerosis leads to hardening of the blood vessels and can lead to infarctions in the brain (Ross, 1999). Endothelial dysfunction is a result of ASCVD, and this alters the delivery of nutrients to the brain. Numerous studies have found that this can lead to cognitive impairment (Iadecola, 2013). Risk factors for both AD and VaD overlap with risk factors for cerebrovascular disease. These include glucose intolerance, diabetes mellitus, hypertension, hyperlipidaemia and obesity (Knopman & Roberts, 2010). Many of these risk factors also overlap with MetS. The ASCVD risk calculator utilises age, race, sex, HDL cholesterol, total cholesterol, systolic blood pressure, use of antihypertensive treatment and current smoking and diabetes status. It was hypothesised in the current study that

lower risk for developing ASCVD would results in better performance on cognitive tests compared to individuals with higher risk for developing ASCVD. We did not find support for this hypothesis; however this could be due to sample size.

Other studies have found an effect of CVD and cognition. For example, high blood pressure alone can cause white matter lesions, which in turn can lead to cognitive impairment (den Heijer et al., 2005). We compared participants with and without hypertension, but were unable to detect a significant difference between these two groups. There is also a well-established link between lipid-dysregulation and AD (Di Paolo & Kim, 2011), and between diabetes mellitus and cognitive dysfunction (Knopman et al., 2001). In the latter study, the digit symbol substitution test (DSST), which is a measure of psychomotor speed, was most strongly associated with diabetes. Other studies have also found that diabetes is linked to slower processing speed as well as lowered mental flexibility in particular (Brands et al., 2005). As only four of the participants in our group had diabetes, we could not statistically test whether these individuals performed worse on the cognitive tests compared to non-diabetic individuals as the chance of making type 2 errors was too high in such a small sample size.

Several studies report a link between CVD factors and cognition, either as individual factors or in combination to other risk factors. One longitudinal study reported an effect between midlife-CVD and verbal memory 25 years later, where individuals with higher incidents of abdominal aortic calcified plaques (AAC) showed worse performance compared to those without AAC on the delayed recall subtype of a verbal memory test (Reis et al., 2013). Reis et al. (2013) also found that those with higher incidents of coronary artery calcified plaques in addition to ACC performed worse on the DSST in addition to the delayed recall subtest of verbal memory. Our results are consistent with regard to the memory test, as we also found trends where those with lower risk for ASCVD performed better on VM than those with higher risk for ASCVD. However, our findings relate to the immediate recall subtype and not the late recall subtype. It could be argued that specific types of CVD risk factors affect specific aspects of cognition differently, as the study by Reis et al. (2013) showed that specific types of atherosclerotic calcification in midlife can have specific effects on cognition 25 years later.

Surprisingly, we also found that participants with high risk for ASCVD showed trends of performing better than those with low risk for ASCVD on DSB, and that there were trends of a relationship between these two factors. This is contradicting to previous findings, where on study showed that participants with vascular risk factors displayed impairment of cognitive functions including working memory (Raz, Rodrigue, Kennedy, & Acker, 2007). In this study, vascular risk factors included hypertension, diabetes mellitus and minor strokes to mention a few. As many of the factors used in

the calculation of risk for ASCVD overlaps with the factors used in classifying individuals with MetS, it could also be conceivable that the similar protective effects that has been found to take place in individuals with MetS after a certain age also takes place for individuals with high risk for developing ASCVD.

Another possible explanation to our lack of significant associations and somewhat inconsistent findings between the ASCVD risk-score and cognitive decline is due to the low incidence of diabetes, smoking and low severity of hypertension and dyslipidaemia. In other words, our study population might have been "too" healthy for us to detect an association between ASCVD and cognition. Similar risk-scores as the one used in the present study have also been used previously to look for an association between CVD-risk score and cognition. For example, the Framingham stroke risk profile (FSRP) offers a 10-year risk-estimation for incidence stroke using age, sex, systolic blood pressure, antihypertensive treatment, diabetes, smoking status, CVD and atrial fibrillation as factors. One study found that for every 10% point increase in FSRP, global cognitive function decreased with 0.4 SD (Llewellyn et al., 2008). Another study compared 2 different Framingham risk-scores (Framingham CVD and Framingham stroke) with the dementia risk score which is based on the Cardiovascular Risk Factors, Ageing and Dementia (CAIDE) (Kaffashian et al., 2013). Kaffashian et al. (2013) found that all 3 risk scores were associated with a 10-year cognitive decline. As a final suggestion, it could be argued that the body, even though experiencing age-related physical decline, is robust enough to compensate for a certain level of deterioration and abnormalities. The effects of risk for ASCVD may be clearer after a longer period of time and/or with higher grades of severity.

4.5 Limitations

4.5.1 Study population

Because of the low incidence of very unhealthy individuals, we might have been unable to detect a true difference between the healthier groups and the less healthy group, as the less healthy groups were still of fairly good health. In other words, it is possible that our study population were "too" healthy for an effect to be found. It would be interesting to conduct a similar study with more participants covering the entire range of fitness, MetS risk factors and ASCVD scores. One could argue that healthy individuals and/or individuals with an interest in healthy living and physical activity are more inclined to participate in a study such as the current, and that these individuals have higher $VO2_{peak}$ and lower incidence of CVD risk factors. This can lead to an underestimation of the current findings as well as sampling bias. It is possible to investigate whether sampling bias occurred in our study population but doing so goes beyond the scope of this master's thesis.

Much of the data in the current study were based on self-report; education, smoking, diabetes, use of medication and so on. Parts of the inclusion and exclusion criteria were also based on self-report. This may have yielded unreliable data, as it is common that individuals in this age range have diminished memory which could lead to under and/or over report of medical incidences. It could also be that some participants were untruthful, did not want to report relevant information or did not see the need to. Such behaviour would lead to less reliable data and possibly obscure the presence of a true phenomenon.

Educational attainment and occupation, i.e. socioeconomic status (SES), has been shown to affect the prevalence of AD, where the presence of both low levels of education and low occupational attainment demonstrate the highest risk of developing dementia (Stern et al., 1994). Stern et al. (1994) also found a higher incidence of stroke in this group. Another study found that the association between AD and low levels of education and low income diminished after correcting for diabetes and cognitive and physical functioning (Avendano et al., 2006). A possible explanation is that individuals with lower SES are more likely to have poor diet, suffer from obesity, smoke, and to be inactive; all of which contributes to greater chance of vascular risk factors (Knopman & Roberts, 2010). Contrary to this, one would expect individuals with higher SES to have better diet, to not be obese or smoke and to be more physically active. Nevertheless, we found no correlation between education and $VO2_{peak}$, or between education and any of the other physical measurements. Even so, the high level of education in our study population may result in some form of sampling bias as there appears to be an under-representation of individuals from lower SES in our study population. This makes the results from the current work difficult to generalise to other populations.

4.5.2 Limitations to physical measurements

It is difficult to ascertain whether the G100 project researchers were able to obtain all relevant information. For example, participants may suffer from unknown diseases that could affect cognition. Furthermore, various factors can cause variations in the participants' physical and cognitive conditions.

Not all participants reached $VO2_{max}$ as some participants stopped the test before reaching $VO2_{max}$ and were given the suboptimal measure of $VO2_{peak}$. One could argue that not all participants have a true measure of their oxygen consumption. However, due to frailty and decline in motor functions in older individuals it is hard to achieve optimal maximum fitness values (Church et al., 2008). Nonetheless, $VO2_{peak}$ has been judged a valid substitute for $VO2_{max}$ (Day et al., 2003).

The ASCVD risk estimator was used as tool to assess cerebro-cardiovascular disease. However, this risk estimator was developed in 2012. Consequently, there is little normative data produced as of

today and we can therefore not compare the prevalence of ASCVD risk in our group with other groups.

4.5.3 Methodological considerations

Employing a cross-sectional study design makes it harder to draw inferences and conclusions based on differences between individuals. In other words, one cannot determine causality. By using longitudinal studies, one is better able to distinguish the effects of health and associated variables on cognitive functioning. It will be of great interest to compare the current baseline data with the future measurements of the same study population, as findings from the current study may be confirmed and further investigated in that way.

Another important limitation was the small sample size. We found many interesting trends in the current study, but were unable to confirm these trends due to the small sample size. This makes it hard to decide whether the trends occurred due to chance and random variation in the sample or whether they were due to measures of health. For example, with regard to the $VO2_{peak}$ analysis, we found trends where those in the low $VO2_{peak}$ group performed better on VM (late.rec) compared to those in the high $VO2_{peak}$. Calculations of sample size show that it would take a total of 94 participants in this analysis, whereas we had only 26. Furthermore, trends showed that hypertensive participants performed better on DSB compared to normotensive participants, and calculations of sample size show that it would take a total of 296 participants in this analysis, whereas we had 85. The effect sizes of these two analyses were -0.428 and 0.240 respectively, showing medium and small effect sizes. It is therefore hard to conclude whether these trends are actually true effects or simply random variations in the sample.

A few participants reported that they were not very familiar using a computer or the internet, and this could lead to a varying degree of validity in performance on the neuropsychological tests. Problems may also arise by allowing participants to perform the tests in their own homes. Lack of computer/internet skills, reduced hearing of verbal instructions from the computer, noise and everyday disturbances from a spouse or other family members are possible factors that can interfere with the validity of the test scores. Some participants reported that they contacted the researchers when experiencing trouble during the test, while others reported that they experienced problems but did not contact the researchers. Moreover, by allowing participants to complete the tests in their own homes, one cannot control for cheating. Inviting participants to complete the tests at the MR-centre could have controlled for these factors, however, this was considered unnecessary trouble for the participants.

Some participants reported that they experienced the tests as long and tiresome, possibly resulting in decreased performance towards the end of the test-battery. A few participants completed the tests in two trials, allowing these individuals rest that other participants did not get. However, the three questionnaires were strategically placed towards the end of the test. Still, the DSB were also among these last tests.

Our findings could have been affected or explained by factors we have not considered in the present study, for example genetics in relation to VO2; it has been shown that different variants of the human mitochondrion can influence oxygen consumption (Marcuello et al., 2009). As a result, some individuals might have a genetic advantage over others with regard to oxygen consumption and therefore also maximal fitness testing. Other factors we have not considered are neurotropic factors such as levels of BDNF, who has been found to indirectly rise with increased aerobic fitness (Erickson et al., 2011). These are possible targets for future research.

4.6 Future directions

In this study, only healthy participants were included. In order to further the findings of the present study, one could carry out the same tests but include clinical groups with more extreme measurements. In this way, one would be better able to detect a true impact of different risk factors and levels of physical fitness on cognition. It would also be of interest to compare various measures of health in different clinical groups of participants longitudinally, such as individuals with MCI, AD and VaD. In this way, one could compare the cognitive development of healthy controls to the cognitive development of a greater variety of individuals to see how various health measurements affect cognition, at what time these health measurements are relevant, and in what sequence the cognitive changes occur. For example, it would be interesting to see whether cognitive impairment leads to worsening of physical health or vice versa, if vascular risk factors have a negative impact on cognition up to a certain point in life where it changes to have a protective role, and how much exercise is needed for positive effects to be seen in cognition in both healthy and pathological ageing. It would also be of interest to perform cardiorespiratory testing in individuals who have already been diagnosed with MCI or AD, as well as investigating the prevalence of MetS and risk of ASCVD in these groups.

5 Conclusion

In this study of physical health and cognitive functions in older adults, we found that individuals with higher levels of $VO2_{peak}$ had faster processing speed than older adults with lower levels of $VO2_{peak}$. Trends show that this may be true for executive functions as well. A possible explanation for this is that higher levels of VO2 leads to better protection of white matter tissue and integrity of associated fibre tracts in the brain and that this in turn leads to better speed of processing and possibly executive functions.

Furthermore, we found that having MetS or high risk for developing cerebro-vascular disease within the next 10 years did not seem to significantly affect cognition. Nevertheless, trends show that having several factors contributing to the classification of MetS might have a protective role in older adults.

As many of the relevant health factors considered in both MetS and ASCVD overlap and indirectly affect each other as well as cardiorespiratory fitness, it seems likely that different cognitive functions are affected by specific aspects or combinations of physical health. Even so, it appears that speed of processing and possibly executive functions, but not other cognitive abilities, are more sensitive to cardiorespiratory fitness than other measures of health used in the present study.

6 References

Ahlskog, J. E., Geda, Y. E., Graff-Radford, N. R., & Petersen, R. C. (2011). Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. *Mayo Clin Proc, 86*(9), 876-884. doi: 10.4065/mcp.2011.0252

Alexander, G. M., Packard, M. G., & Peterson, B. S. (2002). Sex and spatial position effects on object location memory following intentional learning of object identities. *Neuropsychologia, 40*(8), 1516-1522. doi: http://dx.doi.org/10.1016/S0028-3932(01)00215-9

Angevaren, M., Aufdemkampe, G., Verhaar, H. J., Aleman, A., & Vanhees, L. (2008). Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. *Cochrane Database Syst Rev*(3), Cd005381. doi: 10.1002/14651858.CD005381.pub3

Aspenes, S. T., Nilsen, T. I., Skaug, E. A., Bertheussen, G. F., Ellingsen, O., Vatten, L., & Wisloff, U. (2011). Peak oxygen uptake and cardiovascular risk factors in 4631 healthy women and men. *Med Sci Sports Exerc, 43*(8), 1465-1473. doi: 10.1249/MSS.0b013e31820ca81c

Avendano, M., Kawachi, I., Van Lenthe, F., Boshuizen, H. C., Mackenbach, J. P., Van den Bos, G. A., . . . Berkman, L. F. (2006). Socioeconomic status and stroke incidence in the US elderly: the role of risk factors in the EPESE study. *Stroke, 37*(6), 1368-1373. doi: 10.1161/01.str.0000221702.75002.66

Back, S. A., Kroenke, C. D., Sherman, L. S., Lawrence, G., Gong, X., Taber, E. N., . . . Montine, T. J. (2011). White matter lesions defined by diffusion tensor imaging in older adults. *Ann Neurol, 70*(3), 465-476. doi: 10.1002/ana.22484

Baddeley, A. (2003). Working memory and language: an overview. *Journal of Communication Disorders, 36*(3), 189-208. doi: 10.1016/s0021-9924(03)00019-4

Bakker, A., Kirwan, C. B., Miller, M., & Stark, C. E. (2008). Pattern separation in the human hippocampal CA3 and dentate gyrus. *Science, 319*(5870), 1640-1642. doi: 10.1126/science.1152882

Beck, I. R., Gagneux-Zurbriggen, A., Berres, M., Taylor, K. I., & Monsch, A. U. (2012). Comparison of verbal episodic memory measures: consortium to establish a registry for Alzheimer's disease--Neuropsychological Assessment Battery (CERAD-NAB) versus California Verbal Learning Test (CVLT). *Arch Clin Neuropsychol, 27*(5), 510-519. doi: 10.1093/arclin/acs056

Bennett, I. J., & Madden, D. J. (2013). Disconnected aging: Cerebral white matter integrity and age-related differences in cognition. *Neuroscience*. doi: 10.1016/j.neuroscience.2013.11.026

Bondi, M. W., Jak, A. J., Delano-Wood, L., Jacobson, M. W., Delis, D. C., & Salmon, D. P. (2008). Neuropsychological contributions to the early identification of Alzheimer's disease. *Neuropsychol Rev, 18*(1), 73-90. doi: 10.1007/s11065-008-9054-1

Bondi, M. W., Salmon, D. P., Galasko, D., Thomas, R. G., & Thal, L. J. (1999). Neuropsychological function and apolipoprotein E genotype in the preclinical detection of Alzheimer's disease. *Psychol Aging, 14*(2), 295-303.

Borg, G. A. (1982). Psychophysical bases of perceived exertion. *Med Sci Sports Exerc, 14*(5), 377-381.

Brands, A. M., Biessels, G. J., de Haan, E. H., Kappelle, L. J., & Kessels, R. P. (2005). The effects of type 1 diabetes on cognitive performance: a meta-analysis. *Diabetes Care, 28*(3), 726-735.

Brown, L. A., Brockmole, J. R., Gow, A. J., & Deary, I. J. (2012). Processing speed and visuospatial executive function predict visual working memory ability in older adults. *Exp Aging Res, 38*(1), 1-19. doi: 10.1080/0361073x.2012.636722

Brumpton, B. M., Camargo, C. A., Jr., Romundstad, P. R., Langhammer, A., Chen, Y., & Mai, X. M. (2013). Metabolic syndrome and incidence of asthma in adults: the HUNT study. *Eur Respir J, 42*(6), 1495-1502. doi: 10.1183/09031936.00046013

Bryan, J., & Luszcz, M. A. (1996). Speed of information processing as a mediator between age and free-recall performance. *Psychol Aging, 11*(1), 3-9.

Bunce, D., & Murden, F. (2006). Age, aerobic fitness, executive function, and episodic memory. *European Journal of Cognitive Psychology, 18*(2), 221-233. doi: 10.1080/09541440540000185

Burgmans, S., Gronenschild, E. H. B. M., Fandakova, Y., Shing, Y. L., van Boxtel, M. P. J., Vuurman, E. F. P. M., . . . Raz, N. (2011). Age differences in speed of processing are partially mediated by differences in axonal integrity. *Neuroimage, 55*(3), 1287-1297. doi: http://dx.doi.org/10.1016/j.neuroimage.2011.01.002

Camarata, S., & Woodcock, R. (2006). Sex differences in processing speed: Developmental effects in males and females. *Intelligence, 34*(3), 231-252. doi: http://dx.doi.org/10.1016/j.intell.2005.12.001

Cepeda, N. J., Blackwell, K. A., & Munakata, Y. (2013). Speed isn't everything: complex processing speed measures mask individual differences and developmental changes in executive control. *Dev Sci, 16*(2), 269-286. doi: 10.1111/desc.12024

Christensen, H., Korten, A. E., Jorm, A. F., Henderson, A. S., Jacomb, P. A., Rodgers, B., & Mackinnon, A. J. (1997). Education and decline in cognitive performance: compensatory but not protective. *Int J Geriatr Psychiatry, 12*(3), 323-330.

Church, T. S., Gill, T. M., Newman, A. B., Blair, S. N., Earnest, C. P., & Pahor, M. (2008). Maximal fitness testing in sedentary elderly at substantial risk of disability: LIFE-P study experience. *J Aging Phys Act, 16*(4), 408-415.

Clark, P. G., Blissmer, B. J., Greene, G. W., Lees, F. D., Riebe, D. A., & Stamm, K. E. (2011). Maintaining exercise and healthful eating in older adults: the SENIOR project II: study design and methodology. *Contemp Clin Trials, 32*(1), 129-139. doi: 10.1016/j.cct.2010.10.002

Colcombe, S. J., Erickson, K. I., Scalf, P. E., Kim, J. S., Prakash, R., McAuley, E., . . . Kramer, A. F. (2006). Aerobic exercise training increases brain volume in aging humans. *J Gerontol A Biol Sci Med Sci, 61*(11), 1166-1170.

Colcombe, S. J., & Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults: A Meta-Analytic study. *Psychological Science, 14*(2), 125-130. doi: 10.1111/1467-9280.t01-1-01430

Davis, H. P., & Klebe, K. (2001). A longitudinal study of the performance of the elderly and young on the tower of hanoi puzzle and rey recall. *Brain Cogn, 46*(1–2), 95-99. doi: http://dx.doi.org/10.1006/brcg.2000.1269

Day, J. R., Rossiter, H. B., Coats, E. M., Skasick, A., & Whipp, B. J. (2003). The maximally attainable VO2 during exercise in humans: the peak vs. maximum issue. *J Appl Physiol, 95*(5), 1901-1907. doi: 10.1152/japplphysiol.00024.2003

den Heijer, T., Launer, L. J., Prins, N. D., van Dijk, E. J., Vermeer, S. E., Hofman, A., . . . Breteler, M. M. (2005). Association between blood pressure, white matter lesions, and atrophy of the medial temporal lobe. *Neurology, 64*(2), 263-267. doi: 10.1212/01.wnl.0000149641.55751.2e

den Heijer, T., Vermeer, S. E., van Dijk, E. J., Prins, N. D., Koudstaal, P. J., Hofman, A., & Breteler, M. M. (2003). Type 2 diabetes and atrophy of medial temporal lobe structures on brain MRI. *Diabetologia, 46*(12), 1604-1610. doi: 10.1007/s00125-003-1235-0

Di Angelantonio, E., Gao, P., Pennells, L., Kaptoge, S., Caslake, M., Thompson, A., . . . Danesh, J. (2012). Lipid-related markers and cardiovascular disease prediction. *Jama, 307*(23), 2499-2506. doi: 10.1001/jama.2012.6571

Di Paolo, G., & Kim, T. W. (2011). Linking lipids to Alzheimer's disease: cholesterol and beyond. *Nat Rev Neurosci, 12*(5), 284-296. doi: 10.1038/nrn3012

Edvardsen, E., Scient, C., Hansen, B. H., Holme, I. M., Dyrstad, S. M., & Anderssen, S. A. (2013). Reference values for cardiorespiratory response and fitness on the treadmill in a 20- to 85-year-old population. *Chest, 144*(1), 241-248. doi: 10.1378/chest.12-1458

Erickson, K. I., Raji, C. A., Lopez, O. L., Becker, J. T., Rosano, C., Newman, A. B., . . . Kuller, L. H. (2010). Physical activity predicts gray matter volume in late adulthood: the Cardiovascular Health Study. *Neurology, 75*(16), 1415-1422. doi: 10.1212/WNL.0b013e3181f88359

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., . . . Kramer, A. F. (2011). Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A, 108*(7), 3017-3022. doi: 10.1073/pnas.1015950108

Farmer, J., Zhao, X., van Praag, H., Wodtke, K., Gage, F. H., & Christie, B. R. (2004). Effects of voluntary exercise on synaptic plasticity and gene expression in the dentate gyrus of adult male sprague–dawley rats in vivo. *Neuroscience, 124*(1), 71-79. doi: http://dx.doi.org/10.1016/j.neuroscience.2003.09.029

Fein, G., Di Sclafani, V., Tanabe, J., Cardenas, V., Weiner, M. W., Jagust, W. J., . . . Chui, H. (2000). Hippocampal and cortical atrophy predict dementia in subcortical ischemic vascular disease. *Neurology, 55*(11), 1626-1635.

Forti, P., Pisacane, N., Rietti, E., Lucicesare, A., Olivelli, V., Mariani, E., . . . Ravaglia, G. (2010). Metabolic syndrome and risk of dementia in older adults. *J Am Geriatr Soc, 58*(3), 487-492. doi: 10.1111/j.1532-5415.2010.02731.x

Fotuhi, M., Hachinski, V., & Whitehouse, P. J. (2009). Changing perspectives regarding late-life dementia. *Nat Rev Neurol, 5*(12), 649-658. doi: 10.1038/nrneurol.2009.175

Goff, D. C. J., Lloyd-Jones, D. M., Bennett, G., O'Donnell, C. J., Coady, S., Robinson, J., . . . Wilson, P. W. F. (2013). ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*(0). doi: http://dx.doi.org/10.1016/j.jacc.2013.11.005

Haferstrom, E. (2013). *Comparing web-based neuropsychological tests of verbal and spatial memory with standardized pen and paper versions.* NTNU trykk.

Hedden, T., & Gabrieli, J. D. (2004). Insights into the ageing mind: a view from cognitive neuroscience. *Nat Rev Neurosci, 5*(2), 87-96. doi: 10.1038/nrn1323

Helsedirektoratet. (2011). http://helsedirektoratet.no/helse-og-omsorgstjenester/omsorgstjenester/demens/sider/default.aspx. Retrieved 13.05.2014

Herrmann, C. (1997). International experiences with the Hospital Anxiety and Depression Scale--a review of validation data and clinical results. *J Psychosom Res, 42*(1), 17-41.

Hornberger, M., Piguet, O., Kipps, C., & Hodges, J. R. (2008). Executive function in progressive and nonprogressive behavioral variant frontotemporal dementia. *Neurology, 71*(19), 1481-1488. doi: 10.1212/01.wnl.0000334299.72023.c8

Iadecola, C. (2004). Neurovascular regulation in the normal brain and in Alzheimer's disease. *Nat Rev Neurosci, 5*(5), 347-360. doi: 10.1038/nrn1387

Iadecola, C. (2013). The Pathobiology of Vascular Dementia. *Neuron, 80*(4), 844-866. doi: http://dx.doi.org/10.1016/j.neuron.2013.10.008

Jagust, W., Harvey, D., Mungas, D., & Haan, M. (2005). Central obesity and the aging brain. *Arch Neurol, 62*(10), 1545-1548. doi: 10.1001/archneur.62.10.1545

Janssen, I., Katzmarzyk, P. T., & Ross, R. (2004). Waist circumference and not body mass index explains obesity-related health risk. *Am J Clin Nutr, 79*(3), 379-384.

Kaffashian, S., Dugravot, A., Elbaz, A., Shipley, M. J., Sabia, S., Kivimaki, M., & Singh-Manoux, A. (2013). Predicting cognitive decline: a dementia risk score vs. the Framingham vascular risk scores. *Neurology, 80*(14), 1300-1306. doi: 10.1212/WNL.0b013e31828ab370

Karantzoulis, S., & Galvin, J. E. (2011). Distinguishing Alzheimer's disease from other major forms of dementia. *Expert Rev Neurother, 11*(11), 1579-1591. doi: 10.1586/ern.11.155

Karlamangla, A. S., Singer, B. H., Reuben, D. B., & Seeman, T. E. (2004). Increases in serum non-high-density lipoprotein cholesterol may be beneficial in some high-functioning older adults: MacArthur studies of successful aging. *J Am Geriatr Soc, 52*(4), 487-494. doi: 10.1111/j.1532-5415.2004.52152.x

Kassi, E., Pervanidou, P., Kaltsas, G., & Chrousos, G. (2011). Metabolic syndrome: definitions and controversies. *BMC Med, 9*, 48. doi: 10.1186/1741-7015-9-48

Kennedy, K. M., & Raz, N. (2009). Aging white matter and cognition: differential effects of regional variations in diffusion properties on memory, executive functions, and speed. *Neuropsychologia, 47*(3), 916-927. doi: 10.1016/j.neuropsychologia.2009.01.001

Kerchner, G. A., Racine, C. A., Hale, S., Wilheim, R., Laluz, V., Miller, B. L., & Kramer, J. H. (2012). Cognitive Processing Speed in Older Adults: Relationship with White Matter Integrity. *PLoS One, 7*(11), e50425. doi: 10.1371/journal.pone.0050425

Kessels, R. P., Boekhorst, S. T., & Postma, A. (2005). The contribution of implicit and explicit memory to the effects of errorless learning: a comparison between young and older adults. *J Int Neuropsychol Soc, 11*(2), 144-151.

Kirwan, C. B., & Stark, C. E. (2007). Overcoming interference: an fMRI investigation of pattern separation in the medial temporal lobe. *Learn Mem, 14*(9), 625-633. doi: 10.1101/lm.663507

Knopman, Boland, L. L., Mosley, T., Howard, G., Liao, D., Szklo, M., . . . Folsom, A. R. (2001). Cardiovascular risk factors and cognitive decline in middle-aged adults. *Neurology, 56*(1), 42-48.

Knopman, Mosley, T. H., Catellier, D. J., & Sharrett, A. R. (2005). Cardiovascular risk factors and cerebral atrophy in a middle-aged cohort. *Neurology, 65*(6), 876-881. doi: 10.1212/01.wnl.0000176074.09733.a8

Knopman, & Roberts, R. (2010). Vascular risk factors: imaging and neuropathologic correlates. *J Alzheimers Dis, 20*(3), 699-709. doi: 10.3233/jad-2010-091555

Lamar, M., Resnick, S. M., & Zonderman, A. B. (2003). Longitudinal changes in verbal memory in older adults: distinguishing the effects of age from repeat testing. *Neurology, 60*(1), 82-86.

Laudisio, A., Marzetti, E., Pagano, F., Cocchi, A., Franceschi, C., Bernabei, R., & Zuccala, G. (2008). Association of metabolic syndrome with cognitive function: the role of sex and age. *Clin Nutr, 27*(5), 747-754. doi: 10.1016/j.clnu.2008.07.001

Launer, L. J., Hughes, T., Yu, B., Masaki, K., Petrovitch, H., Ross, G. W., & White, L. R. (2010). Lowering midlife levels of systolic blood pressure as a public health strategy to reduce late-life dementia: perspective from the Honolulu Heart Program/Honolulu Asia Aging Study. *Hypertension, 55*(6), 1352-1359. doi: 10.1161/HYPERTENSIONAHA.109.147389

Llewellyn, D. J., Lang, I. A., Xie, J., Huppert, F. A., Melzer, D., & Langa, K. M. (2008). Framingham Stroke Risk Profile and poor cognitive function: a population-based study. *BMC Neurol, 8*, 12. doi: 10.1186/1471-2377-8-12

Luchsinger, J. A. (2008). Adiposity, hyperinsulinemia, diabetes and Alzheimer's disease: an epidemiological perspective. *Eur J Pharmacol, 585*(1), 119-129. doi: 10.1016/j.ejphar.2008.02.048

Majeres, R. L. (1983). Sex differences in symbol-digit substitution and speeded matching. *Intelligence, 7*(4), 313-327. doi: http://dx.doi.org/10.1016/0160-2896(83)90007-7

Marcuello, A., Martínez-Redondo, D., Dahmani, Y., Casajús, J. A., Ruiz-Pesini, E., Montoya, J., . . . Díez-Sánchez, C. (2009). Human mitochondrial variants influence on oxygen consumption. *Mitochondrion, 9*(1), 27-30. doi: http://dx.doi.org/10.1016/j.mito.2008.10.002

Milner, B., Johnsrude, I., & Crane, J. (1997). Right medial temporal-lobe contribution to object-location memory. *Philos Trans R Soc Lond B Biol Sci, 352*(1360), 1469-1474. doi: 10.1098/rstb.1997.0133

NOEIE Panel. (1998). Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary. Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults. *Am J Clin Nutr, 68*(4), 899-917.

Panza, F., Frisardi, V., Capurso, C., Imbimbo, B. P., Vendemiale, G., Santamato, A., . . . Solfrizzi, V. (2010). Metabolic syndrome and cognitive impairment: current epidemiology and possible underlying mechanisms. *J Alzheimers Dis, 21*(3), 691-724. doi: 10.3233/JAD-2010-091669

Peila, R., Rodriguez, B. L., & Launer, L. J. (2002). Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: The Honolulu-Asia Aging Study. *Diabetes, 51*(4), 1256-1262.

Pereira, A. C., Huddleston, D. E., Brickman, A. M., Sosunov, A. A., Hen, R., McKhann, G. M., . . . Small, S. A. (2007). An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proc Natl Acad Sci U S A, 104*(13), 5638-5643. doi: 10.1073/pnas.0611721104

Pertzov, Y., Dong, M. Y., Peich, M. C., & Husain, M. (2012). Forgetting what was where: the fragility of object-location binding. *PLoS One, 7*(10), e48214. doi: 10.1371/journal.pone.0048214

Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *J Intern Med, 256*(3), 183-194. doi: 10.1111/j.1365-2796.2004.01388.x

Pinzka, C. (2010). *Adapting neuropsychological tests for online adminstration.* NTNU trykk.

Poirier, P., Giles, T. D., Bray, G. A., Hong, Y., Stern, J. S., Pi-Sunyer, F. X., & Eckel, R. H. (2006). Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation, 113*(6), 898-918. doi: 10.1161/circulationaha.106.171016

Postma, A., Kessels, R. P. C., & van Asselen, M. (2008). How the brain remembers and forgets where things are: The neurocognition of object–location memory. *Neuroscience & Biobehavioral Reviews, 32*(8), 1339-1345. doi: http://dx.doi.org/10.1016/j.neubiorev.2008.05.001

Pradhan, A. D., Manson, J. E., Rifai, N., Buring, J. E., & Ridker, P. M. (2001). C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *Jama, 286*(3), 327-334.

Psychological Corporation. (2002). *WAIS-III/WMS-III Technical Manual*: San Antonio Harcourt Brace & Company.

Rainville, C., Lepage, E., Gauthier, S., Kergoat, M. J., & Belleville, S. (2012). Executive function deficits in persons with mild cognitive impairment: a study with a Tower of London task. *J Clin Exp Neuropsychol, 34*(3), 306-324. doi: 10.1080/13803395.2011.639298

Raz, N., Rodrigue, K. M., Kennedy, K. M., & Acker, J. D. (2007). Vascular health and longitudinal changes in brain and cognition in middle-aged and older adults. *Neuropsychology, 21*(2), 149-157. doi: 10.1037/0894-4105.21.2.149

Reis, J. P., Launer, L. J., Terry, J. G., Loria, C. M., Zeki Al Hazzouri, A., Sidney, S., . . . Carr, J. J. (2013). Subclinical atherosclerotic calcification and cognitive functioning in middle-aged adults: The CARDIA study. *Atherosclerosis, 231*(1), 72-77. doi: http://dx.doi.org/10.1016/j.atherosclerosis.2013.08.038

Resnick, S. M., Pham, D. L., Kraut, M. A., Zonderman, A. B., & Davatzikos, C. (2003). Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain. *J Neurosci, 23*(8), 3295-3301.

Ridker, P. M., Buring, J. E., Shih, J., Matias, M., & Hennekens, C. H. (1998). Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. *Circulation, 98*(8), 731-733.

Roberts, R. O., Geda, Y. E., Knopman, D. S., Cha, R. H., Boeve, B. F., Ivnik, R. J., . . . Petersen, R. C. (2010). Metabolic syndrome, inflammation, and nonamnestic mild cognitive impairment in older persons: a population-based study. *Alzheimer Dis Assoc Disord, 24*(1), 11-18. doi: 10.1097/WAD.0b013e3181a4485c

Roivainen, E. (2011). Gender differences in processing speed: A review of recent research. *Learning and Individual Differences, 21*(2), 145-149. doi: http://dx.doi.org/10.1016/j.lindif.2010.11.021

Ross, R. (1999). Atherosclerosis — An Inflammatory Disease. *New England Journal of Medicine, 340*(2), 115-126. doi: doi:10.1056/NEJM199901143400207

Royle, J., & Lincoln, N. B. (2008). The Everyday Memory Questionnaire-revised: development of a 13-item scale. *Disabil Rehabil, 30*(2), 114-121. doi: 10.1080/09638280701223876

Saad, M. A., Cardoso, G. P., Martins, W. D., Velarde, L. G., & Cruz Filho, R. A. (2014). Prevalence of Metabolic Syndrome in Elderly and Agreement among Four Diagnostic Criteria. *Arq Bras Cardiol, 102*(3), 263-269.

Salami, A., Eriksson, J., Nilsson, L., & Nyberg, L. (2012). Age-related white matter microstructural differences partly mediate age-related decline in processing speed but not cognition. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1822*(3), 408-415. doi: http://dx.doi.org/10.1016/j.bbadis.2011.09.001

Salat, D. H., Kaye, J. A., & Janowsky, J. S. (1999). Prefrontal gray and white matter volumes in healthy aging and Alzheimer disease. *Arch Neurol, 56*(3), 338-344.

Salthouse, T. A., & Babcock, R. L. (1991). Decomposing adult age differences in working memory. *Developmental Psychology, 27*(5), 763-776. doi: 10.1037/0012-1649.27.5.763

Sasson, E., Doniger, G. M., Pasternak, O., Tarrasch, R., & Assaf, Y. (2012). Structural correlates of cognitive domains in normal aging with diffusion tensor imaging. *Brain Struct Funct, 217*(2), 503-515. doi: 10.1007/s00429-011-0344-7

Satistics Norway. (2013). Population's level of education. Retrieved 20.05.2014

Shallice, T. (1982). Specific impairments of planning. *Philos Trans R Soc Lond B Biol Sci, 298*(1089), 199-209.

Squire, L. R., & Alvarez, P. (1995). Retrograde amnesia and memory consolidation: a neurobiological perspective. *Curr Opin Neurobiol, 5*(2), 169-177.

Squire, L. R., & Zola, S. M. (1996). Structure and function of declarative and nondeclarative memory systems. *Proc Natl Acad Sci U S A, 93*(24), 13515-13522.

St. Olav's Hospital. (2014). Laboratoriemedisinsk klinikk. Retrieved 16.05.2014

Stampfer, M. J. (2006). Cardiovascular disease and Alzheimer's disease: common links. *J Intern Med, 260*(3), 211-223. doi: 10.1111/j.1365-2796.2006.01687.x

Stern, Y., Gurland, B., Tatemichi, T. K., Tang, M. X., Wilder, D., & Mayeux, R. (1994). Influence of education and occupation on the incidence of Alzheimer's disease. *Jama, 271*(13), 1004-1010.

Sullivan, E. V., & Pfefferbaum, A. (2003). Diffusion tensor imaging in normal aging and neuropsychiatric disorders. *European Journal of Radiology, 45*(3), 244-255. doi: http://dx.doi.org/10.1016/S0720-048X(02)00313-3

Sullivan, E. V., Pfefferbaum, A., Adalsteinsson, E., Swan, G. E., & Carmelli, D. (2002). Differential rates of regional brain change in callosal and ventricular size: a 4-year longitudinal MRI study of elderly men. *Cereb Cortex, 12*(4), 438-445.

Tang, Y., Whitman, G. T., Lopez, I., & Baloh, R. W. (2001). Brain volume changes on longitudinal magnetic resonance imaging in normal older people. *J Neuroimaging, 11*(4), 393-400.

Terry, R. D. (2000). Cell death or synaptic loss in Alzheimer disease. *J Neuropathol Exp Neurol, 59*(12), 1118-1119.

Tzourio, C., Dufouil, C., Ducimetiere, P., & Alperovitch, A. (1999). Cognitive decline in individuals with high blood pressure: a longitudinal study in the elderly. EVA Study Group. Epidemiology of Vascular Aging. *Neurology, 53*(9), 1948-1952.

Uylings, H. B., & de Brabander, J. M. (2002). Neuronal changes in normal human aging and Alzheimer's disease. *Brain Cogn, 49*(3), 268-276.

van den Berg, E., Biessels, G. J., de Craen, A. J., Gussekloo, J., & Westendorp, R. G. (2007). The metabolic syndrome is associated with decelerated cognitive decline in the oldest old. *Neurology, 69*(10), 979-985. doi: 10.1212/01.wnl.0000271381.30143.75

Voss, M. W., Prakash, R. S., Erickson, K. I., Basak, C., Chaddock, L., Kim, J. S., . . . Kramer, A. F. (2010). Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. *Front Aging Neurosci, 2*. doi: 10.3389/fnagi.2010.00032

Watts, A. S., Loskutova, N., Burns, J. M., & Johnson, D. K. (2013). Metabolic syndrome and cognitive decline in early Alzheimer's disease and healthy older adults. *J Alzheimers Dis, 35*(2), 253-265. doi: 10.3233/jad-121168

Weintraub, S., Wicklund, A. H., & Salmon, D. P. (2012). The neuropsychological profile of Alzheimer disease. *Cold Spring Harb Perspect Med, 2*(4), a006171. doi: 10.1101/cshperspect.a006171

WHO. (1948). World Health Organization. Retrieved 13.05.2014

Wilson, I. A., Gallagher, M., Eichenbaum, H., & Tanila, H. (2006). Neurocognitive aging: prior memories hinder new hippocampal encoding. *Trends in Neurosciences, 29*(12), 662-670. doi: http://dx.doi.org/10.1016/j.tins.2006.10.002

Yaffe, K., Blackwell, T., Kanaya, A. M., Davidowitz, N., Barrett-Connor, E., & Krueger, K. (2004). Diabetes, impaired fasting glucose, and development of cognitive impairment in older women. *Neurology, 63*(4), 658-663.

Yaffe, K., Haan, M., Blackwell, T., Cherkasova, E., Whitmer, R. A., & West, N. (2007). Metabolic syndrome and cognitive decline in elderly Latinos: findings from the Sacramento Area Latino Study of Aging study. *J Am Geriatr Soc, 55*(5), 758-762. doi: 10.1111/j.1532-5415.2007.01139.x

Yaffe, K., Kanaya, A., Lindquist, K., Simonsick, E. M., Harris, T., Shorr, R. I., . . . Newman, A. B. (2004). The metabolic syndrome, inflammation, and risk of cognitive decline. *Jama, 292*(18), 2237-2242. doi: 10.1001/jama.292.18.2237

Yaffe, K., Lindquist, K., Penninx, B. W., Simonsick, E. M., Pahor, M., Kritchevsky, S., . . . Harris, T. (2003). Inflammatory markers and cognition in well-functioning African-American and white elders. *Neurology, 61*(1), 76-80.

Yassa, M. A., Lacy, J. W., Stark, S. M., Albert, M. S., Gallagher, M., & Stark, C. E. (2011). Pattern separation deficits associated with increased hippocampal CA3 and dentate gyrus activity in nondemented older adults. *Hippocampus, 21*(9), 968-979. doi: 10.1002/hipo.20808

Ystad, M., Hodneland, E., Adolfsdottir, S., Haász, J., Lundervold, A. J., Eichele, T., & Lundervold, A. (2011). Cortico-striatal connectivity and cognition in normal aging: A combined DTI and resting state fMRI study. *Neuroimage, 55*(1), 24-31. doi: http://dx.doi.org/10.1016/j.neuroimage.2010.11.016

Zook, N., Welsh, M. C., & Ewing, V. (2006). Performance of healthy, older adults on the Tower of London Revised: Associations with verbal and nonverbal abilities. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn, 13*(1), 1-19. doi: 10.1080/13825580490904183

Appendix

Appendix A1: Questions about participants' sleep and alertness.

Appendix A2: Questions about the computer in use and current surroundings.