The Effect of Vascular Risk Factors in Dementia of the Alzheimer’s Type

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ABSTRACT

The influence of vascular risk factors on Alzheimer's disease and its clinical presentation is an area of intense scientific debate. There is now growing evidence to suggest that the presence of vascular risk factors in early-stage Alzheimer's disease might accelerate its clinical presentation. Previous studies have also demonstrated that clinically healthy individuals with vascular risk factors perform below expectations on cognitive assessment. Further, the burden of vascular risk factors might be a predictor of future cognitive decline. However, the relationship between vascular risk factors and cognitive deterioration in healthy older adults has not been clearly established.

The aim of this study was to investigate the relationship between vascular risk factors and cognitive function in a large cohort of 768 cognitively healthy older individuals drawn from the Australian Imaging, Biomarkers and Lifestyle (AIBL) Study of Ageing. This thesis addresses four main questions: (1) is there a difference in cognitive performance between individuals with and without vascular risk factors?, (2) does the presence of vascular risk factors affect the rate of cognitive change? (3) does the number of vascular risk factors influence cognition? and (4) does the presence of vascular risk factors increase the likelihood of developing Mild Cognitive Impairment?

Participants were aged between 60–95 years, (M= 69.9 ± 6.9). All participants underwent a comprehensive baseline assessment and three additional serial
assessments were repeated at 18-month intervals over a 54-month period. By the end of the study period, 172 individuals had withdrawn from the cohort. Of the remaining 596 participants, 43 had attracted a classification of Mild Cognitive Impairment.

The sample was divided into subgroups of those with and without vascular risk factors. Participants in the vascular risk factors sub-group had at least one of the following risk factors: (1) hypertension, (2) diabetes, (3) dyslipidaemia, (4) Body Mass Index > 30 kg/m², (5) chronic kidney disease, (6) smoking history of more than 20 cigarettes per day for more than one year, and (7) elevated homocysteine levels (males>16.2 μmol/L; females>13.6 μmol/L).

This thesis comprises a series of analyses. For the first analysis, demographic characteristics of individuals with and without vascular risk factors was compared. The data suggested that vascular risk factors were associated with older age ($F (1, 712) = 8.1, p = 0.005$), lower level of education ($\chi^2 (1, n =711) = 7.8, p = 0.005$) and apolipoprotein E ε4 carriage ($\chi^2 (1, n = 714) =6.9, p = 0.009$).

In the second analysis, a statistically significant difference in cognitive performance between individuals with and without vascular risk factors was identified ($F (4, 669) = 4.28, p = 0.002; \text{partial \ eta \ square} = 0.03$). The results revealed that participants with vascular risk factors demonstrated poorer performance on variables that assessed visual cognition and executive functions than participants without vascular risk factors.
In the third analysis, from a longitudinal perspective, five specific neuropsychological tests were subjected to a linear mixed model adjusted for age and apolipoprotein E ε4 carriage. The presence of vascular risk factors was associated with increased rates of cognitive decline on measures of verbal fluency ($F (2, 1096.8) = 3.03, p < 0.05$) and visuospatial skills ($F (1204.6, 1) = 1.055; p < 0.05$).

The relationship between vascular risk factors and cognitive decline became more evident in the fourth analysis when the neuropsychological test battery was reduced into cognitive composite measures. Participants with vascular risk factors showed significantly greater decline on measures of verbal ($F (624.016, 1) = 7.2; p = 0.01$) and visual ($F (1775.533, 1) = 6.89; p = 0.01$) memory, as well as on visuospatial skills ($F (1204.6, 1) = 1.055; p = 0.03$) and executive functions ($F (1821.035, 1) = 4.48; p = 0.03$). No difference was found in the language composite measure.

In the fifth analysis, higher vascular risk factor burden was associated with increased rates of cognitive decline, suggesting the presence of a dose-response relationship. In individuals with three or more vascular risk factors, a higher magnitude of decline on tasks that measure executive functions (Cohen's $d = 0.35$), visuospatial skills (Cohen's $d = 0.35$) and visual memory (Cohen's $d = 0.47$) was identified. No dose-response relationship was found in either the language or verbal memory cognitive domains.

The sixth analysis focused on the group of participants who attracted a diagnosis of MCI over the 54 months. The data showed that there was a significant difference in the vascular risk factor burden distribution between individuals who
remain cognitively stable and those who transition to Mild Cognitive Impairment ($X^2 (2) = 44.88, p < 0.001$), with greater risk factor burden observed in the latter. The interaction effect between clinical classification and presence/absence of vascular risk factors on the cognitive composite factors was further investigated. The only cognitive variable that showed a statistically significant difference was the visuospatial skill composite ($1, 513 = 5.52; p = 0.019; \text{partial eta square} = 0.011$). Finally, the analysis showed that vascular risk factors increased the likelihood of developing Mild Cognitive Impairment by 39%.

In conclusion, the data suggest that vascular risk factors confer a degree of cognitive vulnerability on cognitively healthy older adults. This effect appears to be selective, impacting executive functions and visuospatial cognition but not language and verbal memory. Executive functions and visuospatial cognition are complex cognitive domains and share extensive distributed networks, which may increase their susceptibility to vascular risk factors over time.

Based on the overall findings of this research, we propose that vascular risk factors – in combination with genetic and demographic factors – contribute to a reduction of brain reserve, precipitating an earlier onset of cognitive decline in the transition to Mild Cognitive Impairment. This implies that individuals who suffer from several risk factors may have less brain reserve and may therefore be more susceptible to developing dementia. Vascular risk factors are preventable for at least 95% of people with relatively simple changes in diet and lifestyle. The findings from this thesis contribute to a developing literature suggesting that decreases in vascular risk may reduce susceptibility for dementia and cognitive decline in later life.
DECLARATION OF AUTHORSHIP

This is to certify that:

The thesis comprises only my original work towards the PhD.

Due acknowledgement has been made in the text to all other material used.

The thesis is fewer than 100,000 words in length, exclusive of tables, bibliographies and appendices.

Carolina Restrepo
1. This thesis contains no work submitted for other “qualifications”, or work carried out prior to PhD candidature.

2. This thesis was conducted within the context of the Australian Imaging, Biomarkers and Lifestyle (AIBL) Flagship Study of Ageing (www.aibl.csiro.au).

3. All research procedures reported in this thesis were approved by and complied with the regulations of the institutional research and ethics committees of Austin Health, St. Vincent’s Health, Hollywood Private Hospital, and Edith Cowan University.
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DEDICATION

I grew up in Bogotá, Colombia. I am one of 27 grandchildren and 23 great-grandchildren. My family is originally from the coffee region, an area where older women are the family leaders and those whom the family is built around. Growing up, my family instilled in me a deep respect and admiration for older people. The values learned in my family were fundamental to my passion and motivation to focus my professional and academic career on working in the field of dementia. I would like to dedicate this thesis to my grandparents for their love and wisdom, and for being the foundation of a wonderful family.

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AWARDS

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Alzheimer's Australia Dementia Research Foundation PhD Top-Up Scholarship

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2011

Australian Postgraduate Award (APA)

2009

Scholarship-Loan Colfuturo. Colombian national government non-profit foundation.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>Aβ</td>
<td>β-amyloid</td>
</tr>
<tr>
<td>AD</td>
<td>Alzheimer's disease</td>
</tr>
<tr>
<td>ADI</td>
<td>Alzheimer's disease International</td>
</tr>
<tr>
<td>AIBL</td>
<td>Australian Imaging, Biomarkers, and Lifestyle Study of Ageing</td>
</tr>
<tr>
<td>APOE</td>
<td>Apolipoprotein E (gene)</td>
</tr>
<tr>
<td>ATP III</td>
<td>The National Cholesterol Education Program's Adult Treatment Panel III</td>
</tr>
<tr>
<td>BBB</td>
<td>Blood-brain-barrier</td>
</tr>
<tr>
<td>BDNF</td>
<td>Brain-Derived Neurotrophic Factor</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>BNT</td>
<td>Boston Naming Test</td>
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<tr>
<td>C/D Stroop</td>
<td>Stroop interference task (Victoria version)</td>
</tr>
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<td>CKD</td>
<td>Chronic Kidney Disease</td>
</tr>
<tr>
<td>CSIRO</td>
<td>Commonwealth Scientific and Industrial Research Organisation</td>
</tr>
<tr>
<td>CVLT-II</td>
<td>California Verbal Learning Test, Second Edition</td>
</tr>
<tr>
<td>DAT</td>
<td>Dementia of the Alzheimer's Type</td>
</tr>
<tr>
<td>DET</td>
<td>CogState Detection task</td>
</tr>
<tr>
<td>FAS D-KEFS</td>
<td>D-KEFS Verbal Fluency Test</td>
</tr>
<tr>
<td>GDS-15</td>
<td>The Geriatric Depression Scale</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular Filtration Rate</td>
</tr>
<tr>
<td>VaD</td>
<td>Vascular Dementia</td>
</tr>
<tr>
<td>IDN</td>
<td>CogState Identification task</td>
</tr>
<tr>
<td>MCI</td>
<td>Mild Cognitive Impairment</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini Mental State Examination</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>NARI</td>
<td>National Ageing Research Institute</td>
</tr>
<tr>
<td>NINCDS-ADRDA</td>
<td>National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association</td>
</tr>
<tr>
<td>OBK</td>
<td>CogState One Back task</td>
</tr>
<tr>
<td>OCL</td>
<td>CogState One Card Learning task</td>
</tr>
<tr>
<td>PET</td>
<td>Position Emission Tomography</td>
</tr>
<tr>
<td>PiB</td>
<td>Pittsburgh Compound B</td>
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<tr>
<td>RCFT</td>
<td>Rey Complex Figure Test</td>
</tr>
<tr>
<td>SMC</td>
<td>Subjective memory complainers</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for the Social Science</td>
</tr>
<tr>
<td>VRF</td>
<td>Vascular Risk Factors</td>
</tr>
<tr>
<td>WAIS-III</td>
<td>Wechsler Adult Intelligence Scale, Third Edition</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>WMS</td>
<td>Wechsler Memory Scale</td>
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<tr>
<td>WTAR</td>
<td>Wechsler Test of Adult Reading</td>
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“While the lesions associated with senile conditions are well known, it is still an unsolved problem why senile psychose occur in some old persons but not in others. Therefore it seems worthwhile to review the subject in an attempt to determine whether certain newly developed ideas and methods of approach may throw light on the problem. The question whether alterations of the blood-cerebrospinal fluid barrier may be a pathogenetic factor in senile dementia is of interest because certain authors ... have suggested that circulatory disturbances may play a role in the production of the cerebral changes found in senile conditions.”

Rothschild (1937) pg. 758-9

“Brain infarcts may play an important role in determining the presence and severity of the clinical symptoms of Alzheimer’s disease. Other manifestations of cerebrovascular disease, such as atherosclerosis, also may be involved in this process. Further research will be needed before it is known whether the prevention of cerebrovascular disease can mute the clinical expression of Alzheimer’s disease.”

Snowdon (1997) pg. 817
CHAPTER ONE - OVERVIEW

This chapter provides a brief overview of the substantial increase in the prevalence of vascular risk factors worldwide and describes the lifestyle changes that society is facing as a consequence of urbanisation and industrialisation. A summary of the projection of dementia incidence in developed and developing countries is then presented. The chapter concludes by highlighting the potential impact of vascular risk factors on cognitive function and the onset of dementia, which is central to the focus of this thesis.

The Study of Vascular Risk Factors

In Australia the major cause of death, with 43,603 attributed deaths in 2013, is Cardiovascular disease (Australian Heart Foundation, 2013). Despite improvements over the last few decades, it remains one of the biggest health challenges in the country (Grøntved & Hu, 2011). The risk of developing cardiovascular disease is closely associated with the presence of vascular risk factors such as smoking, physical inactivity, poor nutrition and the harmful use of alcohol, some of which in turn contribute to obesity, high blood pressure and high blood cholesterol levels. Importantly, however, each of these risk factors is modifiable (Black, 1992). Chronic diseases, once they develop, can often be effectively controlled through behavioural change, medication and other lifestyle-based interventions. Although Australia has had some success in preventing and treating cardiovascular disease, prevalence
continues to grow as the population increases and better treatment allows people to live longer (Lloyd-Jones et al., 2010).

Vascular risk factors are preventable for at least 95% of people, with relatively simple changes in diet and lifestyle (Daubenmier et al., 2007; Marioni, van den Hout, Rosengren, Dotevall, Eriksson, & Wilhelmsen, 2001; Scarmeas & Stern, 2003; Williams & Kemper, 2010). A recent report from the American College of Cardiology and the American Heart Association Task Force on Practice Guidelines (Stone et al., 2014) concluded that lifestyle modification, such as following a healthy diet, regular exercise habits, avoidance of smoking, and maintenance of a healthy weight, remains a critical component of vascular risk factors reduction. Large bodies of observational data show an inverse dose-response relationship between particular dietary patterns, nutrient intake and increased physical activity, with low rates of vascular risk factors (Sattelmair et al., 2011; Shiroma & Lee, 2010; US Department of Health Human Services, 2008; Warburton, Charlesworth, Ivey, Nettlefold, & Bredin, 2010; World Health Organization, 2010).

Previous research has shown that increasing physical activity, quitting smoking and decreasing the amount of alcohol intake, together with high consumption of fruits and vegetables, is associated not only with a reduction in vascular risk factors, but also with improvements in quality of life (Artaud et al., 2013). The beneficial effects of lifestyle modifications on quality of life have been observed even among individuals with cardiovascular disease (Lavie, Lavie, & Milani, 1997). Observational data suggest that improvement of quality of life can significantly reduce development of other processes such as cognitive deterioration.
As such, the identification of associations between vascular risk factors and cognitive decline is critical, especially for the development of prevention and intervention strategies for dementia (Yaffe, Barnes, Nevitt, Lui, & Covinsky, 2001).

**Characterisation of Vascular Risk Factors**

The term "arteriosclerotic brain syndrome" or "arteriosclerotic psychosis" was first used more than 50 years ago to describe mental deterioration in the elderly (Mayer-Gross, 1944; Mohler, 1960; Rothschild, 1942). This senile syndrome was diagnosed when there was evidence of progressive cognitive decline, characterised by disorientation and memory loss (Kay, Beamish, & Roth, 1964). It was proposed that cerebral atherosclerosis was the result of persistent decrease of the brain's blood-supply which led to progressive chronic ischaemia (Harrison, Thomas, Duboulay, & Marshall, 1979). Cerebral blood flow was also observed to be lower in patients with cognitive decline compared to control participants (Hachinski et al., 1975). Conversely, others observed that it was possible to reverse some of the mental changes associated with this condition by controlling the risk factors that make individuals prone to atherosclerosis and cardiovascular disease (i.e., vascular risk factors, such as hypertension or dyslipidaemia) (Bowen, Smith, White, & Davison, 1976). This has led to an increased interest in the study of the effect of these vascular risk factors on cognitive function, and on the risk for developing dementia.

The Framingham Heart Study, which commenced after World War II, was the first longitudinal study to investigate factors that may impact an individual's predisposition for the development of cardiovascular and cerebrovascular disease
(Kannel & McGee, 1979). For example, they found that older adults with high levels of hypertension exhibited greater cognitive decline (Elias, Elias, Sullivan, Wolf, & D'agostino, 2003). Additionally, older adults who were diagnosed with Type II diabetes were more likely to develop Alzheimer’s disease (AD) (Akomolafe et al., 2006). The definition of vascular risk factors has evolved since the first published report from the Framingham Heart Study, and newly identified vascular risk factors are periodically added to the list (Hackam & Anand, 2003). During the last few decades, over 300 vascular risk factors have been described worldwide (Black, 1992). However, the majority of vascular risk factors meet three broad criteria: (1) high prevalence in many populations; (2) significant independent impact on the risk for vascular disease; and (3) treatment and control results in reduced risk of cardiovascular disease (Mackay et al., 2010). The most common vascular risk factors are hypertension, dyslipidaemia, diabetes and obesity (Mahmood, Levy, Vasan, & Wang, 2014).

**Lifestyle Changes and Prevalence of Vascular Risk Factors**

The origin of the word pandemic is derived from the Greek πᾶν (pan) “all” and δῆμος (demos) “people”, and is used to describe a disease that has spread through human populations across extensive geographic areas. After influenza and the human immunodeficiency virus, cardiovascular disease is now also considered a pandemic of the XXI century (van Dieren, Beulens, van der Schouw, Grobbee, & Neal, 2010). Lifestyle changes have contributed to a global increase in the incidence of vascular risk factors. A growing body of literature suggests a causal relationship between the presence of vascular risk factors and the onset of cardiovascular disease (D’Agostino
et al., 2008; Ryan, 2007; Yusuf et al., 2004). Even though the concept of vascular risk factors has only evolved over the past 50 years (Black, 1992), it is now well known that vascular risk factors have a significant impact on all populations around the world.

The growing prevalence of vascular risk factors has been attributed at least in a large part to the adoption of a Western ‘modern’ lifestyle characterised by a diet with excessive caloric intake and high levels of saturated fats, high incidence of smoking, excessive alcohol use, and low consumption of fruits and vegetables (Gorelick et al., 2011; Sacks et al., 2001), coupled with decreased physical activity associated with lower levels of walking and cycling to meet daily travel needs (Yusuf et al., 2004; Yusuf, Reddy, Ōunpuu, & Anand, 2001). The impact of vascular risk factors epidemiologically is so significant that some researchers predict that the presence of vascular risk factors will soon cause the first decline in life expectancy in 100 years in developed countries (Gunstad, Lhotsky, Wendell, Ferrucci, & Zonderman, 2010).

**Demographic Characteristics and Prevalence of Vascular Risk Factors**

According to the theory of *epidemiologic transition*, which focuses on the relationship between demographic characteristics and health patterns (Omran, 1971), the modern world is facing dramatic changes (Yusuf, Reddy, Ōunpuu, et al., 2001). While the prevalence of vascular risk factors has risen significantly worldwide, demographic characteristics, such as gender, age, marital status, social class and educational level, can significantly contribute to the prevalence of vascular risk factors within a particular population (Laaksonen, Prättälä, & Lahelma, 2003). As
developing countries become increasingly modernised and urbanised, their residents face a rapid change in lifestyle, which can lead to significant public health problems (Jaacks, Jaacks, Slining, & Popkin, 2015). Indeed, for the first time in human history, more people are suffering from obesity than from being underweight (Popkin, 2007). This increase in the prevalence of vascular risk factors in developing countries is similarly observed in Latin America. For example, obesity amongst older adults in Mexico went from 10–19% in 1970 to more than 50% in the year 2000, and in Bolivia and Peru obesity affects more than 40% of the older-adult population (Kordas, Fonseca Centeno, Pachón, & Jimenez Soto, 2013).

The prevalence of vascular risk factors has been found to be strongly associated with socioeconomic status (Groth, Fagt, Stockmarr, Matthiessen, & Biltoft-Jensen, 2009; Roskam et al., 2010; Wang & Beydoun, 2007; Zaninotto, Head, Stamatakis, Wardle, & Mindell, 2009), and multiple vascular risk factors are more common in populations with low educational level (Berrigan et al., 2003; Dumith et al., 2012; Kaplan & Keil, 1993; Laaksonen et al., 2003; Tobias, Tobias, Jackson, Yeh, & Huang, 2007; Tunstall-Pedoe, 1988; Winkleby, Jatulis, Frank, & Fortmann, 1992). Studies have shown that individuals from unskilled manual backgrounds were more than three times at risk to have vascular risk factors than professionals. Similarly, those with no formal qualifications were more than five times as likely to have vascular risk factors than those with high levels of training (Borenstein et al., 2005; Buck & Frosini, 2012). As the prevalence of vascular risk factors are more likely to be higher in individuals from low socioeconomic backgrounds (Artaud et al., 2013), additional care needs to be provided to these ‘at risk’ individuals when planning health promotion and prevention initiatives.
Rates of vascular risk factors have risen greatly in low-income and middle-income countries, with about 80% of the global burden now occurring in these areas (Murray & Lopez, 1997). In one generation, for instance, Asia has changed from having one of the lowest rates of vascular risk factors to having one of the highest (Anand et al., 2000; Ueshima et al., 2008). In India, it has been reported that 1.2 million people suffered from vascular disease in 2003, and this is expected to increase by 111% by 2020 (Gupta & Gupta, 2004). In sub-Saharan Africa, recent studies have found that the prevalence of hypertension has reached significant levels (Kilander, H. Kilander, M. Nyman, H. Boberg, & Lithell, 1997; Thorogood et al., 2007). Figure 1 summarises the prevalence of vascular risk factors in both developing and developed countries.

The marked growth in vascular risk factors in developing countries is likely a result of increased industrialisation and urbanisation, and a consequent shift away from rural lifestyles that typically involve healthier diets and higher levels of physical activity (World Health Organization, 2011). This, coupled with lower levels of public health education about the consequences of tobacco use, alcohol consumption and obesity, may have resulted in an exponential increase in the prevalence of vascular risk factors in developing countries (Lao et al., 2014).
The Relationship between Age and Vascular Risk Factors

Advancing age remains unequivocally the main risk for the presence of vascular risk factors (Di Carlo et al., 2000; Haan & Mayeda, 2010; Yusuf et al., 2004; Yusuf, Reddy, Ôunpuu, et al., 2001). Evidence suggests that vascular risk factors are particularly prevalent in people aged 50 years and older (Johannson & Zarit, 1997; Tracy et al., 1997). The rapidly growing proportion of older people, combined with the fact that the presence of vascular risk factors is potentially modifiable, makes early detention of ‘at risk’ healthy older adults a major public healthcare focus (Laaksonen et al., 2003; Polikar, Topalis, Green, Kounios, & Clark, 2007). Effective prevention thus requires a global strategy based on the understanding of the prevalence of vascular risk factors in different geographic regions and among various ethnic and demographic groups (Buck & Frosini, 2012).
Vascular Risk Factors and Cognitive Deterioration

Vascular risk factors are linked to many common cognitive disorders associated with ageing, including mild cognitive impairment (MCI) (Kivipelto et al., 2001; Lopez et al., 2003), Alzheimer’s disease (the most common cause of dementia) (Gorelick, 2004; Kivipelto, T. Ngandu, L. Fratiglioni, & et al., 2005; Li et al., 2011) and vascular dementia (VaD) (Hachinski, Lassen, & Marshall, 1974; Roman et al., 2010; Skoog, 1998). Even at subclinical levels, epidemiological studies have shown that vascular risk factors can affect cognitive functioning (Breteler et al., 1994; Di Carlo et al., 2000). Understanding the relationship between cognitive function and vascular risk factors is critical since, while more common as people age, dementia is not a normal aspect of the ageing process (Kivipelto et al., 2001).

Research has suggested a potential relationship, whereby the same risk factors that make individuals prone to cardiovascular disease may also put them at risk for dementia (Goldberg & Griffith, 2011). Results have indicated that the presence of vascular risk factors may affect and reduce cognitive performance (Akomolafe et al., 2006; K. Anstey, C. von Sanden, A. Salim, & R. O’Kearney, 2007; Craft, 2009; Dregan, Stewart, & Gulliford, 2012; Etgen, 2010; Schneider et al., 2014; Wiederkehr, Laurin, Simard, Verrault, & Lindsay, 2009). It has been suggested that vascular risk factors have an effect on cognitive function even in non-demented older adults (Bangen, L. Delano - Wood, et al., 2010; Bender, Daugherty & Raz, 2012; Dahle, Dahle, Jacobs, & Raz, 2009; Nation, 2010; Okonkwo et al., 2010; Reijmer et al., 2011; Yaffe et al., 2014). Given that the prevalence of vascular risk factors is a global health concern that has reached epidemic proportions during the last decade, the study of
the relationship between vascular risk factors and cognitive function has become increasingly important.

It has been proposed that the treatment of vascular risk factors in the prevention of dementia will be most effective at the pre-symptomatic stage before further irreversible brain damage has occurred (Howieson et al., 1997). Although evidence revealed by previous studies indicated that the management of vascular risk factors may assist in the prevention and treatment of dementia (Kalaria et al., 2008; Li et al., 2011; Naismith et al., 2009), further research is needed to elucidate this potential relationship more clearly as there are studies with conflicting results (Kearney, M. Whelton, et al., 2005; Muller, van der Graaf, Visseren, Mali, & Geerlings, 2012; Raz et al., 2011; Waldstein, 2008). A better characterisation of the neuropsychological profile of individuals with vascular risk factors and thus at a high risk of cognitive deterioration is needed.

**Global Burden of Dementia**

Over the past decades there has been a considerable increase in the number of people with cognitive impairment caused by dementia (Fillit, Simon, Doniger, & Cummings, 2008). We currently face a profound and growing incidence of Alzheimer’s disease, the leading cause of dementia in the elderly, throughout much of the world in people living in their 70’s, 80’s, and beyond (Kawas, 2006). In 2005, Alzheimer’s disease International (ADI) commissioned an international group of experts to review all available data and reach a consensus on dementia prevalence in the 14 World Health Organization (WHO) regions. The results, published in the ADI Delphi Consensus Study, suggested that the number of people living with dementia
would grow from approximately 24.3 million in 2001 to 42.3 million in 2020 and 81.1 million in 2040 (a near doubling every 20 years) (Bosco et al., 2005). A recent study by Prince and colleagues (Prince et al., 2013) estimated an even faster growth, as they identified that 35.6 million people lived with dementia worldwide in 2010, and projected that the number of people with dementia would reach 65.7 million in 2030 and 115.4 million in 2050 (Figure 2).

![Figure 2: Estimation of the prevalence of dementia in the world](image)

According to the 2005 ADI Delphi study, North America and Western Europe have the highest relative prevalence of dementia, with around 6.4 and 5.4% of the population, respectively, compared to a world average of 3.9%. However, the overall incidence of dementia shows that the largest number of people with dementia live in the developing world and that most of the growth will occur in these countries (Bosco et al., 2005).
In 2010, 58% of all people with dementia lived in countries with low or middle incomes, with this proportion anticipated to rise to 63% in 2030 and 71% in 2050 (Prince et al., 2013). The health system in many of these countries is not able to provide appropriate treatment to preserve or enhance their quality of life, leading to a potential global health crisis.

In Australia, the situation is equally concerning; dementia is the single greatest cause of disability in older Australians (aged 65 years or older) and the third leading cause of disability burden overall in the country. Dementia is also the third leading cause of death in Australia (the second leading cause in women) (McCallum, 2015). Almost one in ten people over the age of 65 and three in ten people over 85 have dementia. Today, there are around 340,000 Australians living with dementia. In Australia, the proportion of people aged 65 years and over is around 13.6% and is estimated to rise to around 20% by 2040 and 23% by 2061 (Vecchio, Fitzgerald, Radford, & Fisher, 2015). As a result of the combined effect of an ageing population and the lack of a cure for dementia, the number of people with dementia in Australia is expected to increase to 400,000 in the next ten years (approximately 18%) (Krockenberger, 2015).

It has been estimated that, without prevention, the prevalence of dementia would increase to 924,624 people living with dementia in Australia in 2050 (a near tripling in 35 years), with 245,813 of those in Victoria (Economics Deloitte Access, 2011). However, these projections could be significantly changed if the onset of the disease was delayed. With a delay of 5 years, the prevalence would decrease by 44%, and with ‘only’ a 6-month delay, the prevalence would decrease by 6% (Jorm, Dear, &
Burgess, 2005). Approximately half of dementia cases are potentially attributable to modifiable risk factors, such as vascular risk factors (Barnes & Yaffe, 2011). These results suggest that identifying the possible causes of dementia must remain a critical area of investigation, with potentially profound implications for disease prevention and the initiation of treatment when it may have optimal benefit (Hayden et al., 2006).

In the absence of definitive biomarkers, the diagnosis of dementia relies on the identification of clinical diagnostic criteria. Different sets of diagnostic criteria for dementia have been developed, including those defined in the various editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM), the International Classification of Diseases (ICD) and the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX). However, these criteria can produce different estimates of the prevalence of this disorder. For example, in a cohort of 1879 men and women aged 65 years or older who were enrolled in the Canadian Study of Health and Aging, the frequency of dementia was 3.1 % when the ICD-10 criteria were used, 4.9 % with the CAMDEX, 5.0 % with ICD-9, 13.7 % with DSM-IV, 17.3 % with the DSM-III-R and 29.1 % with the DSM-III criteria – a factor of 10 difference between the highest and lowest frequencies (Erkinjuntti, Østbye et al. 1997). Based on this empirical knowledge, estimates of dementia can vary significantly depending on the diagnostic criteria used.
Importance of Early Detection of "at Risk" Individuals for Cognitive Deterioration

Early detection and differential diagnosis of dementia are essential for choosing proper therapies aimed at removing the causes of reversible dementias or adequately treating cognitive and behavioural symptoms of progressive dementias (Pasquier, 1999). Therefore, identifying strategies that stop or delay the progression of disease processes associated with cognitive decline is extremely important. Additionally, pharmacological and non-pharmacological treatment is most effective at improving life expectancy and quality of life when initiated in the early stages of dementia (Polikar et al., 2007). For these reasons, early detection of individuals that are at risk of developing dementia has become one of the most important areas of clinical focus, with profound implications for establishing the prevalence of dementia and understanding the pathobiology and clinical presentation of the disease.

There is a critical need to accurately detect the onset of cognitive changes that signal the beginning of a progressive dementia syndrome and to differentiate among disorders with distinct aetiologies and sites of pathology. Despite this being a particularly difficult task given the insidious onset and slow progression of most neurodegenerative diseases, it is critically important given the lack of a reliable biological marker that can distinguish dementia from normal ageing or other neurodegenerative disorders that lead to dementia (Salmon & Bondi, 2009). The process of diagnosing a person with incipient dementia in the preclinical state is extremely difficult. As a result, there is strong impetus for clinical and epidemiological research to focus on the identification of neurocognitive markers and
risk factors that may be modified at a preclinical and early clinical stage of dementia (Valls-Pedret, Luis Molinuevo, & Rami, 2010).

Identifying older adults who do not currently have dementia but are at risk of developing dementia is critical so that they can be targeted for the implementation of preventative strategies. Vascular risk factors have an important role in the progression to dementia. Given that the prevalence of vascular risk factors is preventable and easily modified, a better characterisation of the neuropsychological profile of individuals with vascular risk factors and thus at risk of cognitive deterioration is crucial as it may promote the development of more effective prevention strategies for dementia.
The previous chapter presented a summary of the prevalence of vascular risk factors and dementia, emphasising the importance of studying the impact of these risk factors on the onset of dementia. This chapter will describe the current knowledge about the relationship between vascular risk factors and Alzheimer's disease (the most common cause of dementia), and vascular risk factors and cognitive function. The review will firstly summarise the most salient aspects presented in the literature examining the role of vascular risk factors in the pathogenesis of Alzheimer's disease. Secondly, a summary of the main studies to date that have investigated the relationship between specific vascular risk factors and cognition is presented. Thirdly, the brain reserve hypothesis is introduced as a potential explanation of the link between vascular risk factors and cognitive deterioration, highlighting the current gaps in the literature and leading to a description of the objectives of this study in addressing these gaps. This chapter will finalise with a brief summary of each of the forthcoming experimental analyses.

**Alzheimer's Disease Pathology Stages**

Alzheimer's disease is a neurodegenerative disease characterised by synaptic and neuronal loss, resulting in impairment in cognition and function. Definitive AD diagnosis can only be made post-mortem by neuropathological examination. Abnormal structures called β-amyloid (Aβ) plaques and neurofibrillary tangles are classic biological hallmarks of the disease (Braak & Braak, 1991). Senile plaques are
the result of accumulation of Aβ (Selkoe & Selkoe, 1991), while neurofibrillary tangles, on the other hand, have been associated with the protein tau (Braak & Braak, 1991). The pathogenesis of AD onset remains unclear, although it is postulated that either excessive Aβ production or reduced Aβ clearance may result in the accumulation and deposition of Aβ plaques in the brain (Abdullah et al., 2009; Cummings, Doody, & Clark, 2007; Okazaki et al., 2010).

In 1991, Braak and Braak identified a number of age-associated stages in the AD continuum. They stated that "progressions" through Braak stages result in "regressions" in cognitive function (Braak & Braak, 1991, 1997). Braak stage I is a "preclinical" brain-change state, consistent with a pathological diagnosis of early AD. There are no clinical symptoms at this stage and it may take up to four decades before there is noticeable dementia (Villemagne et al., 2013). In other words, the pathological process underlying AD can be recognised over extended periods of time before the onset of clinical symptoms (Jack et al., 2010; Sperling et al., 2011; Villemagne et al., 2013).

At stages III–IV, severe destruction of the cortex is already observed; however, the most significant damage is observed in the entorhinal region and adjoining areas (Braak & Braak, 1991). There are at least 30 years between Braak stage I and stage III, and approximately 18 years between stage III and stage V (Braak & Braak, 1991). As a result, AD pathological processes occur for many years before clinical symptoms are evident. Theoretical models of AD (Jack et al., 2010) that have now been empirically validated (Villemagne et al., 2013) show that there is a long preclinical period characterised by abnormal Aβ depositions and progressive neuronal
degeneration, which ultimately leads to overt cognitive impairment consistent with the clinical presentation of AD.

**Vascular Changes in Alzheimer’s Disease**

Although age is the most important risk factor for the transition between stages I and II to stages III and IV of the Braak spectrum, other factors, such as vascular risk factors, may also increase the risk for developing the clinical symptomatology of AD (Barone, Rosenbaum, Zhou, & Crystal, 2009; Dufouil et al., 2000; Gorelick, 2004; Hayden et al., 2006; Weller et al., 1998). It has been hypothesised that continuous exposure to vascular risk factors (over an extended period of time) can lead to a number of changes in cerebrovascular physiology that have been described in AD brains: (1) decreased microvascular density, (2) basement membrane thickening, (3) endothelial and pericyte damage, (4) diminished glucose transport across the blood-brain barrier (BBB), (5) vessels that express inflammatory markers, (6) perivascular fibrosis, (7) capillaries with fewer branches, (8) atrophic vessels, (9) changes in vessel diameter, (10) accumulation of collagen, (11) atherosclerotic plaques, (12) cerebral amyloid angiopathy, and (13) microglial activation in degenerating endothelial cells or thrombotic lesions (Humpel, 2011).

Uncertainty remains with respect to whether the cerebrovascular changes found in AD brains are an initial cause for development of AD, or whether they occur in late stages of the disease. Histopathological evidence of cerebrovascular disease in large or small vessels is found in about 70-90% of those who die with AD (Emmerling, Gracon, & Roher, 1999). It has also been found that neuropathological AD cases with concomitant vascular pathology are more likely to present the clinical
symptoms of AD than those without infarcts (88% vs. 57%) (Snowdon et al., 1997). These results suggest that pathological alterations in the cerebral vasculature (linked to the presence of vascular risk factors) appear to be associated with AD pathology (Jonsson et al., 2010). Even though vascular brain lesions are more common in AD brains, it is still unknown if there is a pathological link between the presence of vascular risk factors and the deposition of Aβ in the brain, which is considered a key step in the onset of AD (Gentile et al., 2009).

**Theoretical Model: Blood-Brain Barrier Permeability**

A possible theoretical model for the interaction between vascular risk factors and AD pathology argues that there may be an increase in blood-brain-barrier (BBB) permeability in individuals with vascular risk factors, which could facilitate Aβ deposition in the brain (Wardlaw, 2010). This may be due to BBB dysfunction increasing the possibility that substances from serum, such as proteins, inflammatory biomarkers and inflammatory and red cells reach the brain, where they may initiate a cascade resulting in Aβ accumulation and AD pathology (Lammie, Brannan, & Wardlaw, 1998). The observation of proteins in the brain that originally are in the serum is considered an index of BBB permeability. Therefore, it has been proposed that BBB dysfunction may be involved in the aetiology and pathogenesis of AD (Kalaria, 1992).

Vascular endothelial cells play an important role in maintaining vaso-activity and the functional integrity of the BBB. About 90% of AD individuals at autopsy show endothelial cell damage, compared to 30% in control brains (Jonsson et al., 2010). Moreover, the extent of endothelial cell damage correlates with the amount of Aβ
deposition, suggesting a potential role for endothelial dysfunction in the pathogenesis of AD (Brenner et al., 2010; Jonsson et al., 2010; Kalaria, 1999; Salmina, Inzhutova, Malinovskaya, & Petrova, 2010; Soon-Tae et al., 2010).

The role of the BBB and vascular endothelium in AD has been further explored in both patients and experimental models (Bennett, Grant, & Aldred, 2009). Apoptosis of endothelial cells may be associated with the presence of vascular risk factors. For instance, Poulet and colleagues showed that chronic hypertension impairs BBB permeability, which can lead to increases in \( \text{A}\beta \) deposition in the brain and thus suggests a potential link between vascular risk factors and AD pathogenesis (Poulet et al., 2006). In addition, \( \text{A}\beta \) protein is involved in the degeneration of both the larger perforating arterial vessels, as well as the cerebral capillaries that represent the BBB.

**Vascular Risk Factors and Dementia**

In addition to the link between AD pathology and vascular risk factors, a relationship has also been identified between the presence of vascular risk factors and cognitive decline. MCI is considered the intermediate stage between normal ageing and dementia, and is characterised by cognitive deterioration greater than expected for age but not reaching the severity for a dementia diagnosis (Kurz, Diehl, Riemenschneider, Pernecky, & Lautenschlager, 2004; Petersen, 1999; Winblad et al., 2004). Some studies have proposed that the presence of vascular risk factors, when occurring in the setting of incipient AD, may accelerate the transition to MCI (Barone et al., 2009; Kalaria et al., 2008; Kivipelto et al., 2006; Luchsinger & Mayeux, 2004; Misciagna, Masullo, Giordano, & Silveri, 2005; I Skoog et al., 1996; Whitmer, Sidney,
Selby, Johnston, & Yaffe, 2005). Ott and colleagues found that of 6370 cognitively healthy participants with vascular risk factors, 2% were diagnosed with dementia after 2.1 years (Ott et al., 1999). In a longer longitudinal study, from a total of 5367 people with vascular risk factors, 25.4% were diagnosed with dementia after a follow-up period of 23 years (Rusanen, Kivipelto, Quesenberry, Zhou, & Whitmer, 2011). Another study reported that, from a total of 837 participants identified as having vascular risk factors at baseline, 298 converted to MCI within 5 years (Li et al., 2011). Nevertheless, the nature of the interaction between vascular risk factors and the development of dementia is poorly understood.

Dementia of the Alzheimer’s type (DAT) has been defined as the clinical syndrome of AD, characterised by impairment of cognitive function, with significant effects on occupational, social and functional ability. This progressive, and at present, incurable condition results in cognitive impairment in at least three of the following mental functions: language, memory, visuospatial skills or executive functions (Cummings, 1984). On neuropsychological tests, DAT is defined as performance of two standard deviations below normative data in at least two different cognitive domains, together with impairment in activities of daily living and occupational dysfunction (McKhann et al., 2011).

Significant cognitive decline (up to five years prior to the diagnosis of DAT) in the presence of vascular risk factors has been identified (Schneider et al., 2014; I. Skoog et al., 1996; van Vliet et al., 2010). Indeed, an emerging consensus in the field proposes that cognitive decline, attributable to the presence of vascular risk factors, should be viewed along a continuum, going from minimal cognitive impairment to
frank dementia (Gorelick et al., 2011). Although there is increased recognition that older adults with vascular risk factors experience cognitive decline, even in the absence of stroke (Duron & Hanon, 2008; Kivipelto, et. al, 2005), an understanding of the nature and extent of cognitive decline secondary to the presence of vascular risk factors has not been elucidated.

Specific Vascular Risk Factors and Cognition

The main vascular risk factors which have been found to have an effect on cognitive function include (1) hypertension (Kivipelto et al., 2001; Knopman et al., 2001; S. R. Waldstein, 2008; Whitmer et al., 2005), (2) type II diabetes (Akomolafe et al., 2006; Arvanitakis, Wilson, Bienias, Evans, & Bennett, 2004; Luchsinger, Tang, Shea, & Mayeux, 2004), (3) dyslipidaemia (Kivipelto et al., 2001; Moroney et al., 1999; Notkola et al., 1998; Solomon & Kivipelto, 2009), (4) obesity (Gustafson, Rothenberg, Blennow, Steen, & Skoog, 2003; Rosengren, Skoog, Gustafson, & Wilhelmsen, 2005; Whitmer et al., 2005), (5) smoking (Aggarwal, Bienias, Bennett, Wilson, & Morris, 2006; Juan et al., 2004; Reitz, Heijer, Duijn, Hofman, & Breteler, 2007), (6) chronic kidney disease (Kurella et al., 2005; Kurella et al., 2011; Slinin et al., 2008; Yaffe et al., 2010), and (7) raised plasma homocysteine (Dufouil, Alperovitch, Ducros, & Tzourio, 2003; Kim et al., 2008).

A systematic review was conducted in order to identify previous studies that compare the incidence of dementia or progression to cognitive decline in individuals who suffer from the aforementioned vascular risk factors. In March 2010 the first electronic database search was performed in MEDLINE, PsycINFO, PubMed and the Cochrane Library. This search used a combination of keywords for cardiovascular
risk (i.e. vascular risk factors, hypertension, type 2 diabetes, smoking, BMI and obesity, cholesterol and triglycerides levels, chronic kidney disease or homocysteine levels) and cognition (i.e. cognitive function, cognitive performance, cognitive decline, memory, language, attention, processing speed, executive functions or visuospatial abilities), together with dementia or mild cognitive impairment. This search was limited to human studies only. In addition, reference lists of the selected publications were used for other relevant articles. Subsequent reviews were performed in order to identify novel literature in the field. Metabolic Syndrome

The National Cholesterol Education Program’s Adult Treatment Panel III report (ATP III) described the metabolic syndrome as multiple vascular risk factor disorder, which might result in cardiovascular disease (Carr, et. al. 2004). Six components for the metabolic syndrome have been identified: (1) abdominal obesity, (2) atherogenic dyslipidaemia, (3) raised blood pressure, (4) insulin resistance and glucose intolerance, (5) pro-inflammatory state and (6) pro-thrombotic state (Antonopoulos, 2002). Obesity is the most common vascular risk factor associated with metabolic syndrome, followed by diabetes and hypertension. Lifestyle modifications, with particular emphasis on weight reduction, should be the primary target of intervention for metabolic syndrome (Grundy et al., 2005). Pharmacological treatment, in order to reduce insulin resistance, is also essential in the reduction of metabolic syndrome (Ninomiya et al., 2004).

The following sections present a summary of the main longitudinal studies for each of the vascular risk factors included in the present study.
Hypertension

Hypertension is defined by the presence of either systolic blood pressure above 140 mmHg or diastolic blood pressure above 90 mmHg (de Toledo et al., 2010). This is a condition that has a high prevalence in many populations; it is estimated that nearly one billion people (or around 25%) of the adult population suffer from hypertension worldwide. Furthermore, epidemiological surveys conducted in the United States and Europe concluded that hypertension prevalence in the elderly ranges between 53% and 72% (Kearney, M. Whelton, et al., 2005).

A large number of longitudinal studies have found that hypertension increases the risk for cognitive decline (Table 1). These studies have a large number of participants, in some cases in the thousands.
Table 1: Relationship between Hypertension and Neurocognitive Outcome

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>N</th>
<th>Mean age</th>
<th>Follow-up</th>
<th>Relationship</th>
<th>Cognitive Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td>(Elias, Wolf et al. 1993)</td>
<td>1702</td>
<td>57</td>
<td>13</td>
<td>Yes</td>
<td>Cognitive decline</td>
</tr>
<tr>
<td>1995</td>
<td>(Yoshitake, Kiyohara et al. 1995)</td>
<td>828</td>
<td>74</td>
<td>7</td>
<td>Yes</td>
<td>Dementia</td>
</tr>
<tr>
<td>1996</td>
<td>(Skoog, Nilsson et al. 1996)</td>
<td>382</td>
<td>70</td>
<td>13</td>
<td>Yes</td>
<td>Dementia</td>
</tr>
<tr>
<td>1997</td>
<td>(Starr, Deary et al. 1997)</td>
<td>603</td>
<td>&gt;69</td>
<td>4</td>
<td>Yes</td>
<td>Cognitive Decline</td>
</tr>
<tr>
<td>1998</td>
<td>(Zhu, Viitanen et al. 1998)</td>
<td>924</td>
<td>&gt;75</td>
<td>3</td>
<td>No</td>
<td>Cognitive decline</td>
</tr>
<tr>
<td>1998</td>
<td>(Kilander, Nyman et al. 1998)</td>
<td>999</td>
<td>50</td>
<td>20</td>
<td>Yes</td>
<td>Cognitive impairment</td>
</tr>
<tr>
<td>1998</td>
<td>(Swan, Carmelli et al. 1998)</td>
<td>717</td>
<td>45</td>
<td>27</td>
<td>Yes</td>
<td>Poorer cognitive performance</td>
</tr>
<tr>
<td>2001</td>
<td>(Knopman, Boland et al. 2001)</td>
<td>10963</td>
<td>60</td>
<td>6</td>
<td>Yes</td>
<td>Cognitive decline</td>
</tr>
<tr>
<td>2001</td>
<td>(Kivipelto, Helkala et al. 2001)</td>
<td>1449</td>
<td>53</td>
<td>21</td>
<td>Yes</td>
<td>Dementia (AD)</td>
</tr>
<tr>
<td>2005</td>
<td>(Whitmer, Sidney et al. 2005)</td>
<td>8845</td>
<td>42</td>
<td>30</td>
<td>Yes</td>
<td>Dementia</td>
</tr>
<tr>
<td>2010</td>
<td>(Hajjar, Quach et al. 2011)</td>
<td>4700</td>
<td>74.7</td>
<td>7</td>
<td>Yes</td>
<td>Cognitive decline</td>
</tr>
<tr>
<td>2012</td>
<td>(Wysocki, Luo et al. 2012)</td>
<td>224</td>
<td>84.9</td>
<td>20</td>
<td>Yes</td>
<td>Rate of cognitive decline</td>
</tr>
</tbody>
</table>

*Note: Year: represents the year of publication. N: represents the size of the cohort. Mean age: represents the average age of the sample at baseline. Follow-up: represents the length in years of the follow up period. Relationship: represents whether or not there was a relationship between the respective vascular risk factor and cognitive decline. Cognitive Outcome: represents the neurocognitive outcome (dependent variable).*
A possible explanation for the link between hypertension and cognitive decline is that hypertension might contribute to cognitive disturbances in the elderly by silent cerebral large and small vessel lesions (Kilander, Nyman, Boberg, Hansson, & Lithell, 1998). Hypertension may cause vessel wall changes and can potentially damage the hippocampus through ischaemia caused by atherosclerosis (Den Heijer et al., 2005; Dhikav & Anand, 2011; Obisesan & Obisesan, 2009). Since the hippocampus is a plastic structure and atrophy of this structure is closely related to the pathophysiology of AD, if it is possible to control blood pressure in patients with AD, this may not only improve disease control but could also potentially affect the rate of disease progression (Korf, Scheltens, Barkhof, & de Leeuw, 2005; Middleton & Yaffe, 2009; Skoog & Gustafson, 2006).

*Type II Diabetes*

Diabetes mellitus is a common metabolic disease characterised by hyperglycaemia caused by defects in the secretion of, or resistance to insulin (or both). The most common form is type II diabetes, in which resistance to insulin is accompanied by an inadequate compensation in its secretion (Brands, Kessels, de Haan, Kappelle, & Biessels, 2004). The incidence varies substantially in different parts of the world, primarily because of environmental and lifestyle factors, but has consistently increased worldwide during the last years (Green, Hirsch, & Pramming, 2003). Diabetes is considered an epidemic disease nowadays, with about 173 million diabetic people around the world (around 2.5% of the global population) (Alencar, Cobas, & Gomes, 2010).
Diabetes is a chronic disease that can lead to long-term complications, including risk of cognitive changes. There is substantial evidence to support the link between cognitive decline and Type II Diabetes Mellitus (Table 2). These studies showed that people with diabetes demonstrated greater cognitive change across time as compared to people without diabetes.
<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>N</th>
<th>Mean age</th>
<th>Follow-up</th>
<th>Relationship</th>
<th>Cognitive Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>(Curb, Rodriguez et al. 1999)</td>
<td>3774</td>
<td>53</td>
<td>25</td>
<td>No</td>
<td>Vascular Dementia</td>
</tr>
<tr>
<td>1999</td>
<td>(Ott, Stolk et al. 1999)</td>
<td>6370</td>
<td>69</td>
<td>2.1</td>
<td>Yes</td>
<td>Dementia (AD &amp;VaD)</td>
</tr>
<tr>
<td></td>
<td>(Hassing, Johansson et al. 2002)</td>
<td>702</td>
<td>84</td>
<td>6</td>
<td>No</td>
<td>Vascular Dementia</td>
</tr>
<tr>
<td>2002</td>
<td>(MacKnight, Rockwood et al. 2002)</td>
<td>5574</td>
<td>74</td>
<td>5</td>
<td>No</td>
<td>Dementia</td>
</tr>
<tr>
<td>2002</td>
<td>(Peila, Rodriguez et al. 2002)</td>
<td>2574</td>
<td>77</td>
<td>2.9</td>
<td>Yes</td>
<td>Dementia (AD &amp; VaD)</td>
</tr>
<tr>
<td>2003</td>
<td>(Yamada, Kasagi et al. 2003)</td>
<td>1774</td>
<td>43</td>
<td>30</td>
<td>Yes</td>
<td>Dementia</td>
</tr>
<tr>
<td>2003</td>
<td>(Arvanitakis, Wilson et al. 2004)</td>
<td>847</td>
<td>75</td>
<td>5.5</td>
<td>Yes</td>
<td>Cognitive decline</td>
</tr>
<tr>
<td>2004</td>
<td>(Whitmer, Sidney et al. 2005)</td>
<td>8845</td>
<td>42</td>
<td>35</td>
<td>Yes</td>
<td>Increase risk of dementia</td>
</tr>
<tr>
<td>2005</td>
<td>(Luchsinger, Reitz et al. 2005)</td>
<td>1138</td>
<td>76.2</td>
<td>5.5</td>
<td>Yes</td>
<td>Dementia (AD)</td>
</tr>
<tr>
<td>2005</td>
<td>(Akomolafe, Beiser et al. 2006)</td>
<td>2210</td>
<td>70</td>
<td>12.7</td>
<td>Yes</td>
<td>Dementia (AD)</td>
</tr>
<tr>
<td>2006</td>
<td>(van den Berg, Reijmer et al. 2010)</td>
<td>122</td>
<td>65.6</td>
<td>4</td>
<td>Yes</td>
<td>Cognitive decline</td>
</tr>
<tr>
<td>2010</td>
<td>(McCrimmon, Ryan et al. 2012)</td>
<td>190</td>
<td>62.7</td>
<td>6</td>
<td>Yes</td>
<td>Poorer cognitive performance</td>
</tr>
</tbody>
</table>

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Patients with longer duration of diabetes achieved lower score in cognitive tests; in addition, the presence of type II diabetes increased the risk of cognitive decline in perceptual speed by 44% (Arvanitakis, R. Wilson, Bienias, D. Evans, & D. Bennett, 2004).

Two mechanisms whereby diabetes may cause cognitive impairment have been described in the scientific literature: (1) through diabetic complications such as renal disease, hypertension, and hyperlipidaemia, which may lead to impaired cognitive performance; and (2) through chronic hyperglycaemia which is associated with both structural and functional alterations in the cerebral vascular system. Cerebral blood flow has been reported to be lower in people with diabetes, thus increasing the risk of white matter hyperintensities, lacunae and stroke (D’Agostino et al., 2008; de Toledo et al., 2010; Luchsinger et al., 2004).

**Obesity**

Before the 20th century, obesity was not common; however, in 1997 the World Health Organisation (WHO) formally recognised obesity as a global epidemic problem. In 2005, it was estimated that at least 400 million adults worldwide were obese (around 6% of the world’s population), with higher rates among women than men (Caballero, 2007). Furthermore, severe obesity in the United States, Australia and Canada, among other countries, is increasing faster than the global rate of obesity (Howard, Taylor, Gill, & Chittleborough, 2008). A number of studies have found a strong correlation between body mass index (BMI - a proxy for overweight and obesity) and cognition (Table 3). Some studies have found that weight gain is associated with poor cognitive outcome (Morley, 2010; Razay, Vreugdenhil, &
Wilcock, 2006). In addition, other studies have reported a relationship between lower BMI and the incidence of dementia (Nourhashémi, Deschamps et al. 2003). Therefore, an U-shape relationship between BMI and dementia has been established, suggesting that both obesity and underweight conditions can increase the risk of dementia and that this may also be related to age (Whitmer et al., 2008).

The nature of the interaction between BMI and cognitive decline is poorly understood. Furthermore, no consensus has been reached as to whether BMI has a direct impact on DAT incidence (Beydoun, Beydoun, & Wang, 2008). Excess abdominal fat places middle-aged people at risk for dementia later in their lives (Debette et al., 2010). A 2003 study by Gustafson and her team found that for every point of increase in the BMI score at 70 years of age, the risk of developing dementia increased by about 36% (Gustafson et al., 2003).
### Table 3: Relationship between BMI and Neurocognitive Outcome

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>N</th>
<th>Mean age</th>
<th>Follow-up</th>
<th>Relationship</th>
<th>Cognitive Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>(Kalmijn, Foley et al. 2000)</td>
<td>3734</td>
<td>45-68</td>
<td>25</td>
<td>Yes</td>
<td>Dementia</td>
</tr>
<tr>
<td></td>
<td>(Gustafson, Rothenberg et al. 2003)</td>
<td>382</td>
<td>70</td>
<td>18</td>
<td>Yes</td>
<td>Dementia (AD)</td>
</tr>
<tr>
<td>2003</td>
<td>(Nourhashémi, Deschamps et al. 2003)</td>
<td>3646</td>
<td>&gt; 65</td>
<td>8</td>
<td>No</td>
<td>Dementia</td>
</tr>
<tr>
<td>2005</td>
<td>(Rosengren 2005)</td>
<td>7402</td>
<td>47-55</td>
<td>25</td>
<td>Yes</td>
<td>Dementia</td>
</tr>
<tr>
<td></td>
<td>(Whitmer, Gunderson et al. 2005)</td>
<td>1027</td>
<td>40-45</td>
<td>27</td>
<td>Yes</td>
<td>Dementia</td>
</tr>
<tr>
<td>2005</td>
<td>(Kivipelto, Ngandu et al. 2005)</td>
<td>1449</td>
<td>50.6</td>
<td>21</td>
<td>Yes</td>
<td>Dementia (AD)</td>
</tr>
<tr>
<td>2010</td>
<td>(Dahl, Hassing et al. 2010)</td>
<td>781</td>
<td>42</td>
<td>16</td>
<td>Yes</td>
<td>Rate of cognitive decline</td>
</tr>
<tr>
<td>2010</td>
<td>(Gunstad, Lhotsky et al. 2010)</td>
<td>1703</td>
<td>55</td>
<td>20</td>
<td>Yes</td>
<td>Poorer cognitive performance</td>
</tr>
</tbody>
</table>

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A probable explanation for the effect of obesity on cognitive decline may be related to other risk factors such as deficiencies in leptin. Recently, a study found that leptin plays a role in memory and contributes to memory impairment in diseases where leptin deficiencies or resistance occur (Paz-Filho, Wong, & Licinio, 2010).

1 Peptide hormone that is produced by fat cells and plays a role in body weight regulation by acting on the hypothalamus to suppress appetite and burn fat stored in adipose tissue.
Additionally, there is a link between obesity at older age with decreased hippocampal volume and increased brain white matter ischaemia, which may underlie cognitive decline and dementia (Razay et al., 2006).

**Dyslipidaemia**

Dyslipidaemia is understood as an abnormal concentration of lipids or lipoproteins in the blood, which is usually due to diet and lifestyle. Cholesterol and triglycerides are two types of lipids that are needed to form cell membranes and hormones, and for other bodily functions. However, high levels of cholesterol and triglycerides can lead to clogging of the arteries, increasing the risk of heart attack and ischaemic stroke. Furthermore, high cholesterol and triglycerides causes around a third of all cardiovascular disease worldwide (World Health Organization, 2010).

Epidemiologic studies examining the association between dyslipidaemia and cognitive decline have reported conflicting results (Table 4). Potential sources of these discrepancies include: (1) whether cholesterol and triglycerides are measured in mid versus late life (high cholesterol and triglycerides in mid-life, but not late life, are a risk factor); (2) whether cholesterol and triglycerides are measured early versus late in the course of the disease process; and (3) cholesterol and triglycerides being an essential molecule for many physiologic processes and potentially having several beneficial effects (Mielke et al., 2005).
### Table 4: Relationship between Dyslipidaemia and Neurocognitive Outcome

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>N</th>
<th>Mean age</th>
<th>Follow-up</th>
<th>Re/ship</th>
<th>Cognitive Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>(Notkola, Sulkava et al. 1998)</td>
<td>444</td>
<td>70-89</td>
<td>30</td>
<td>Yes</td>
<td>Dementia (AD)</td>
</tr>
<tr>
<td>1999</td>
<td>(Moroney 1999)</td>
<td>1111</td>
<td>75</td>
<td>2.1</td>
<td>Yes</td>
<td>Dementia (AD &amp; VaD)</td>
</tr>
<tr>
<td>2001</td>
<td>(Kivipelto, Ngandu et al. 2005)</td>
<td>1449</td>
<td>53</td>
<td>21</td>
<td>Yes</td>
<td>Dementia (AD)</td>
</tr>
<tr>
<td>2003</td>
<td>(Tan, Seshadri et al. 2003)</td>
<td>1026</td>
<td>76</td>
<td>8</td>
<td>No</td>
<td>Dementia (AD)</td>
</tr>
<tr>
<td>2004</td>
<td>(Tilvis, Kähönen Väre et al. 2004)</td>
<td>650</td>
<td>75-85</td>
<td>10</td>
<td>Yes</td>
<td>Cognitive decline</td>
</tr>
<tr>
<td>2004</td>
<td>(Reitz, Tang et al. 2004)</td>
<td>2820</td>
<td>77.2</td>
<td>4.8</td>
<td>No</td>
<td>Dementia (AD)</td>
</tr>
<tr>
<td>2005</td>
<td>(Elias 2005)</td>
<td>1894</td>
<td>63.6</td>
<td>17</td>
<td>Yes</td>
<td>Poorer cognitive performance</td>
</tr>
<tr>
<td>2005</td>
<td>(Mielke, Zandi et al. 2005)</td>
<td>392</td>
<td>70</td>
<td>18</td>
<td>No</td>
<td>Dementia</td>
</tr>
<tr>
<td>2009</td>
<td>(Solomon, Kåreholt et al. 2009)</td>
<td>1382</td>
<td>70</td>
<td>21</td>
<td>Yes</td>
<td>Poorer cognitive performance</td>
</tr>
<tr>
<td>2011</td>
<td>(Raffaitin, Féart et al. 2011)</td>
<td>7087</td>
<td>&gt;65</td>
<td>4</td>
<td>Yes</td>
<td>Cognitive decline</td>
</tr>
</tbody>
</table>

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Despite the discrepancies in the results, an association between dietary factors and incidence of dementia has been identified. Countries that have high dietary fat consumption also tend to have a higher prevalence of dementia. A high saturated fat and cholesterol intake has been linked with increased risk of dementia (Anstey, Lipnicki, & Low, 2008; Kalmijn et al., 1997). High total cholesterol concentrations were associated with faster cognitive decline in patients with incident AD (Battistin,
Leontino, Cagnin, & Annachiara, 2010). Furthermore, serum concentration of total cholesterol has been found to be higher in individuals with AD than in normal elderly subjects (Tan et al., 2003).

Dyslipidaemia is increasingly recognised to play a major role in the pathogenesis of AD. However, its role is not well defined yet. It is known that cholesterol does not pass the BBB and is synthesised locally in the brain and then transported outside the brain into the bloodstream. Hence, it is hypothesised that a breakdown of the BBB causes influx of cholesterol and triglycerides, with subsequent activation of Aβ production (Humpel, 2011). Therefore, cholesterol may alter the degradation of the amyloid precursor protein, which plays a major role in the pathogenesis of AD (Burns & Duff, 2002). Importantly, dyslipidaemia levels are a risk factor that can be modified (reduced) through strategies such as lowering stress, exercising regularly and eating a healthy low-fat diet (Huang et al., 2009).

**Smoking**

Smoking behaviour has decreased during the last decades. In fact, smoking rates in Australia have fallen by about 32% over the past two decades, with about 17% of Australians now daily smokers. Despite this positive behaviour change, smoking remains the single most important cause of ill health in Australia (Australian Institute of Health and Welfare, 2010). A common misunderstanding is that the only major risk from smoking is lung cancer. However, in addition to lung cancer, smoking is responsible for a fifth of cardiovascular disease worldwide, and a central cause for heart attack and stroke (Ambrose & Barua, 2004). The risk increases in people who began smoking before the age of 16. Overall, it has been estimated that 30 to 40% of
the approximately 500,000 deaths from coronary heart disease each year can be attributed to smoking (Anstey et al., 2007). Smoking promotes cardiovascular disease through a number of mechanisms: (1) damages the endothelium lining of the blood vessels, (2) increases cholesterol plaques, (3) increases clotting and (4) promotes coronary artery spasm. Additionally, nicotine accelerates the heart rate and raises blood pressure (Cervilla, Prince, & Mann, 2000). These physiological changes lead to the presence of silent cerebrovascular lesions (Andersen, Launer, & Dewey, 1999). Furthermore, it has been found that smoking may be associated with an increased risk of cognitive decline (Table 5).
Table 5: Relationship between Smoking and Neurocognitive Outcome

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>N</th>
<th>Mean age</th>
<th>Follow-up</th>
<th>Relationship</th>
<th>Cognitive Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>(Whittington and Huppert 1997)</td>
<td>7414</td>
<td>&gt;50</td>
<td>7</td>
<td>No</td>
<td>Cognitive performance</td>
</tr>
<tr>
<td>1999</td>
<td>(Richards, Jarvis et al. 2003)</td>
<td>3035</td>
<td>53</td>
<td>50</td>
<td>Yes</td>
<td>Rate of cognitive decline</td>
</tr>
<tr>
<td>1999</td>
<td>(Merchant, Tang et al. 1999)</td>
<td>2128</td>
<td>77.2</td>
<td>2</td>
<td>Yes</td>
<td>Dementia</td>
</tr>
<tr>
<td>1999</td>
<td>(Andersen, Launer et al. 1999)</td>
<td>12945</td>
<td>&gt;65</td>
<td>9</td>
<td>Yes</td>
<td>Dementia</td>
</tr>
<tr>
<td>2004</td>
<td>(Juan, Zhou et al. 2004)</td>
<td>2820</td>
<td>66.9</td>
<td>2</td>
<td>No</td>
<td>Dementia</td>
</tr>
<tr>
<td>2006</td>
<td>(Aggarwal, Bienias et al. 2006)</td>
<td>1064</td>
<td>&gt;65</td>
<td>4.1</td>
<td>Yes</td>
<td>Dementia (AD)</td>
</tr>
<tr>
<td>2007</td>
<td>(Reitz, den Heijer et al. 2007)</td>
<td>6868</td>
<td>&gt;55</td>
<td>7.1</td>
<td>Yes</td>
<td>Dementia (AD)</td>
</tr>
<tr>
<td>2012</td>
<td>(Sabia, Elbaz et al. 2012)</td>
<td>10308</td>
<td>56</td>
<td>10</td>
<td>Yes</td>
<td>Rate of cognitive decline</td>
</tr>
</tbody>
</table>

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The mechanisms that underlie this association are complex; neuronal nicotine binding sites, oxidative stress, inflammation and vascular deficits associated to smoking-related atherosclerosis may explain the neuro-structural and cognitive deficits linked to smoking (de Toledo et al., 2010).
Chronic Kidney Disease

Chronic Kidney Disease (CKD) is a worldwide public health problem, with adverse outcomes of kidney failure, cardiovascular disease and premature death (Levey et al., 2005). The number of patients with CKD is increasing worldwide: The average number of patients with CKD is around 135 per million people in Europe and 336 per million people in the United States (Hamer & Nahas, 2006). Additionally, the prevalence of CKD in the world is most prominent in the elderly (Kurella et al., 2005).

It has been demonstrated that CKD is a risk factor for cardiovascular events (Gruberg, Mintz et al. 2000, Muntner, He et al. 2002, Manjunath, Tighiouart et al. 2003, Manjunath, Tighiouart et al. 2003, Weiner, Tighiouart et al. 2004), in addition, individuals suffering from CKD have a higher prevalence of other vascular risk factors, including type 2 diabetes mellitus (Goldschmid, Domin et al. 1995, UK Prospective Diabetes Study Group 1998, Alwakeel, Isnani et al. 2011) and hypertension (Hasslacher, Wolfrum et al. 1987, Ravid, Brosh et al. 1998, Williams 2011) Recent studies indicate that cognitive impairment is present at early stages of CKD (Table 6). However, whether CKD accelerates the presence of dementia symptoms has not been rigorously addressed (Yaffe et al., 2010).
Table 6: Relationship between Chronic Kidney Disease and Neurocognitive Outcome

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>N</th>
<th>Mean age</th>
<th>Follow-up</th>
<th>Relationship</th>
<th>Cognitive Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>(Seliger, Siscovick et al. 2004)</td>
<td>3349</td>
<td>&gt;65</td>
<td>6</td>
<td>Yes</td>
<td>Dementia (AD &amp; VaD)</td>
</tr>
<tr>
<td>2005</td>
<td>(Kurella, Chertow et al. 2005)</td>
<td>3034</td>
<td>&gt;65</td>
<td>4</td>
<td>Yes</td>
<td>Risk of developing dementia</td>
</tr>
<tr>
<td>2008</td>
<td>(Slinin, Paudel et al. 2008)</td>
<td>5529</td>
<td>73.6</td>
<td>5</td>
<td>Yes</td>
<td>Cognitive decline</td>
</tr>
<tr>
<td>2010</td>
<td>(Yaffe, Ackerson et al. 2010)</td>
<td>825</td>
<td>64.9</td>
<td>Cross-Sectional</td>
<td>Yes</td>
<td>Poorer cognitive performance</td>
</tr>
<tr>
<td>2011</td>
<td>(Kurella Tamura, Xie et al. 2011)</td>
<td>3591</td>
<td>58.2</td>
<td>Cross-Sectional</td>
<td>Yes</td>
<td>Cognitive impairment</td>
</tr>
<tr>
<td>2013</td>
<td>(Davey, Elias et al. 2013)</td>
<td>590</td>
<td>62.1</td>
<td>5</td>
<td>Yes</td>
<td>Rate of cognitive decline</td>
</tr>
</tbody>
</table>

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**Homocysteine**

Homocysteine is an amino acid that occurs naturally in all humans. High levels of homocysteine in the blood are believed to increase the chance of: (1) heart disease, (2) stroke, (3) osteoporosis and (4) cognitive decline (Dwivedi, Tripathi et al. 2011). Homocysteine has appeared as a new and potentially important vascular risk factor that increases with age; its public health impact is yet to be determined.
In 1969, a homocysteine theory of atherosclerosis was formulated (McCully 1996), which was empirically validated in 1976 by Wilcken and Wilcken (Wilcken and Wilcken 1976) who published their pioneering work on abnormal homocysteine levels in patients with coronary artery disease. Additional evidence has been supporting the relationship between high levels of homocysteine and cardiovascular disease (Graham, Graham et al. 1997, Clarke, Smith et al. 1998, Bostom, Rosenberg et al. 1999, Den Heijer, Launer et al. 2005).

The results of several cross-sectional and longitudinal studies of older adults indicate that homocysteine is inversely associated with performance on some cognitive tests (Riggs, Spiro et al. 1996, Budge, Johnston et al. 2000, McCaddon, Hudson et al. 2001, Morris, Jacques et al. 2001, Duthie, Whalley et al. 2002, Ravaglia, Forti et al. 2003, Kado, Mooijaart, Gusseldoo et al. 2005, Nurk, Refsum et al. 2005, Tucker, Qiao et al. 2005). In a cross-sectional analysis of 2096 dementia-and stroke-free participants in the Framingham Offspring Study, plasma homocysteine was inversely associated with performance on a range of cognitive tests in persons 60 years of age or older (Elias, Sullivan et al. 2005). Table 7 summarises a series of studies that analysed the relationship between high levels of homocysteine and cognitive function. Moreover, elevated levels of homocysteine have also been associated with confirmed AD (Hogervorst, Ribeiro, Molyneux, Budge, & Smith, 2002). Homocysteine may have direct and indirect neurotoxicity effects (Lepara et al., 2009). Links between increased homocysteine and white matter lesions have also been found (Ho et al., 2011).
Table 7: Relationship between Homocysteine Levels and Neurocognitive Outcome

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>N</th>
<th>Mean age</th>
<th>Follow-up</th>
<th>Relationship</th>
<th>Cognitive Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>(Kalmijn, Launer et al. 1999)</td>
<td>702</td>
<td>67.7</td>
<td>2.7</td>
<td>No</td>
<td>Cognitive decline</td>
</tr>
<tr>
<td></td>
<td>(McCaddon, Hudson et al. 2001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cognitive decline</td>
</tr>
<tr>
<td>2001</td>
<td></td>
<td>32</td>
<td>74</td>
<td>5</td>
<td>Yes</td>
<td>Rate of cognitive decline</td>
</tr>
<tr>
<td></td>
<td>(Dufouil, Alprovitch et al. 2003)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cognitive decline</td>
</tr>
<tr>
<td>2003</td>
<td>(Rowan, Dickinson et al. 2007)</td>
<td>1241</td>
<td>61-73</td>
<td>4</td>
<td>Yes</td>
<td>Rate of cognitive decline</td>
</tr>
<tr>
<td>2007</td>
<td></td>
<td>354</td>
<td>&gt;65</td>
<td>2</td>
<td>No</td>
<td>Cognitive decline</td>
</tr>
<tr>
<td>2008</td>
<td>(Kim, Stewart et al. 2008)</td>
<td>625</td>
<td>&gt;65</td>
<td>2.4</td>
<td>Yes</td>
<td>Dementia (AD)</td>
</tr>
<tr>
<td>2010</td>
<td>(Oulhaj, Refsum et al. 2009)</td>
<td>97</td>
<td>&gt;65</td>
<td>9.5</td>
<td>Yes</td>
<td>Rate of cognitive decline</td>
</tr>
</tbody>
</table>

Note. Year: represents the year of publication. N: represents the size of the cohort. Mean age: represents the average age of the sample at baseline. Follow-up: represents the length in years of the follow up period. Relationship: represents whether or not there was a relationship between the respective vascular risk factor and cognitive decline. Cognitive Outcome: represents the neurocognitive outcome (dependent variable).

Methodological Issues

A synergistic effect of vascular risk factors on cognitive decline and the pathogenesis of dementia has been suggested. Nevertheless, the majority of studies that have examined the effect of vascular risk factors on cognition have investigated individual risk factors while adjusting for others (Elias et al., 2003; Kilander et al.,
1998; Kivipelto et al., 2001; Kivipelto, Ngandu, L. Fratiglioni, & e. al, 2005; Knopman et al., 2001; Launer, 2009; Xu, Qiu, Gatz, Pedersen, & Johansson, 2009). This statistical approach might result in the elimination of true associations (Leritz, McGlinchey, Kellison, Rudolph, & Milberg, 2011). It has been reported that the prediction of cognitive decline can be enhanced by accounting for several vascular risk factors in combination (Luchsinger, Reitz, et al., 2005). Therefore, using an additive approach may have a greater impact on the understanding of the relationship between vascular risk factors and cognition.

The evaluation of cognitive difficulties in the aforementioned studies was based on either brief cognitive screening tests (Guo, Fratiglioni et al. 1997, Starr, Deary et al. 1997, Zhu, Viitanen et al. 1998) or short neuropsychological assessments (Carmelli, et al., 1998; Gupta, et al., 2008; McGuinness, et al., 2009). As a result, a number of cognitive domains were addressed in less detail, lowering the sensitivity to detect cognitive impairment. The Mini-Mental State Examination (MMSE) (Folstein, Folstein et al. 1975) was broadly used in the previous studies with the intention of assessing cognitive function. In a review of a range of MMSE studies, Tombaugh et al. (Tombaugh and McIntyre 1992) found that the MMSE demonstrated high levels of sensitivity for cognitive deficits in patients suffering from moderate to severe dementia, and reflected the cognitive decline typical of dementia patients. Studies suggest that sensitivity is lower (30-60%) when attempting to diagnose those with mild dementia. Thus, the ability of the MMSE to detect mild or early dementia continues to be questioned (Chopard, Pitard et al. 2007).
In addition, clinical studies have shown that MMSE scores are affected by a wide range of demographic characteristics, including educational level, age, ethnic group and language (Escobar, Burnam et al. 1986, Tombaugh and McIntyre 1992, Ostrosky-Solís, López-Arango et al. 2000, Kahle-Wrobleski, Corrada et al. 2007). It can thus be argued that the MMSE is an instrument with limited screening utility among participants with a low level of education (Ostrosky-Solís, López-Arango et al. 2000). The MMSE can also show a ceiling effect. Individuals with a higher level of education, even those with cognitive impairment, could have very high scores and in some cases even a perfect score (30/30). This ceiling effect may limit the sensitivity of the MMSE as well, especially for highly educated individuals with mild cognitive impairment or mild dementia (Holsinger, Deveau et al. 2007). In view of the above, the MMSE is not a reliable measurement of cognitive change, especially in cognitively healthy populations. Participants with a lower level of education and different cultural background may perform poorly even when cognitively intact, while those with high level of education may perform well even when cognitively impaired.

**Vascular Risk Factors and Cognitive Outcomes**

Language (Nation, 2010) and episodic memory (Arvanitakis et al., 2004; Bender et al., 2012; Bender, Daugherty, & Raz, 2013; Bennett et al., 2009; Solfrizzi et al., 2004; Solomon & Kivipelto, 2009) have been reported as a specific focus of impairment in healthy older individuals with vascular risk factors. A link between vascular risk factors and poorer delayed recall of name-picture associations was identified in a group of 104 adult participants recruited from a community in the United States (Dahle et al., 2009). Additionally, a longitudinal decline in episodic
memory was found among older individuals from the Baltimore Longitudinal Study who have been followed for 11 years. Those with vascular risk factors performed more poorly than those with no vascular risk factors at all measurement time points (Waldstein, Waldstein, Giggey, Thayer, & Zonderman, 2005). After a four-year follow-up period, participants with vascular risk factors exhibited a greater risk of memory and executive decline relative to individuals with no vascular risk factors (Dregan, Stewart, & Gulliford, 2013).

Current evidence from both longitudinal (Bangen, Delano-Wood, et al., 2010; Carmelli et al., 1998; DeBette et al., 2011; Reijmer et al., 2011) and cross-sectional (Jefferson, Poppas, Paul, & Cohen, 2007; McGuinness et al., 2009; Smith, 2011) studies have demonstrated a link between the presence of vascular risk factors and deleterious impacts on executive functions, such as attention, working memory, abstraction, reasoning, mental flexibility and verbal fluency. In particular, executive dysfunction has been considered to be a characteristic of individuals with vascular risk factors (O’Brien et al., 2003; Sachdev et al., 2004).

This association has been identified in a number of different populations; for instance, an inverse relationship was found between executive functions and the presence of vascular risk factors in a group of older African Americans (Pugh, Pugh, Kiely, Milberg, & Lipsitz, 2003). In addition, Knopman and colleagues followed 10,963 subjects (aged 47 to 70) over 6 years and found that those with vascular risk factors had significant decline in measures of executive function compared to those with no vascular risk factors (Knopman et al., 2001). Finally, in a group of elderly women, those with vascular risk factors were twice as likely to suffer severe cognitive decline.
on executive functions but not in general cognition (Gregg, Yaffe, Cauley, & et al., 2000).

Studies have reported a negative association between the presence of vascular risk factors and psychomotor speed and speed of processing information (Gupta, Solanki, & Pathak, 2008). Rosano and colleagues found slower information processing speed in a cohort of 235 older adults (65 years old and older) with vascular risk factors but free from stroke or dementia (Rosano et al., 2012). A negative association between the presence of vascular risk factors and speed of information processing was also found in a sample of 128 participants (50 men and 78 women) between 43 and 87 years of age (Jacobs et al., 2013).

The particular susceptibility of working memory impairment to the presence of vascular risk factors has been recognised. McGuinness and colleagues (2009) assessed both verbal and visuospatial working memory and noted dissociation between both. Verbal performance was less impaired than visuospatial functioning, suggesting that executive functions which were more reliant on visuospatial skills were more susceptible to impairment in the presence of vascular risk factors (McGuinness et al., 2009).

The rate of cognitive change has been reported to be different across a variety of cognitive domains. Okonkwo and colleagues demonstrated that cognitive change occurred in a linear trend for language and executive functions, and in a curvilinear fashion for visuospatial skills and memory (Okonkwo et al., 2010). Similar results, in which individuals with vascular risk factors displayed changes in specific cognitive domains but not in others, have been reported previously. Two different studies, with
one year of follow-up period, showed that participants with vascular risk factors displayed improvements in memory tasks but not in tests that assess executive functions (de Jager & de, 2004; Hoth et al., 2008). No clear explanation for this discrepancy between trajectories has been developed; however a possible hypothesis could be that the curvilinear outcomes are the result of a gradual recovery of cognitive functioning in the context of intensive treatment.

Brain Reserve Hypothesis and the Role of Protective and Risk Factors

A yet unanswered question is why some individuals with AD pathology do not present DAT, despite the fact that the presence of this pathology increases the risk of developing dementia symptoms. In addition, discrepancies have been observed between the extent of AD pathology at autopsy and the degree of clinical difficulties experienced by an individual. This suggests that the pathological processes underlying AD need to reach certain level of accumulation in order to cause cognitive impairment (Fratiglioni & Wang, 2007; Stern & Stern, 2003; Valenzuela & Sachdev, 2006).

The likelihood of developing dementia can be explained by the concept of brain reserve (Katzman et al., 1988; Scarmeas & Stern, 2003). The brain reserve hypothesis postulates that the pathological processes that underlay AD need to accumulate to some extent in order to be clinically manifested as cognitive difficulties sufficiently severe to meet the criteria for diagnosis of dementia (Barnes, Barnes, & Yaffe, 2011; Fratiglioni & Wang, 2007; Head et al., 2004; Satz, 1993; Valenzuela, 2008). In other words, this hypothesis can be thought of as the brain’s ability to cope
with, or compensate for the neuropathological changes associated with AD (Barnes et al., 2011; Wilson & Wilson, 2002).

A direct relationship between the degree of pathology presented in the brain and the degree of cognitive impairment has not been demonstrated (Draganski et al., 2004); nevertheless, growing evidence suggests that individuals with higher brain reserve capacity can better tolerate brain damage (Fratiglioni & Wang, 2007; Valenzuela, 2008). Brain reserve is the result of the interaction among environmental, physiological and genetic factors (Reitz & Mayeux, 2009).

The impact of complex mental activity and complex environments has gained increasing interest, particularly in the field of ageing and dementia because of the suggestion that staying both physically and intellectually active may help in the prevention of cognitive impairment by increasing brain reserve (Kempermann, 2002; Valenzuela, Breakspear, & Sachdeva, 2007; Valenzuela & Sachdev, 2006). Knowledge about the cellular basis of this effect indicates that adult neurogenesis contributes to neuroplasticity in the hippocampal dentate gyrus throughout life. It is now well documented that active neurogenesis does exist throughout the life span in the brain of various species, including humans (Paizanis, Kelaï, Renoir, Hamon, & Lanfumey, 2007).

It is accepted that neurogenesis occurs in two brain regions in adult mammals, namely the hippocampus and olfactory bulb (Elder, De Gasperi, & Sosa, 2006). There is evidence that hippocampal adult neurogenesis is important for learning and memory (Gould, Beylin, Tanapat, Reeves, & Shors, 1999). The effects of environment
and behaviour on the dynamics of the neurogenesis process are very important (Aimone, Wiles, & Gage, 2006).

**Genetic Makeup and Brain Reserve**

Previous studies have shown that the Apolipoprotein E ε4 (APOE ε4) genetic allele, together with neurotrophic factors such as brain-derived neurotrophic factor (BDNF), might play an important role in reducing brain reserve (Raz, Rodrigue, Kennedy, & Land, 2009; Ward et al., 2014). APOE ε4 has been associated with cognitive difficulties (Wisdom, Callahan, & Hawkins, 2011). More specifically, low information processing speed, executive dysfunction and memory problems have been identified in healthy older adults who are APOE ε4 carriers (Small, Rosnick, Fratiglioni, & Bäckman, 2004). In addition, neuroimaging studies have shown that, relative to non-carriers, those who carry the APOE ε4 allele have less hippocampal volume (Lim et al., 2015; Lim et al., 2012; Lind et al., 2006) and reduced cortical thickness in the frontal lobe (Fennema-Notestine et al., 2011).

**BDNF** has been found to play an essential role in nerve growth (Mattson, Maudsley, & Martin, 2004), synaptic excitation (Bramham & Messaoudi, 2005; Lee et al., 2012) and neuronal plasticity (Casey et al., 2009; Ickes et al., 2000; Rossi et al., 2006; Van Praag, Kempermann, & Gage, 2000). A polymorphism, the Val66Met variant, has been associated with cognitive function, whereby carriage of the Met allele results in cognitive impairment, particularly memory difficulties, language impairment and executive dysfunction (Egan et al., 2003; Hariri et al., 2003; Lim et al., 2014; Lim et al., 2014).
Reduced hippocampal volume and changes in cortical thickness have also been observed in Met allele carriers (Forde et al., 2014; Harrisberger et al., 2014). In addition, the BDNF main receptor, tropomyosin-related kinase B, has been shown to be significantly reduced in the hippocampus and the temporal lobe regions in those individuals who are Met allele carriers (Lee et al., 2012). BDNF has been found to act as a mediator of the relationship between cognitive function and lifestyle factors, such as diet or physical activity (Erickson et al., 2011; Ferris, Williams, & Shen, 2007; Gomez-Pinilla, Vaynman, & Ying, 2008; Vaynman, Ying, & Gomez-Pinilla, 2004). Changes in the secretion of BDNF occur in individuals who increase their level of physical activity, resulting in improvement of their cognitive function.

**Lifestyle and Brain Reserve**

Lifestyle and genetic factors, such as education (Del Ser, Hachinski, Merskey, & Munoz, 1999), occupation (Stern, Albert, Tang, & Tsai, 1999) and intelligence (Galioto, Alosco, Spitznagel, Stanek, & Gunstad, 2013; Schmand, Smit, Geerlings, & Lindeboom, 1997), have been strongly associated with the formation of brain reserve (Nithianantharajah & Hannan, 2009; Scarmeas & Stern, 2003). Studies have shown that engaging in cognitive, leisure and social activities may increase brain reserve and decrease the risk of developing dementia (Valenzuela et al., 2007; Wilson, Scherr, Schneider, Tang, & Bennett, 2007). Similarly, physical activity and diet are additional factors linked to the formation and maintenance of brain reserve (Bartrés-Faz & Arenaza-Urquijo, 2011; Scarmeas & Stern, 2003).

A study by Alzheimer’s Australia that examined the international evidence for the prevention and risk reduction of dementia (Woodward & Brodaty, 2007) showed
that protective factors may lower the risk of developing dementia or even delay its onset. The main protective factors identified were: (1) physical activity, (2) ongoing intellectual stimulation, (3) leisure and social activities, (4) higher education, (5) anti-inflammatory drugs, (6) cholesterol lowering drugs, (7) anti-hypertensive drugs (for those with high blood pressure) and (8) moderate alcohol intake. In addition, control of risk factors may also be considered protective. It is important to consider that aspects that benefit a population will not necessarily have the same effect for every individual.

Several reports suggest that vascular risk factors might reduce brain reserve (Craft, 2009; Dregan et al., 2012; Gorelick et al., 2011; Schneider et al., 2014). A potential mechanism that explains this association argues that vascular risk factors increase deterioration of cerebral white matter (Raz, Raz, Yang, Dahle, & Land, 2012). Studies that included functional magnetic resonance imaging have consistently demonstrated that white matter lesions and lacunar infarcts are commonly observed in healthy older adults with vascular risk factors (Alvarez-Sabin & Roman, 2011; Moon et al., 2011; Pannacciulli, Le, Chen, Reiman, & Krakoff, 2007; Pantoni & Garcia, 1995; Pohjasvaara et al., 2007; Raz et al., 2012; Ryglewicz et al., 2002; Tatemichi et al., 1992). Individuals with high levels of white matter lesions and lacunar infarcts tend to show a greater decline on tasks of executive functions, such as information processing speed, conceptual reasoning and poor inhibition (Boone & Boone, 1992; Gunning Dixon, Gunning Dixon, Brickman, Cheng, & Alexopoulos, 2009; Madden, Madden, Bennett, & Song, 2009; Wang et al., 2011).
Additional vascular changes have been identified in individuals with vascular risk factors. Several investigations have suggested an association between vascular risk factors and micro-bleeds, demyelination, capillary loss, tortuosity of arterioles and accumulation of collagen in veins and venules (Kilander, Nyman, Boberg, Hansson, & Lithell, 1998; Raz et al., 2005; Raz et al., 2012). A decrease of total brain volume has also been described in individuals with vascular risk factors (Carmelli et al., 1998; Debette et al., 2011; Van-Swieten et al., 1991).

**Apolipoprotein E Genotype and Cognitive Function**

Multiple genetic variants have been identified as risk factors for dementia; however, the Apolipoprotein E ε4 genotype is the one that has been associated with a significantly increased risk of AD (Hsiung, Sadovnick, & Feldman, 2004; Rodrigue et al., 2013). APOE is an important transport protein of lipids in the human body. The APOE genotype is determined by three different common alleles, ε2, ε3, and ε4, derived from a specific gene locus at chromosome 19. A meta-analysis of 40 studies concluded that APOE ε4 allele represents a major risk factor for AD in all ethnic groups, across all men and women aged between 40 and 90 years old (Farrer, Cupples, & Haines, 1997). Moreover, another study found that as the number of APOE ε4 alleles increases, the risk of AD increases from 20% to 90% (Jen-Hau, Kun-Pei, & Yen-Ching, 2009).

Compared with the other alleles (ε2 or ε3) the literature has established that the APOE ε4 allele exacerbated cognitive decline when associated with exposure to vascular risk factors (Bangen et al., 2013; Carmelli et al., 1998; Caselli et al., 2011; Haan & Mayeda, 2010; Qiu et al., 2014; Song & Song, 2004; Yasuno et al., 2012).
Additionally, the rate of cognitive change associated with vascular risk factors increased in the presence of *APOE* ε4 allele (Carmelli et al., 1998; Debette et al., 2011; Haan, Shemanski, Jagust, Manolio, & Kuller, 1999; Nebes et al., 2012; Peila, Rodriguez, & Launer, 2002; Rodrigue et al., 2013). Furthermore, some studies have reported that *APOE* genotype influences susceptibility to the presence of vascular risk factors and may increase the risk of vascular dementia (Bangen et al., 2013; Miyata, Miyata, & Smith, 1996).

The *APOE* ε4 allele and vascular risk factors may act in a synergistic fashion leading to cognitive decline (Wang et al., 2015). The causes for these effects are poorly understood, but it has been suggested that *APOE* ε4 carriers are more vulnerable to a variety of pathophysiologic changes in the vascular system (Caselli et al., 2011). It has also been demonstrated that vascular risk factors interact with the *APOE* ε4 genotype to increase deposition of Aβ in cognitively healthy older adults (Rodrigue et al., 2013). In agreement, the Framingham Coronary Risk Profile score (an index of elevated vascular risk factors) has been associated with increased Aβ burden in a group of *APOE* ε4 carriers (Reed et al., 2012). Understanding the mechanisms that underlie this association is an open question in need of further investigation.

**Interim Summary**

The potential role of vascular risk factors in cognitive change is an area of intensive scientific debate. Although the literature suggests the existence of a relationship between vascular risk factors and cognitive deterioration, improved understanding of the impact of vascular risk factors in the appearance of the clinical
symptoms in individuals with Alzheimer's disease pathology is needed. Previous studies have been questioned for the use of screening tests in assessing cognitive function, since these tests generally have high sensitivity but relatively low specificity. This study will address this research gap by using detailed neuropsychological assessment to explore the nature and magnitude of cognitive change in relation to known vascular risk factors. Furthermore, the cross-sectional and longitudinal analyses developed as part of this study involved a large group of healthy older adults. Lastly, this study is novel in that it investigated seven vascular risk factors in combination, as well as the impact of vascular risk factor burden on cognition. The findings of this thesis will improve understanding of the impact of lifestyle aspects in the course of cognitive deterioration and in the onset of dementia.

The current thesis

The overarching aim of this study is to investigate the effect of vascular risk factors on cognitive function in a group of cognitively healthy older adults who have undergone detailed medical and neuropsychological assessments over a long period of time. The effect of vascular risk factors on cognitive function will be determined both cross-sectionally at baseline and prospectively over 54 months. The four main questions that this thesis aims to answer are: (1) is there a difference in cognitive performance between individuals with and without vascular risk factors? (2) does the presence of vascular risk factors relate to the rate of cognitive change? (3) is the number of vascular risk factors present in an individual associated with cognitive performance and cognitive change over time? (4) does the presence of vascular risk factors increase the likelihood of developing MCI?
In order to answer these research questions, this thesis includes four additional chapters. Chapter three includes the methodological aspects of the present research project. All the empirical analysis in this thesis has arisen from the ongoing Australian Imaging, Biomarkers and Lifestyle (AIBL) Flagship Study of Ageing. We explain why the AIBL study provides a unique opportunity to explore our research questions. As such, we present a detailed description of the study protocols, together with the inclusion and exclusion criteria. Then, we offer a description of the AIBL study sample, as well as of the complete assessment that each participant underwent, including neuroimaging and biomarkers tests, as well as the cognitive evaluation. A description of our study cohort and information regarding the change in their condition through the different study time-points is presented. We then offer details of the number and cause of participant withdrawal at each time-point of the research. This chapter ends with a description of each variable measured, together with the statistical models used.

The findings of this study are presented in Chapter four, which begins with the characterisation of the study cohort. In this subsection, the demographic characteristics of the participants are presented (age, gender, estimated IQ and level of education, as well as information about their genetic makeup). The prevalence of vascular risk factors in our group of participants is then summarised. In order to investigate the variations in cognition between individuals with and without vascular risk factors, we analysed demographic differences among individuals with different number of vascular risk factors. The results from the cross-sectional analysis and longitudinal analyses are detailed. The next sub-section explains the nature and magnitude of vascular risk factor burden related to cognitive decline. Finally, we
analysed the risk of developing dementia in individuals with vascular risk factors compared to those with no vascular risk factors.

Chapter five comprises a general discussion and overall conclusions. The findings are discussed within the context of the body of scientific literature. A comparison between the current data and results from other epidemiological studies in regards to increasing incidence of vascular risk factors in different populations is presented, followed by a discussion of the three demographic variables that have shown an association with vascular risk factors, namely age, level of education and Apolipoprotein genotype. A description of a theoretical model that could potentially explain the relationship between the presence of vascular risk factors and cognitive impairment and cognitive decline is presented. Finally, we discuss how lifestyle modifications are essential in order to reduce the prevalence of vascular risk factors and therefore the onset of dementia.

Chapter 6 discusses the broad implication of these findings, and provides recommendations for future directions in research.
This chapter presents the study design and methods used. This thesis reports data collected as part of the AIBL study, so a brief overview of the study is provided below. The author of this thesis has been a member of the AIBL neuropsychological team since 2009 and personally undertook over 700 hours of data collection between October 2009 and July 2012. Following the overview of AIBL, methodological details of the analyses reported in this thesis are outlined.

**The Australian Imaging, Biomarker and Lifestyle Flagship Study of Ageing**

The Australian Imaging, Biomarker and Lifestyle (AIBL) Flagship Study of Ageing, a longitudinal study launched in 2006, is the largest study of its kind in Australia (Ellis et al., 2009; Ellis et al., 2010; Ellis et al., 2014). This study integrates expertise in neuroimaging, biomarkers, neuropsychology and lifestyle interventions to examine a cohort of 1112 individuals with varying risk factor profiles for AD. Its principal objective was to improve understanding of the causes and diagnosis of AD. More specifically, this study aimed to better understand diagnostic, psychometric and biological markers that can be used to objectively monitor disease development and/or progression. Additionally, diet and lifestyle factors were also investigated in order to better understand their relationship with cognitive health and disease development (Ellis et al., 2009).
The AIBL cohort has been followed over a period of 54 months. Participants were recruited through media request, while others volunteered after their treating physician had informed them about the AIBL study. Initially, 4000 individuals undertook a telephonic screening assessment which enquired about demographic information, as well as certain aspects of medical history, including diagnosed dementia, schizophrenia, bipolar disorder, depression, Parkinson’s disease, cancer, cardiovascular disease and whether they perceived any difficulty with their current memory function. Additionally, participants were asked to complete the 15-item Geriatric Depression Scale (GDS-15) (Brink et al., 1982; Yesavage & Sheikh, 1986; Yesavage et al., 1982).

After the screening assessment, participants were excluded if they had a history of any of the following conditions: (1) schizophrenia; (2) depression (Geriatric Depression Scale Score of 6 or greater); (3) Parkinson disease; (4) cancer (other than basal cell skin carcinoma) within the last 2 years; (5) obstructive sleep apnoea; (6) symptomatic stroke; (7) uncontrolled diabetes, or (8) current regular alcohol use exceeding two standard drinks per day for women or four per day for men (Ellis et al., 2009). The most common reasons for exclusion were excessive alcohol consumption, past serious head injury, current clinical depression, withdrawal of consent and history of stroke(s).

From the initial 4000 individuals, 1166 individuals presented for AIBL assessment and 54 individuals were excluded (Figure 3). Specifically, volunteers were excluded as follows: sixteen volunteers had a history of stroke(s), six had history of past serious head injury, six had excessive alcohol intake, two had epilepsy,
two had an existing diagnosis of frontotemporal dementia, two had Parkinson's disease, two were taking morphine at the time of assessment, one had a previous episode of amnesia, one had previously been admitted to hospital for hypoxia, one had insufficient English to complete the assessment, one had depression not apparent at screening, five volunteers did not have enough information gathered at assessment (for example due to advanced dementia), and nine withdrew consent (Ellis et al., 2009).
Figure 3: Flowchart of Study Cohort. For Pre-Assessment and Baseline Timepoints
A cohort of 1112 participants were eligible to participate and completed baseline assessments. A subgroup of 211 were classified as AD patients as defined by NINCDS-ADRDA criteria (Dubois et al., 2007), 133 individuals were classified as MCI (Winblad et al., 2004) and 768 were healthy without cognitive impairment, referred to as cognitive healthy participants. All participants underwent extensive neuropsychological assessments, which included completion of cognitive and mood tests, assessment of vital signs, collection of medical history (personal and family) and medication information, as well as questionnaires about diet and exercise lifestyle factors. The neuropsychological battery covered the main domains of interest in assessing AD-related cognitive impairment (see detailed description relevant to current thesis below). After the baseline evaluation, serial assessments were repeated at 18-month intervals.

The study assessments took place in two different cities, Melbourne and Perth, according to where the participants lived or where they undertook brain imaging. In order to complete the blood test, volunteers attended the session in the morning after an overnight fast. Vital signs, such as weight, height, abdominal girth, sitting blood pressure and pulse were measured. Following breakfast (which was provided), cognitive and mood assessments were completed.

The AIBL study was approved by the institutional ethics committees of Austin Health, St. Vincent’s Health, Hollywood Private Hospital and Edith Cowan University. Each participant provided informed written consent.

In order to identify participants who change their clinical classification during the study period, a clinical panel consisting of psychiatrists, neurologists,
geriatricians and neuropsychologists reviewed the participants’ performance on the neuropsychological tests and identified those individuals who scored at least 1.5 standard deviations below published normative data on two cognitive measures. Diagnosis was based on internationally agreed criteria (McKhann et al., 1984; Petersen, 1999; Winblad et al., 2004).

For the investigation of biological markers, each participant was asked to provide an 80ml sample of blood at the baseline assessment. The blood sample was divided in portions; the first part was subjected to clinical pathology screening and to biomarker examinations; the second proportion was used for genetic analysis (APOE genotype); and the remaining blood was fractionated into serum, plasma, platelets, red blood cell, white blood cell - dH20 and white blood cell - RNA later, Ambion and stored in liquid nitrogen. Additionally, a subgroup of participants (n = 250) underwent scans using the structural neuroimaging with Magnetic Resonance Imaging (MRI) and Aβ imaging with Pittsburgh Compound B (PiB) Positron Emission tomography (PET) methods.

In summary, the AIBL study is ideally suited for the purpose of this research project as it provides an opportunity to study the nature and magnitude of cognitive change in relation to vascular risk factors in a relatively large group of well-characterised cognitively healthy individuals. The AIBL participants have been assessed for 54 months using a comprehensive battery of both conventional neuropsychological (Ellis et al., 2009) and computerised cognitive tests (Lim et al., 2012). This enables the investigation of dementia-related cognitive change in the context of vascular risk factors, in both individuals in the prodromal stage of disease.
and in which cognition is borderline compared to normal ageing. Since there is a high likelihood that these individuals may eventually develop MCI and dementia upon longitudinal observation (Ferris, Pepeu et al. 2004), it is necessary that this research includes both cross-sectional and longitudinal approaches.

**Study Cohort**

For the purpose of the present research project, the 768 cognitive healthy individuals from the AIBL study were included as the study cohort. All participants were at least 60 years of age. At the end of the follow-up period, a total of 172 individuals were excluded from the study; n = 156 withdrew from the study and n = 16 were deceased. Of the remaining individuals, 43 met the criteria for MCI by the 54-month assessment (Figure 4).
Figure 4: Flowchart of Study Cohort. Transitioners are those who attracted diagnosis of mild cognitive impairment.
AIBL Participants Assessment

Neuropsychological assessment is a fundamental component in the dementia diagnostic process. The main objectives of neuropsychological assessment are to: (1) identify early cognitive impairment; (2) make a differential diagnostic; (3) establish the stage of the disease; (4) detect a baseline useful for comparisons with future assessments and evaluation of the evolution and prognosis of the dementia; (5) determine the rate of decline; (6) assess the efficiency of pharmacological and non-pharmacological treatments; and (7) participate in research projects (Crook, Larue, Lebowitz, Storandt, & Young, 1998). Accurate neuropsychological assessment is essential in dementia diagnosis because of its value in distinguishing between age-related and disease-related cognitive changes (Plitas, Tucker, Kritikos, Walters, & Bardenhagen, 2009).

In the last years there has been great proliferation of assessment tools for dementia that have contributed to advancing diagnosis and treatment. For example, a battery for detecting dementia, including measures of new learning, delayed recall, attention, and executive function, could provide valuable information for screening and diagnosis if interpreted properly (Collie & Maruff, 2000; Pasquier, 1999; Petersen et al., 2001).

Neuropsychological Battery

The AIBL cognitive battery included both paper-and-pencil (Ellis et al., 2009) and computerised tasks (Lim et al., 2012). The Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) and the Wechsler Test of Adult Reading
(WTAR) (Wechsler, 2001) were administered to participants in order to measure general cognition and estimated IQ. The neuropsychological assessments were administered by a team of trained research assistants. Table 8 summarises the neuropsychological battery grouped by cognitive domain. A detailed description of each test is also presented.

Table 8: Neuropsychological Battery

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Neuropsychological Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Memory</td>
<td>California Verbal Learning Test II</td>
</tr>
<tr>
<td></td>
<td>Wechsler Memory Scale – Logical Memory I and II (story A)</td>
</tr>
<tr>
<td>Visual Memory</td>
<td>Rey Complex Figure Test – Recall &amp; Recognition</td>
</tr>
<tr>
<td>Executive Functions</td>
<td>Stroop task (Victoria version)</td>
</tr>
<tr>
<td></td>
<td>Wechsler Adult Intelligence Scale – Coding and Digit-Span subtests</td>
</tr>
<tr>
<td>Language</td>
<td>30-item Boston Naming Test</td>
</tr>
<tr>
<td></td>
<td>D-KEFS Verbal Fluency Test</td>
</tr>
<tr>
<td>Visuospatial Skills</td>
<td>Rey Complex Figure Test – Copy</td>
</tr>
<tr>
<td>Psychomotor, attentional, working memory and visual learning functions</td>
<td>CogState Brief Battery</td>
</tr>
</tbody>
</table>
Paper-and-Pencil Tests

Test: Stroop Test – Victorian Version (Strauss, Sherman, & Spreen, 2006)

Domain: Attention, cognitive inhibition and speed of processing information.

Description: The Stroop Test measures the relative speed of reading names of colours, naming colours, and naming colours used to print an incongruous colour name. The task requires the participant to override a reading response.


Domain: Auditory short term memory, concentration and attention.

Description: The individual is given sets of digits that he/she needs to repeat initially forwards and then backwards. The task requires the participant to remember a small amount of information for a relatively short period of time.

Test: WAIS – Coding Subtest (Wechsler, 1997).

Domain: Attention and speed of processing information.

Description: The individual is given a set of nine digit-symbol pairs followed by a list of digits. The task requires the participant to write down the corresponding symbol under each digit as fast as possible, and the number of correct symbols within the allowed time is measured.

Test: Boston Naming Test (Saxton et al., 2000).

Domain: Confrontation naming involves several stages of information processing: (1) perception of the object, (2) semantic identification, (3) retrieval of the label that
corresponds to that semantic concept, (4) encoding the articulatory program, and (5) correct articulation of that label or name.

Description: Participants are allowed 20 seconds to name each item. Stimulus cues are offered to correct for misperception errors. They are followed by phonemic cues, which provide the first phonemes of the word, facilitating the lexical retrieval. The total score of the test is the number of correct responses produced spontaneously and with the aid of the stimulus cue.

Test: D-KEFS verbal fluency (Delis, Kaplan, & Kramer, 2001).

Domain: Verbal fluency is a component of executive function. However, it also includes attention, memory, cognitive flexibility, inhibition and language.

Description: Persons are asked to generate as many unique words as possible that begin with a particular letter of the alphabet or semantic category in a given time period (usually 1 min).

Test: Rey-Osterrieth Complex Figure Test (RCFT) (Meyers & Meyers, 1995).

Domain: Visuoperceptual, constructional skills, spatial organisational skills and visual memory.

Description: The RCFT consists of a complex two-dimensional line drawing containing 18 details (including crosses, squares, triangles and a circle) arranged around a central rectangle. The individual is asked to copy the design on a piece of paper. The figure, according to the authors, does not require a high level of graphic aptitude. Each of the details is simple to reproduce separately and the difficulty of the task is based on the arrangement of the elements. Organisational strategy is documented by
having the patient use different colour pencils when executing the task. Additionally, according to the standard procedure, participants are asked to recall the figure without being forewarned after a 3- and 30-minute delay.

**Test:** California Verbal Learning Test (CVLT-II) (Delis, Kramer, Kaplan, & Ober, 2000).

**Domain:** Episodic memory.

**Description:** The CVLT-II is a multi-trial recall and recognition word-list learning test. The list of words contains four items from each of the following categories: vegetables, animals, ways of travelling and furniture. After each of the five trials, the subject is asked to recall as many words as he/she can in any order (free recall). List B, which is used in the interference trial, shares two categories from List A (vegetables and animals) and has two unshared categories (musical instruments and parts of buildings). Neither list uses the most common exemplars of each category in order to minimise ceiling effects and to be more sensitive to intrusion errors. Free and cued recall of list A are tested immediately (short-delay). After a 20-minute delay, filled with non-verbal tasks, long-delay and recognition is assessed. Both word lists on the CVLT-II are introduced as shopping lists because it is the kind of task that people often face in their daily routine.

**Test:** WMS – Logical Memory Subtest (Wechsler, 1945).

**Domain:** Episodic memory.

**Description:** The individual is read a story and immediately asked to recall it from memory. The score is based on the accuracy of the immediate recall of the story.
Approximately 30 minutes later the subject is again asked to recall the story. The Logical Memory II score reflects the accuracy of the delay recall.

**CogState Computarised Battery**

*Test: CogState Battery (Lim et al., 2012)*

*Domain: General cognitive function*

*Description:* The CogState Brief Battery consists of four tasks that utilise playing card stimuli which are presented on a laptop computer. At the presentation of the stimulus, the participant is asked to respond either “Yes” or “No” by pressing some keys on the computer keyboard as quickly and as accurately as possible. For each task, the speed and accuracy of each response was recorded and was expressed as a mean reaction time (in milliseconds) and accuracy (proportion correct).

1. The first task is called the Detection Task (DET) and is a simple reaction time test shown to measure psychomotor function. In this task, the participant had to answer the question: “Has the card turned over?”

2. The second task is the Identification task (IDN) which is a choice reaction time test shown to measure visual attention. In this task, the participant had to answer to the question: “Is the card red?”

3. The third task is the One Card Learning Task (OCL) and is a continuous visual recognition learning task that assesses visual learning within a pattern separation model. In this task the participant has to answer the question “Have you seen this card before in this task?”
4. Finally, the fourth task is the One-Back Task (OBK) which measures working memory and attention. The question the participant has to answer in this task is: “Is this card the same as that on the immediately previous trial?” The primary performance measure for the last two tasks was the proportion of correct answers (accuracy).

*Threshold Criteria for Vascular Risk Factors*

The AIBL study includes a number of variables that have been associated with ageing and dementia, such as lifestyle and biomarkers factors (Ellis et al., 2009; Ellis et al., 2010; Ellis et al., 2014). AIBL participants completed a series of questionnaires to examine their lifestyle patterns and provided an 80ml sample of blood for pathology and biomarkers analysis.

The cohort of 768 cognitively healthy participants was divided into 2 groups: those with and those without vascular risk factors. The criteria to determine if a participant was classified as having a specific vascular risk factor were based on established cut-offs and in consultation with clinical members of the AIBL study team (to ensure a unified approach to measuring cardiovascular risk in the study cohort). According to published guidelines, the criteria used in this study were based on three aspects of the AIBL assessment:

1. Self-report - the participants were asked to report a history of the vascular risk factors under consideration. The two questions asked were: (a) have you had any history of diabetes? and (b) have you had any history of hypertension?
(2) Records of medications – each participant was requested to give information about his/her pharmacological treatment. After analysing all medications used by each of the 768 participants, medicines belonging to any of the following categories were selected: (a) antihypertensive medications, (b) statin or fibrate medications, (c) oral antihyperglycemic medications or insulin and (d) antiplatelet medications.

(3) Pathology and vital signs tests – this part of the assessment provided results that allowed the identification of participants that were over a specific threshold for each respective vascular risk factor.

Participants who suffer from hypertension had a history of high blood pressure, or had both systolic and diastolic blood pressure levels greater than or equal to the specific thresholds for hypertension (Chobanian, Roccella, & Comm, 2003), or are currently being treated with antihypertensive medications. The same process applied for diabetes (Rubins et al., 2002) and dyslipidaemia (Ninomiya et al., 2004). Participants with a BMI greater than 30 (World Health Organization, 2000), which is the threshold for obesity; those who had a glomerular filtration rate (GFR) of less than 45 millilitres per minute (Go, Chertow, Fan, McCulloch, & Hsu, 2004); males and females who had homocysteine levels above 16.2 and 13.6 micromoles per litre, respectively (Wang & Beydoun, 2007); and those how had a smoking history of more than 20 cigarettes per day for over a year, were also included. The criteria for each vascular risk factor are shown in Table 9.
Table 9: Vascular Risk Factors

<table>
<thead>
<tr>
<th>Vascular Risk Factors</th>
<th>Threshold Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension:</td>
<td>Medical history of hypertension, blood pressure ≥ 140/90 mm Hg, or use of antihypertensive medication</td>
</tr>
<tr>
<td>Diabetes:</td>
<td>Medical history of diabetes, fasting plasma glucose &gt; 7mmol/L, or use of diabetes medication</td>
</tr>
<tr>
<td>Dyslipidaemia:</td>
<td>Fasting serum total cholesterol ≥ 6.22mmol/L, or use of statins or fibrates</td>
</tr>
<tr>
<td>Obesity:</td>
<td>BMI &gt; 30 kg/m^2</td>
</tr>
<tr>
<td>Smoking:</td>
<td>Smoking history of more than 20 cigarettes per day for more than one year.</td>
</tr>
<tr>
<td>Chronic Kidney Disease:</td>
<td>Estimated GFR &lt; 45 ml/min</td>
</tr>
<tr>
<td>Homocysteine:</td>
<td>Males &gt;16.2 μmol/L and Females&gt; 13.6 μmol/L</td>
</tr>
</tbody>
</table>

The use of BMI as measure of vascular risk has been an area of debate, and it has also been proposed that excess fat in the abdominal region is an increased risk for cardiovascular disease (Dobbelsteyn, Joffres, MacLean, & Flowerdew, 2001; Lapidus et al., 1984; Larsson et al., 1984). In the current study, BMI was used as a measure of obesity. Research has shown that BMI is strongly correlated with the gold-standard methods for measuring body fat (Gallagher, Visser et al. 1996). Moreover, BMI is an easy way for clinicians to identify individuals who might be at greater risk of health problems due to their weight (Force 2003, Artaud et al., 2013;
Beydoun et al., 2008; Gustafson et al., 2003; Kalmijn et al., 2000; Kivipelto, Ngandu, Fratiglioni, & et al., 2005; Mendall et al., 1997; Ravaglia et al., 2006; Razay et al., 2006; Rosengren et al., 2005; Tan et al., 2003; Yamada et al., 2003). Indeed, the WHO has agreed that BMI is a useful international standard measure for identifying overweight and obesity in adult populations (World Health Organization, 2000). A cut-off of 30 and above was used to identify obese individuals, consistent with the WHO criteria (World Health Organization, 2000).

The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III) (Antonopoulos, 2002) recommended that low density lipoproteins cholesterol should be the primary target for vascular risk factors. However, as total serum cholesterol has been widely used in the research literature as a measure of vascular risk factors (Elias, Elias, D’Agostino, Sullivan, & Wolf, 2005; Kalmijn et al., 2000; Kivipelto, Ngandu, L. Fratiglioni, & e. al, 2005; Stewart, White, Xue, & Launer, 2007; Tan et al., 2003; Wilson et al., 1998; Yaffe et al., 2014), and with the purpose of comparing our findings with other studies, we selected total serum cholesterol as the vascular risk factor measure.
Statistical Analyses

In order to investigate the effect of vascular risk factors on cognitive function, this study implemented an additive approach which provides a meaningful approximation for the combined effect of several vascular risk factors on cognition – one point was given for each vascular risk factor present. We aimed to examine the seven most commonly identified vascular risk factors associated with cognition (see Chapter 2 for review). These vascular risk factors are: hypertension, type II diabetes, dyslipidaemia, obesity, smoking history, chronic kidney disease and high levels of homocysteine. To our knowledge, no other studies have included the seven vascular risk factors selected for the present study in combination.

The analyses undertaken in this thesis were developed using the Statistical Package for the Social Science (SPSS, version 19.0).

First Analysis – Demographic Information

For the first analysis, demographic characteristics of individuals with and without vascular risk factors were compared. Descriptive statistics were used to define the basic features of the sample. Differences between and within groups for demographic variables were analysed using the Chi-square test for independence to compare proportions within categorical variables, such as gender, education and APOE carriage, and analysis of variance (ANOVA) for continuous variables such as age, estimated IQ and MMSE score. Participants’ age and educational level were based on self-report, and this information was corroborated by a family member. Age at examination was recorded in years; education was coded using a binary scale: 0 for twelve or less years of education completed and 1 for more than twelve years; and
APOE ε4 carriage was coded using a binary scale: 0 for negative APOE ε4 carriage and 1 for positive APOE ε4 carriage.

In order to study comorbidity among vascular risk factors, a series of association rules were completed. Associations rules was first introduced in 1993 (Agrawal, Imieliński, & Swami, 1993) to identify patterns in consumer behaviour, such as to determine how items purchased by consumers are related. This statistical model is represented with a mathematical expression of transactional relationship among patterns which is also sensitive to their direction (Zang, 2000). The aim of association rules is to discover the patterns of co-occurrence of attributes in a large dataset (Agrawal & Srikant, 1994). It can predict more than one value of attributes among independent variables and it also has the freedom to predict combinations of attributes (Witten & Frank, 2005). As such, association rules allow capturing all possible rules that explain the presence of some variables according to the presence of other variables (R. Chaves, Ramírez, Górriz, & Illán, 2012; Karabatak & Ince, 2009; Ribeiro et al., 2009).

The association rule model has recently gained attention in the medical setting (Berardi, Lapi, Leo, & Loglisci, 2005; R Chaves et al., 2011; R. Chaves et al., 2012; Karabatak & Ince, 2009; Ordonez, Ezquerra, & Santana, 2006; Ribeiro et al., 2009; Simon, Li, Jack Jr, & Vemuri, 2011). In this context, association rules can be used to determine the probability of individuals suffering from a specific disorder when they are known to suffer from another condition (Simon et al., 2011). This approach enables the identification of comorbidity among different disorders (R Chaves et al., 2011). The benefits of this model are that it can handle a large amount of data,
manage a substantial number of rules (to determine the potential associations), and maintain the rules over a significantly long period of time (Agrawal, Imieliński, & Swami, 1993, Viveros, Nearhos, & Rothman, 1996). It is important to note that the inference made by an association rule does not necessarily imply causality; instead, it suggests a relationship between the antecedent and consequent components of the rule (Zang, 2000).

This statistical model allowed the identification of the strongest relationships among the vascular risk factors (Hahsler & Chelluboina, 2011). More specifically, the model generates all the association rules that have certain support, confidence and lift values, representing the strength of each association rule (Agrawal & Srikant, 1994). The support value describes the size of the mathematical set in which both vascular risk factors are present. The confidence is the index that describes the (conditional) probability that the second vascular risk factor exists in the presence of the first risk factor. Finally, the lift value represents the impact of each association rule (Tan, Steinbach, & Kumar, 2006; Witten & Frank, 2005). In summary, the algorithm discovers the sets of data that contain a specific vascular risk factor and the likelihood of containing another vascular risk factor.

Second Analysis – Difference in Cognitive Performance between Individuals with and without Vascular Risk Factors: a Cross-Sectional Study

The specific research question addressed in this analysis was: is there a difference in cognitive performance between individuals with and without vascular risk factors? A principal component analysis (PCA) with an orthogonal-varimax rotation was chosen to reduce the number of variables in the neuropsychological
battery into component factors (Field, 2013; Shlens, 2005), and thereby decrease the amount of statistical comparisons (Widaman, 1993). The resulting factors were used as dependent variables in a one-way between groups (vascular risk factors and non-vascular risk factors) multivariate analysis of variance (MANOVA) (Field, 2013). MANOVA also provided univariate results for each of the dependent variables, which made it possible to identify the effect of vascular risk factors on each cognitive variable. This model was ideally suited for this study for two main reasons: (1) several neuropsychological tests were used (Hair, 2010) and (2) a number of cognitive domains were measured (Mertler & Vannatta, 2002).

Third Analysis – Rate of Cognitive Change for Five Specific Cognitive Tests: a Longitudinal Study

From a longitudinal perspective, in the third analysis, further investigations were performed to identify whether the presence of vascular risk factors affects the rate of cognitive change in healthy older adults. Five specific neuropsychological tests - (a) California Verbal Learning Test, (b) Boston Naming Test, (c) Rey Complex Figure Test, (d) Stroop Colour and Word Test, and (e) Control Oral Word Association Test - were subjected to a series of linear mixed models (LMM). This statistical model allowed the identification of changes in cognitive function over time, as well as of random effects that contributed to the covariance of the data (Snijders, 2011). This model also provided the flexibility needed as the information was collected over time on the same group of individuals (Verbeke & Molenberghs, 2009).

We selected these neuropsychological tests because they have been recognised as being sensitive for identifying the neurocognitive markers for
dementia and due to their high levels of reliability and validity. In addition, they enable the independent evaluation of each cognitive domain. A meta-analysis, which aimed to identify the most useful neuropsychological tests in the differentiation of normal aging and early-stage dementia, demonstrated that both verbal and non-verbal memory tests, together with confrontation naming and verbal fluency tests, are particularly sensitive for the identification of cognitive decline associated with dementia (Christensen, Hadzi-Pavlovic, & Jacomb, 1991). Moreover, in a group of healthy older adults who were followed over a period of 2–5 years, Bozoki and colleagues demonstrated that those individuals who exhibited mild cognitive difficulties in several cognitive domains including memory were twice as likely to develop dementia, compared to those individuals who only displayed memory impairment (Bozoki, Giordani, Heidebrink, Berent, & Foster, 2001), highlighting the importance of the assessment of several cognitive domains.

The ability to learn new information is a complex neuropsychological process that can be disrupted as a consequence of a number of neurological and psychiatric disorders (D. C. Delis, Kramer, Freeland, & Kaplan, 1988; Kramer & Delis, 1998). Lower performance in verbal memory tests has been consistently the most important predictor of whether an individual will develop DAT in the future (Albert, Moss, Tanzi, & Jones, 2001; Bondi et al., 1994; Collie & Maruff, 2000; Rubin et al., 1998; Tierney et al., 1996). The CVLT has been used for the evaluation of verbal memory, and for the identification and characterisation of different memory disorders (Lezak, 2004). This test assesses various components of memory, including (1) level of recall, (2) forgetting rates, (3) vulnerability to proactive interference, (4) encoding, (5) retrieval, (6) intrusion rates and (7) recognition discriminability (D. Delis,
Massman, Butters, Salmon, & et, 1991). As such, the CVLT differs from traditional
tests as its scoring system provides results on: (1) semantic and serial learning
strategies, (2) primacy-recency effect, (3) rate of learning across trials, (4)
consistency of item recall across trials, (5) measures of vulnerability to interference,
(6) retention over short and longer delays, (7) learning errors (intrusion and
perseveration) and (8) recognition performance (D. Delis et al., 1991; D. C. Delis et al.,
1988).

Even though memory decline is one of the clinical features of DAT, diagnosis
must be based on an overall view of the clinical picture. Therefore, it is imperative to
document deficits in other cognitive domains (Salmon & Bondi, 2009). The presence
of word finding difficulties has been recognised as another sign of neurodegenerative
diseases (Bayles, Kaszniak, & Tomoeda, 1987; Bayles, Tomoeda, & Trosset, 1992; N. J.
Fisher, Tierney, Snow, & Szalai, 1999), This deficit appears early in the course of the
dementia process and increases with progression in the disorder (Faber‐Langendoen
As such, assessment of naming skills is commonly used to assist in the diagnosis of
AD (Saxton et al., 2000).

The BNT is a confrontation naming test that has been developed for detection
of word-retrieval problems (Kaplan, Goodglass, Weintraub, Segal, & van Loon-
Vervoorn, 2001). The BNT has shown high sensitivity to the effects of AD in cognitive
function (Henry, Crawford, & Phillips, 2004; Lansing, Ivnik, Cullum, & Randolph,
1999), even in early stages of the disease (Hodges & Patterson, 1995). It has been
reported that individuals who suffer from DAT tend to show significant difficulties on
the BNT (Mack, Freed, Williams, & Henderson, 1992; Testa et al., 2004; Williams, Mack, & Henderson, 1989). In addition, longitudinal studies have demonstrated that the BNT has a high sensitivity in detection of the rate of cognitive change, characteristic of DAT patients (Baum, Edwards, Leavitt, Grant, & Deuel, 1988; Knesevich, LaBarge, & Edwards, 1986; Whitworth & Larson, 1988; Williams et al., 1989).

The RCFT is a common test implemented in clinical and research settings to assess a variety of cognitive abilities (Caffarra, Vezzadini, Dieci, Zonato, & Venneri, 2002; Camara, Nathan, & Puente, 2000). This test was initially developed with the objective of measuring visuospatial skills (Rey, 1941); however, nowadays it is recognised for its ability to assess a series of cognitive domains, including non-verbal memory, visuospatial abilities, planning, organisational and problem-solving strategies, and perceptual, motor and visuoconstructional functions (Strauss, Sherman, & Spreen, 2006). Visuospatial difficulties are particularly prominent in individuals with dementia (Tei et al., 1997). A number of studies have confirmed that the RCFT is sensitive in the identification of visuospatial difficulties in individuals with DAT (Ardila et al., 2000; Berry, Allen, & Schmitt, 1991; Bigler, Rosa, Schultz, Hall, & Harris, 1989; Freeman et al., 2000; Tei et al., 1997). When studies have compared cognitively healthy participants with those that suffer DAT, the latter group have consistently exhibited a significant poorer performance on all indices of the RCFT (Bigler et al., 1989; Freeman et al., 2000). Moreover, in studies that have assessed in vivo Aβ burden, those participants in the pre-clinical stage of AD displayed a significant poorer performance in the RCFT compared to a control group (Pike et al., 2007).
There has been accumulating evidence to suggest that individuals in the early-stage of AD suffer from working memory and attentional difficulties (L. M. Fisher, Freed, & Corkin, 1990; Hart, Smith, & Swash, 1988; Martin & Fedio, 1983; Spreen & Benton, 1969), as well as exhibit poorer performance in verbal fluency tasks. Furthermore, executive dysfunction is characteristic of AD patients (Boyle et al., 2003; Buckner, 2004). The Stroop test (Demakis, 2004; Koss, Ober, Delis, & Friedland, 1984; Spieler, Balota, & Faust, 1996; Troyer, Leach, & Strauss, 2006) and the COWAT (Axelrod & Henry, 1992; Hodges et al., 1999; Rodriguez-Aranda & Martinussen, 2006; Tombaugh, Kozak, & Rees, 1999) have been generally recognised for their ability to detect executive function difficulties in dementia patients (Bondi et al., 2002; Nathan, Wilkinson, Stammers, & Low, 2001). Moreover, both tests have also been used as indicators of cognitive changes associated with the earlier stages of dementia (Monsch et al., 1992). Poorer performance in the COWAT before the onset of dementia has been a predictor of later AD (Hodges & Patterson, 1995). Similarly, elevated time in the interference card of the Stroop test has been associated with very-early stages of dementia (Bondi et al., 2002; Nathan et al., 2001).

**Fourth Analysis – Rate of Cognitive Change for Cognitive Composite Factors: a Longitudinal Study**

The relationship between vascular risk factors and cognitive decline was also examined using cognitive composite measures as dependent variables, which allow examination at a cognitive-domain level. In order to obtain the cognitive composite measures, neuropsychological variables were grouped into six factors, described in Table 10. To compute each cognitive composite measure, the raw scores for each
neuropsychological variable were converted to a z-score using the mean and standard deviation of the total cognitively healthy cohort; hence, the composite score for each domain was the z-scores average (Harrington et al., 2013). Each cognitive composite represented a particular cognitive domain, namely verbal memory, visual memory, executive functions, language and visuospatial skills. The use of this approach not only reduced the probability of Type I error, but also floor and ceiling effects (Nuechterlein, Green, et al., 2008).

**Table 10: Cognitive Composite Factors**

<table>
<thead>
<tr>
<th>Composite Measure</th>
<th>Neuropsychological Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Memory</td>
<td>California Verbal Learning Test II (CVLT)</td>
</tr>
<tr>
<td></td>
<td>Wechsler Memory Scale–Logical Memory (II)</td>
</tr>
<tr>
<td>Visual Memory</td>
<td>Rey Complex Figure Test (RCFT) – Recall (3 &amp; 30 min.)</td>
</tr>
<tr>
<td></td>
<td>CogState-One Card Learning (OCL) task</td>
</tr>
<tr>
<td>Executive Functions</td>
<td>D-KEFS Verbal Fluency Test (FAS)</td>
</tr>
<tr>
<td></td>
<td>CogState-The One-Back (OBK) task</td>
</tr>
<tr>
<td></td>
<td>Stroop Test</td>
</tr>
<tr>
<td>Language</td>
<td>30-item Boston Naming Test (BNT)</td>
</tr>
<tr>
<td></td>
<td>D-KEFS Verbal Fluency Test (Animals &amp; Names)</td>
</tr>
<tr>
<td>Visuospatial Skills</td>
<td>Rey Complex Figure Test (RCFT) - Copy</td>
</tr>
</tbody>
</table>

Fifth Analysis – The Effect of Vascular Risk Factor Burden on Cognition

The research question addressed by this analysis was: is the number of vascular risk factors present in an individual associated with cognitive performance and cognitive change over time? In order to answer this question the effect sizes of
differences were calculated. For each of the cognitive variables the magnitude of the difference between the vascular risk factors groups (one, two and three or more vascular risk factors) in terms of the control group (no vascular risk factor group) was estimated using Cohen’s \( d \). This statistical measure allowed understanding the magnitude of differences using standardised benchmarks that have been defined as small (less than 0.29), moderate (0.30-0.49), and large (more than 0.50) effect sizes (Cohen, 1992).

First, we calculated the magnitude of impairment for two factors that were obtained from the cross-sectional analysis: the \textit{visuospatial and visual memory factor}, and the \textit{inhibition factor}. Then we calculated the magnitude of decline for the five specific neuropsychological tests used in the third analysis: (a) California Verbal Learning Test, (b) Boston Naming Test, (c) Rey Complex Figure Test, (d) Stroop Colour and Word Test and (e) Control Oral Word Association Test. Finally, we calculated the magnitude of decline for the cognitive composite factors (Table 10) used in the fourth analysis. In this case we divided the participants into two groups: those with low vascular risk factor burden (with one or two vascular risk factors) and those with high vascular risk factor burden (with three or more vascular risk factors).

\textit{Sixth Analysis - Effect of Vascular Risk Factors on the Clinical Classification of the Participants}

The final analysis investigated whether there was a link between the presence of vascular risk factors and the development of MCI. As was mentioned previously, a total of 768 cognitively healthy participants were recruited at baseline. In order to identify all those participants that attracted the diagnosis of MCI over the 54-month
period, a clinical review panel met periodically to discuss changes in their cognitive performance. The consensus diagnosis assigned for each participant was based on the consideration of standardised diagnostic criteria: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition -DSM-IV (American Psychiatric Association, 1994) and International Classification of Disease (ICD)-10 (World Health Organization, 1992)

The clinical review panel comprised old age psychiatrists, a neurologist, a geriatrician and neuropsychologists. MCI diagnoses were made according to the protocol based upon the criteria of Winblad et al.(Winblad et al., 2004) which are informed by the criteria of Petersen et al.(R. C. Petersen et al., 1999). Individuals to be considered as having MCI had to exhibit a score of 1.5 SD below the relevant normative mean on at least two neuropsychological tasks. These objective cognitive difficulties have to be present in the absence of significant functional loss. In addition, consistent with Winblad criteria, MCI participants had either personally, or through an informant, reported memory difficulties (Winblad et al., 2004). Finally, all participants classified with MCI had a Clinical Dementia Rating (CDR) score of 0.5 (Mattis, 1988; Petersen, 1999). The CDR is an instrument which has been designed to assess the nature and severity of dementia (Monsch et al., 1995). It consists of five subscales, namely attention, initiation or perseveration, construction conceptualisation and memory. These scales aim to evaluate the typical cognitive changes that occur in DAT (O’Bryant et al., 2008).

Over the follow-up period, 43 participants transitioned from the healthy control group to a classification of MCI. Accordingly, we divided the cohort at the 54-
month time-point in two groups, those who remained healthy (referred to as stable) and those who converted to MCI (referred to as transitioners). Initially, we completed a series of Chi-square tests for independence and ANOVA models with the purpose of analysing the demographic characteristics between the two groups with different clinical classification.

A series of Chi-square tests for independence were also used to identify differences in the vascular risk factor burden between individuals who remained cognitive healthy and those who progressed to MCI. We then used the cognitive composite factors (previously described in Table 10) as dependent variables in a two-way between-groups analysis of variance. This statistical model was conducted to explore the interaction effect of clinical classification and presence/absence of vascular risk factors on cognitive function (Field, 2013).

Finally, we calculated the relative risk of developing MCI in individuals with vascular risk factors compared to those with no vascular risk factors. The relative risk is a statistical measure that allows prediction of a categorical outcome, in this case the clinical classification of participants based on a series of predictor variables (such as vascular risk factors) (Zhang & Kai, 1998). This information allowed estimation of the effect of vascular risk factors on both the incidence and prevalence of MCI (McNutt, Wu, Xue, & Hafner, 2003).
This chapter presents the findings of the six analyses completed as part of this thesis. The first analysis presents the demographic characteristics of the sample. The second analysis explores – from a cross-sectional perspective – the difference in cognitive performance between individuals with and without vascular risk factors. The third analysis investigates - prospectively - the rate of cognitive change between individuals with and without vascular risk factors on five specific neuropsychological tests. The fourth analysis evaluates the relationship between vascular risk factors and specific cognitive domains using cognitive composite factors (refer to chapter 3 for a detailed explanation). The fifth analysis investigates whether the number of vascular risk factors present in an individual affects cognitive function. Finally, the sixth analysis focuses on the group of participants who attracted a diagnosis of MCI and explores the risk of developing MCI for those with vascular risk factors.

**First Analysis – Demographic Information**

The 768 study participants were aged between 60 and 95 years old; the mean age was 69.9 with a standard deviation (SD) of 6.9 years. There were 331 male participants and 437 female participants within the cohort. Twenty-seven per cent of participants were *APOE* ε4 carries, almost half had less than 12 years of education, and the majority had an estimated IQ within the high-average range, as well as a MMSE score within the normal range (Table 11).
Table 11: Demographic Information of the Study Sample

<table>
<thead>
<tr>
<th></th>
<th>Cognitively Healthy Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>768</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>69.9 (6.9)</td>
</tr>
<tr>
<td>Female %</td>
<td>56 %</td>
</tr>
<tr>
<td>SMC %</td>
<td>51.4 %</td>
</tr>
<tr>
<td>Apolipoprotein E ε4 %</td>
<td>26 %</td>
</tr>
<tr>
<td>Less than 12 years of Education %</td>
<td>52.3 %</td>
</tr>
<tr>
<td>Mean Estimated IQ - WTAR (SD)</td>
<td>108.22 (7.2)</td>
</tr>
<tr>
<td>MMSE (SD)</td>
<td>28.8 (2.2)</td>
</tr>
</tbody>
</table>

Notes: SD = Standard deviation. SMC: Subjective Memory Complainers. WTAR = Wechsler Test of Adult Reading. MMSE = Mini Mental State Examination.

Prevalence of Vascular Risk Factors in the Study Cohort

At baseline, 80.7% of participants had at least one of the seven vascular risk factors; the distribution of vascular risk factors in the study group is shown in Table 12. The most prevalent vascular risk factors were hypertension and dyslipidaemia, with almost half of participants having at least one of the two. Obesity was the third most common vascular risk factor in this cohort (18% of the participants). The proportion with diabetes, high homocysteine levels or chronic kidney disease was below 10% in all three cases.
Table 12: Distribution of Vascular Risk Factors

<table>
<thead>
<tr>
<th>Vascular Risk Factor</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>45.1%</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>44.3%</td>
</tr>
<tr>
<td>Obesity</td>
<td>18.1%</td>
</tr>
<tr>
<td>Smoking history</td>
<td>13.3%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6.2%</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>3.8%</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

Notes: Since many participants have more than one vascular risk factor, the sum of the independent indices is more than 100%.

Vascular Risk Factors Comorbidity

To understand comorbidity among the seven vascular risk factors, a series of association rules were performed (Table 13). The purpose of the association-rule model is to identify relationships among items in large databases (Agrawal, Imieliński, & Swami, 1993). An association rule model has two parts, an antecedent (if) and a consequent (then), and represents a pattern that states when the antecedent occurs, the consequent also occurs with certain probability (Hahsler & Chelluboina, 2011). Association rules are then created by analysing data for antecedent/consequent patterns and identifying the stronger relationships.
Association rules are implication expressions of the form X → Y, where X and Y are disjoint sets (X \cap Y=0) with categorical variables (Tan et al., 2006). In this study, X and Y would be subsets of the overall set of participants and could represent, for example, individuals identified as meeting the criteria for obesity (X) and diabetes (Y), respectively. In this example, meeting the criteria for obesity (X) would be the ‘antecedent’ and meeting the criteria for diabetes (Y) the ‘consequent’.

The strength of an association is generally measured in terms of its support and confidence. Support determines the frequency with which a rule applies to a dataset; in our example, the proportion of participants that meet the criteria for both obesity and diabetes (X U Y) – a measure of the size of the subset that includes both X and Y. Confidence determines how frequently the consequent occurs when the antecedent has been identified as occurring, thereby measuring the reliability of the inference made by a rule; in our example, the proportion of participants that, having been identified as meeting the criteria for obesity, also meet the criteria for diabetes (the proportion of elements of X that are also part of Y) – allowing to determine the potential association between the two vascular risk factors since the higher the confidence, the more likely it is that individuals meet the criteria for diabetes when they have been determined to meet the criteria for obesity.

The literature has identified that support and a high confidence are not necessarily a reflection of the ‘interest’ factor of a rule (Agrawal & Srikant, 1994; Zang, 2000). A further measure of the strength of an association is the lift factor, which is the ratio between the confidence and the support of the item-set in the rule consequent (Tan et al., 2006); in our example, it would be the proportion of
participants with both obesity and diabetes divided by the product of the proportion of participants with obesity and the proportion of participants with diabetes – \( \frac{P(X U Y)}{P(X)P(Y)} \).

The results of the association rule analyses revealed 12 associations with a lift value greater than 1, which represents a strong relationship (Agrawal et al., 1993; Cheung, Han, Ng, & Wong, 1996) and implies the existence of a pattern of relations (Delgado, Marin, Sánchez, & Vila, 2003). The results of the first association reported in the table, between chronic kidney disease and high levels of homocysteine, has to be interpreted with caution – it has a lift value of 15.5, which would suggest an extremely strong relationship between the two vascular risk factors; however, the number of participants who suffer from either of these two conditions is less than 10% of the overall sample, which means that it cannot be interpreted as a “useful” association (Agrawal & Srikant, 1994).

Amongst the rest of the associations, dyslipidaemia was the most common factor in comorbidity with other vascular risk factors. Dyslipidaemia was present in individuals who also had chronic kidney disease (lift value = 1.59), as well as in those participants who smoke (lift value = 1.11), are obese (lift value = 1.09), and those who suffer from hypertension (lift value = 1.09) and diabetes (lift value = 1.01). Additionally, there were two associations that involved more than two vascular risk factors. In those instances, dyslipidaemia was present in combination with obesity and smoking (lift value = 1.92) and with hypertension and obesity (lift value = 1.28). Obesity was the second vascular risk factor more commonly found in comorbidity with other vascular risk factors. The associations between obesity and
diabetes (lift value = 1.94), smoking (lift value = 1.60), hypertension (lift value = 1.27) and dyslipidaemia (lift value = 1.09) were very strong. As was the case with dyslipidaemia, obesity was also present in those associations that involved more than two vascular risk factors: obesity, dyslipidaemia and smoking (lift value = 1.92) and obesity, dyslipidaemia and hypertension (lift value = 1.28). The results also showed that participants who suffer from hypertension tend to also have diabetes (lift value = 1.65).

Table 13: Association Rules among Vascular Risk factors

<table>
<thead>
<tr>
<th>Vascular Risk Factors Combinations</th>
<th>Support</th>
<th>Confidence</th>
<th>Lift Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Kidney Disease =&gt; Homocysteine</td>
<td>0.01</td>
<td>0.55</td>
<td>15.52</td>
</tr>
<tr>
<td>Obesity =&gt; Diabetes</td>
<td>0.01</td>
<td>0.08</td>
<td>1.94</td>
</tr>
<tr>
<td>Obesity, Dyslipidaemia =&gt; Smoking</td>
<td>0.01</td>
<td>0.15</td>
<td>1.92</td>
</tr>
<tr>
<td>Hypertension =&gt; Diabetes</td>
<td>0.01</td>
<td>0.07</td>
<td>1.65</td>
</tr>
<tr>
<td>Smoking =&gt; Obesity</td>
<td>0.02</td>
<td>0.27</td>
<td>1.60</td>
</tr>
<tr>
<td>Dyslipidaemia =&gt; Chronic Kidney Disease</td>
<td>0.01</td>
<td>0.02</td>
<td>1.59</td>
</tr>
<tr>
<td>Obesity, Dyslipidaemia =&gt; Hypertension</td>
<td>0.01</td>
<td>0.15</td>
<td>1.28</td>
</tr>
<tr>
<td>Obesity =&gt; Hypertension</td>
<td>0.02</td>
<td>0.15</td>
<td>1.27</td>
</tr>
<tr>
<td>Smoking =&gt; Dyslipidaemia</td>
<td>0.02</td>
<td>0.32</td>
<td>1.11</td>
</tr>
<tr>
<td>Obesity =&gt; Dyslipidaemia</td>
<td>0.05</td>
<td>0.31</td>
<td>1.09</td>
</tr>
<tr>
<td>Hypertension =&gt; Dyslipidaemia</td>
<td>0.04</td>
<td>0.31</td>
<td>1.09</td>
</tr>
<tr>
<td>Diabetes =&gt; Dyslipidaemia</td>
<td>0.01</td>
<td>0.29</td>
<td>1.01</td>
</tr>
</tbody>
</table>
Distribution of Participants Based on the Number of Vascular Risk Factors

The cohort was divided according to the number of vascular risk factors. Descriptive statistics revealed the following vascular risk factor burden distribution: n = 138 individuals had no vascular risk factors, n = 253 had one vascular risk factor, n = 224 had two vascular risk factors, n = 72 had three vascular risk factors, n = 24 had four vascular risk factors, n = 3 had five vascular risk factors, n = 1 had six vascular risk factors, n = 0 had seven vascular risk factors (Figure 5).

Figure 5: Vascular risk factor burden distribution at baseline assessment.

The results show that 35% of the participants had only one vascular risk factor; a quarter of the cohort had 2 vascular risk factors; and less than 10% of participants were in any of the groups with 3 or more vascular risk factors. Based on this distribution, four categories were assigned: n = 138 individuals had no vascular risk factors, n = 253 had one vascular risk factor, n = 224 had two vascular risk factors and n = 100 had three or more vascular risk factors.
Once the participants were classified according to the number of vascular risk factors, the relative distribution of each vascular risk factor was analysed within each vascular risk factor burden group (Table 14). The results showed that the ranking of vascular risk factors (according to their prevalence) was very similar for the three vascular risk factor burden groups. The only exception was that smoking history was slightly more prevalent than obesity in the one vascular risk factor group. Hypertension and dyslipidaemia were the two most prevalent vascular risk factors, and diabetes, homocysteine levels and chronic kidney disease were the least prevalent.

Table 14: Distribution of Vascular Risk Factors by Groups of Participants

<table>
<thead>
<tr>
<th>Vascular Risk Factors</th>
<th>One</th>
<th>Two</th>
<th>Three</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension %</td>
<td>41.37</td>
<td>73.03</td>
<td>90.81</td>
</tr>
<tr>
<td>Dyslipidaemia %</td>
<td>40.57</td>
<td>70.79</td>
<td>83.74</td>
</tr>
<tr>
<td>Obesity %</td>
<td>4.73</td>
<td>24.14</td>
<td>52.48</td>
</tr>
<tr>
<td>Smoking history %</td>
<td>7.74</td>
<td>20.12</td>
<td>29.23</td>
</tr>
<tr>
<td>Diabetes %</td>
<td>3.17</td>
<td>8.43</td>
<td>28.16</td>
</tr>
<tr>
<td>Homocysteine %</td>
<td>1.40</td>
<td>2.37</td>
<td>9.06</td>
</tr>
<tr>
<td>Chronic kidney disease %</td>
<td>1.02</td>
<td>1.12</td>
<td>7.34</td>
</tr>
</tbody>
</table>

Note: The three columns represent the proportion of participants that have the respective number of vascular risk factors, as follows: the first column is the proportion that have only one vascular risk factor, the second column is the proportion that have two vascular risk factors and the third column is the proportion that have three or more vascular risk factors. The percentage of the first group add to 100 percent; the percentage of the second group add to 200%; and the percentage of the third group add to 300%.
Demographic Characteristics of Individuals with Different Number of Vascular Risk Factors

Participants were stratified based on the presence or absence of vascular risk factors. Table 15 shows the difference in demographic characteristics between these two groups. Participants with and without vascular risk factors did not differ in terms of gender ($\chi^2 (1, n = 714) = 0.8, p = 0.38$), estimated IQ ($F (1, 709) = 0.6, p = 0.45$) or MMSE score ($F (1, 709) = 1.5, p = 0.22$). However, those with at least one vascular risk factor were older ($F (1, 712) = 8.1, p = 0.005$), more likely to be $APOE \varepsilon 4$ carriers ($\chi^2 (1, n = 714) = 6.9, p = 0.009$) and a larger proportion had less than 12 years of education ($\chi^2 (1, n = 711) = 7.8, p = 0.005$).

Table 15: Demographic Characteristics of the without & with-Vascular Risk Factors Groups

<table>
<thead>
<tr>
<th></th>
<th>Without Vascular Risk Factors</th>
<th>With Vascular Risk Factors</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
<td>138</td>
<td>606</td>
<td></td>
</tr>
<tr>
<td>Mean age ($SD$)</td>
<td>68.3 (6.0)</td>
<td>70.3 (7.0)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Female %</td>
<td>55.1 %</td>
<td>58.7 %</td>
<td>ns</td>
</tr>
<tr>
<td>Apolipoprotein E $\varepsilon 4$ %</td>
<td>18.1 %</td>
<td>28.9 %</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Less than 12 years of Education %</td>
<td>35.5 %</td>
<td>48.2 %</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Estimated IQ - WTAR ($SD$)</td>
<td>108.62 (7.13)</td>
<td>108.17 (7.28)</td>
<td>ns</td>
</tr>
<tr>
<td>MMSE ($SD$)</td>
<td>28.8 (1.3)</td>
<td>28.7 (1.6)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Notes: SD = Standard deviation. WTAR = Wechsler Test of Adult Reading. MMSE = Mini Mental State Examination.
Demographic characteristics according to the number of vascular risk factors were also examined (Table 16). Results revealed that age, education and the presence of APOE ε4 allele were the only variables that showed a significant difference among the four groups. Those with no vascular risk factors are younger compared to those who have three or more vascular risk factors (F (3, 669) = 5.1, p = 0.002); the majority of individuals with three or more vascular risk factors belong to the group with less than 12 years of education (χ² (1, n=667) = 28.0, p = 0.000); and those individuals with three or more vascular risk factors had a higher proportion of APOE ε4 carriers (χ² (1, n=670) = 11.5, p = 0.009).
Table 16: Demographic Characteristics of Individuals with Different Number of Vascular Risk Factors

<table>
<thead>
<tr>
<th>Number of Vascular Risk Factors</th>
<th>None</th>
<th>One</th>
<th>Two</th>
<th>Three or more</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>138</td>
<td>253</td>
<td>224</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Mean Age (SD)</td>
<td>68.3 (6.0)</td>
<td>69.3 (7.0)</td>
<td>70.7 (7.0)</td>
<td>71.1 (6.5)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Female %</td>
<td>55.1 %</td>
<td>60.9 %</td>
<td>59.8 %</td>
<td>57.0 %</td>
<td>ns</td>
</tr>
<tr>
<td>SMC %</td>
<td>52.9 %</td>
<td>48.6 %</td>
<td>52.0 %</td>
<td>59.0 %</td>
<td>ns</td>
</tr>
<tr>
<td>APOE ε4 Carrier %</td>
<td>18.1 %</td>
<td>30.8 %</td>
<td>22.9 %</td>
<td>34.0 %</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Less than 12 years of Education (%)</td>
<td>35.5 %</td>
<td>37.9 %</td>
<td>58.1 %</td>
<td>55.0 %</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Estimated IQ (WTAR)</td>
<td>108.6 (7.1)</td>
<td>108.2 (7)</td>
<td>107.9 (7.8)</td>
<td>107.8 (7.4)</td>
<td>ns</td>
</tr>
<tr>
<td>MMSE (SD)</td>
<td>29.0 (1.2)</td>
<td>29.0 (1.2)</td>
<td>28.8 (1.1)</td>
<td>28.6 (1.3)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Notes: SD = Standard deviation. SMC Subjective Memory Complainers. WTAR = Wechsler Test of Adult Reading. MMSE = Mini Mental State Examination.
Second Analysis – Difference in Cognitive Performance between Individuals with and without Vascular Risk Factors: a Cross-Sectional Study

Reduction of the Cognitive Dataset - Principal Component Analysis

The 13 cognitive variables from the baseline assessment were subjected to a PCA, with the objective of purely reducing the cognitive dataset. The results yielded a 4-component solution that, after a varimax rotation, accounted for 65.8% of the variance (Table 17).

The first factor, (accounting for 32.7% of the total variance), represented measures of verbal memory, including all free immediate, retention, and delay recall from the CVLT-II, as well as the logical memory II subtest. The second factor explained 13.8% of the total variance and represented visuospatial skills and visual memory; it included the three measures of the RCFT (copy, 3-minutes and 30-minutes recall). The third factor (explaining 11.5% of the total variance) was related to language and information processing; it included the following subtests: 30-item Boston Naming Test, D-KEFS Verbal Fluency Test and coding. The fourth factor explained 7.9% of the total variance and included the interference score for the Stroop test.
### Table 17: Factor Analysis of the 13 Cognitive Variables

<table>
<thead>
<tr>
<th>Neuropsychological Tests</th>
<th>Verbal Memory Factor</th>
<th>Visuospatial Skills &amp; Visual Memory Factor</th>
<th>Language &amp; Information Processing Factor</th>
<th>Inhibition Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVLT Delayed Recall</td>
<td>.892</td>
<td>.222</td>
<td>.267</td>
<td>.152</td>
</tr>
<tr>
<td>CVLT Retention</td>
<td>.891</td>
<td>.194</td>
<td>.267</td>
<td>.152</td>
</tr>
<tr>
<td>CVLT 1-5 Trials</td>
<td>.871</td>
<td>.214</td>
<td>.289</td>
<td>.159</td>
</tr>
<tr>
<td>WMS - Logical Memory II</td>
<td>.584</td>
<td>.197</td>
<td>.332</td>
<td>.121</td>
</tr>
<tr>
<td>RCFT 3-minute delay</td>
<td>.305</td>
<td>.927</td>
<td>.154</td>
<td>.135</td>
</tr>
<tr>
<td>RCFT 30-minute delay</td>
<td>.336</td>
<td>.920</td>
<td>.153</td>
<td>.134</td>
</tr>
<tr>
<td>RCFT Copy</td>
<td>.175</td>
<td>.649</td>
<td>.171</td>
<td>.365</td>
</tr>
<tr>
<td>Animals and Names (Fluency) - D-KEFS</td>
<td>.429</td>
<td>.183</td>
<td><strong>.791</strong></td>
<td>.191</td>
</tr>
<tr>
<td>FAS – D-KEFS</td>
<td>.249</td>
<td>.112</td>
<td><strong>.779</strong></td>
<td>.191</td>
</tr>
<tr>
<td>Digit Symbol – Coding (WAIS - IV)</td>
<td>.274</td>
<td>.245</td>
<td><strong>.583</strong></td>
<td>.279</td>
</tr>
<tr>
<td>Fruit/Furniture Switching – D-KEFS</td>
<td>.296</td>
<td>.137</td>
<td><strong>.556</strong></td>
<td>.137</td>
</tr>
<tr>
<td>30-items BNT</td>
<td>.452</td>
<td>.174</td>
<td><strong>.528</strong></td>
<td>.156</td>
</tr>
<tr>
<td>C/D Stroop</td>
<td>-.158</td>
<td>-.083</td>
<td>-.073</td>
<td><strong>.909</strong></td>
</tr>
<tr>
<td><strong>Eigenvalue</strong></td>
<td><strong>4.249</strong></td>
<td><strong>1.794</strong></td>
<td><strong>1.498</strong></td>
<td><strong>1.015</strong></td>
</tr>
</tbody>
</table>

*Note.* CVLT = California Verbal Learning Test II; WMS = Wechsler Memory Scale – Logical Memory (story A only); RCFT = Rey Complex Figure Test; FAS = D-KEFS Verbal Fluency Test; WAIS = Wechsler Adult Intelligence Scale IV; BNT = Boston Naming Test; and C/D Stroop = Stroop interference task (Victoria version).
Difference in Cognitive Performance between Individuals with and without Vascular Risk Factors: Multivariate Analysis of Variance

The four factors obtained from the PCA were used as dependent variables for a one-way between groups multivariate analysis of variance. This analysis showed associations between presence/absence of vascular risk factors and overall cognitive function in the fully adjusted model for age, education and \textit{APOE} ε4 carriage (F (4, 669) = 4.28, \(p = 0.002\); partial eta square = 0.025). Table 18 presents means and standard deviations for each cognitive factor for both the vascular risk factors and non-vascular risk factors groups. When the results for the dependent variables were considered separately, two of the four factors reached statistically significant difference, namely the \textit{visuospatial skills and visual memory factor} (F (1, 676) = 7.30, \(p = 0.01\); partial eta square = 0.01) and the \textit{inhibition factor} (F (1, 676) = 7.47, \(p = 0.01\); partial eta square = 0.01). As shown in Figure 6 and Figure 7 individuals with vascular risk factors presented lower average performance in both factors, compared to those individuals without vascular risk factors.

\textbf{Table 18: Means (Standard Deviation) for the without & with-Vascular Risk Factors Groups for each Cognitive Factor}

<table>
<thead>
<tr>
<th>Cognitive Factor</th>
<th>Without Vascular Risk Factors</th>
<th>With Vascular Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Memory Factor</td>
<td>0.109 (1.03)</td>
<td>-0.008 (0.99)</td>
</tr>
<tr>
<td>Visuospatial Skills and Visual Memory Factor</td>
<td>0.202 (0.97)</td>
<td>-0.050 (1.00)</td>
</tr>
<tr>
<td>Language &amp; Information Processing Factor</td>
<td>0.063 (1.05)</td>
<td>-0.024 (0.99)</td>
</tr>
<tr>
<td>Inhibition Factor</td>
<td>-0.197 (0.96)</td>
<td>0.035 (1.00)</td>
</tr>
</tbody>
</table>
Figure 6: Difference in visuospatial skills and visual memory factor scores (estimated marginal means with 95% C.I.) between individuals with and without vascular risk factors.

Figure 7: Difference in cognitive factor scores (estimated marginal means with 95% C.I.) between individuals with and without vascular risk factors. The measure used in the Inhibition factor was time, whereby the higher the results the worse the performance.
Third Analysis – Rate of Cognitive Change for Five Specific Cognitive Tests: a Longitudinal Study

Data was collected over 54 months, at four different time-points (baseline, 18-month, 36-month and 54-month assessments). By the end of the study period, 172 individuals were excluded from the analysis; 156 individuals withdrew and 16 were deceased. Table 19 presents baseline characteristics for individuals who completed the study and those who withdrew. Comparison of these groups revealed that the withdrawers group did not differ in terms of gender ($\chi^2 (1, n = 767) = 0.04, p = 0.86$), level of education ($\chi^2 (1, n = 740) = 2.1, p = 0.16$), $APOE\varepsilon4$ carriage ($\chi^2 (1, n = 743) = 0.05, p = 0.84$), estimated IQ ($F (1, 762) = 0.01, p = 0.91$) or presence/absence of vascular risk factors ($F (6, 664) = 6.94, p = 0.33$). However, those who withdrew were significantly older ($F (1, 765) = 51.2, p = 0.000$) and had a poorer MMSE score at baseline ($F (1, 762) = 19.3, p = 0.000$) compared to the completers.

Table 19: Demographic Characteristics of Those who completed the Study and Those who withdrew

<table>
<thead>
<tr>
<th></th>
<th>Completers</th>
<th>Withdrawers</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>596</td>
<td>172</td>
<td></td>
</tr>
<tr>
<td>Mean Age at Baseline (SD)</td>
<td>69.1 (6.5)</td>
<td>73.3 (7.7)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Female %</td>
<td>43 %</td>
<td>42.1 %</td>
<td>ns</td>
</tr>
<tr>
<td>$APOE\varepsilon4$ %</td>
<td>26.8 %</td>
<td>25.7 %</td>
<td>ns</td>
</tr>
<tr>
<td>Education &lt; 12 years %</td>
<td>53.7 %</td>
<td>46.8 %</td>
<td>ns</td>
</tr>
<tr>
<td>Estimated IQ (WTAR) (SD)</td>
<td>108.3 (7.2)</td>
<td>108.3 (7.5)</td>
<td>ns</td>
</tr>
<tr>
<td>MMSE Score at Baseline (SD)</td>
<td>29.0 (1.1)</td>
<td>28.5 (1.4)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Presence of VRF</td>
<td>68.9 %</td>
<td>69.8 %</td>
<td>ns</td>
</tr>
</tbody>
</table>

Notes: SD = Standard deviation. WTAR = Wechsler Test of Adult Reading. MMSE = Mini Mental State Examination. VRF: Vascular Risk Factors
Difference in the Rate of Cognitive Change for five Specific Cognitive Test

In order to investigate the change in cognitive performance over time we selected five neuropsychological tests (each assesses a different cognitive domain). These variables were subjected to a LMM analysis, adjusted for age, estimated IQ and APOE ε4 load. The five tests included in the model were: (a) California Verbal Learning Test (b) Boston Naming Test (c) Rey Complex Figure Test (d) Stroop Colour and Word (e) Control Oral Word Association Test.

LMM analysis demonstrated significant difference in the rate of cognitive change for the COWAT and the RCFT scores. No significant differences were identified for the CVLT (F (594.4, 2) = 0.2, p = 0.82), for the BNT (F (1406.7, 2) = 2.41, p = 0.09) or for the Stroop test (F (1376.6, 2) = 2.16, p = 0.12).
For the COWAT (F (1,096.8, 2) = 3.03, p<0.05) (Figure 8), individuals without vascular risk factors displayed an improvement in performance by the third time-point, suggestive of a practice effect, whereas those with vascular risk factors exhibited consistent performance over time (Benedict and Zgaljardic 1998, McCaffrey, Duff et al. 2000). Post hoc comparison demonstrated a significant difference at the 36-month assessment between the groups (F = (1,549) = 8.2, p<0.05).

Figure 8: Rate of Cognitive Change for the Control Oral Word Association Test
Similar to the COWAT findings, individuals with vascular risk factors exhibited a significantly different rate of cognitive change in the RCFT \( (F (12.046, 1) = 1.055; p = p < 0.05) \) (Figure 9). In addition, post hoc comparisons revealed significant cross-sectional differences not only at baseline \( (F = (1,735) = 7.8, p < 0.05) \), but also at 36-month \( (F (1, 609) = 6.1, p < 0.05) \) and 54-month \( (F = (1,513) = 6.7, p < 0.05) \) assessments. This indicates that participants with vascular risk factors showed initially lower RCFT performance in addition to a different rate of cognitive decline, compared to the non-vascular risk factor group.

![Figure 9: Rate of Cognitive Change for the Rey Complex Figure Test.](image-url)
No significant difference in the rate of cognitive change was identified in the Stroop test. However, cross-sectional analysis indicated that the baseline cross-sectional difference outlined in the second study (refer to cross-sectional analysis above) was maintained at the 18-month assessment time point, with participants with vascular risk factors exhibiting lower performance than the non-vascular risk factor participants (Figure 10). Specifically, the one way ANOVA demonstrated significant differences in the performance between the two groups for baseline (F (1, 725) = 5.0, p<0.05) and the 18-month (F (1, 666) = 11.7, p<0.05) time points.

Figure 10: Rate of Cognitive Change for the Stroop Test (reaction time). Higher scores equal worse performance.
Fourth Analysis – Rate of Cognitive Change for Cognitive Composite Factors: a Longitudinal Study

The sensitivity of neuropsychological test batteries to identify cognitive impairment and cognitive decline might be enhanced through the use of composite cognitive measures derived from multiple tests that share the same underlying neuropsychological mechanisms (Johnson, Gross, et al., 2012). When comparing the use of independent tests with cognitive composite measures, the reliability of the latter group is often improved (Nuechterlein, Nuechterlein, et al., 2008). In addition, the use of cognitive composite measures reduces floor and ceiling effects, and enhances the detection of subtle cognitive changes (Gibbons et al., 2012; Johnson, Gross, et al., 2012). Therefore, in this analysis, the neuropsychological tests from the AIBL cognitive battery were grouped in five cognitive composite factors according to cognitive domains (Harrington et al., 2013). The resulting cognitive composite factors included both pencil-and-paper (Ellis et al., 2009) and computerised tasks (Lim et al., 2012), and assessed the following cognitive domains: (1) language, (2) verbal memory, (3) visual memory, (4) executive function and (5) visuospatial skills.
The cognitive composite factors were subjected to a series of LMM analyses adjusted for age, estimated IQ and APOE ε4 load. The results showed that relative to those individuals without vascular risk factors, those with vascular risk factors had a different rate of cognitive change on measures of verbal (F (624.016, 1) = 7.2; p = 0.01) (Figure 12) and visual (F (1775.533, 1) = 6.89; p = 0.01) (Figure 13) memory, as well as on executive functions (F (1821.035, 1) = 4.48; p = 0.03) (Figure 14) and visuospatial skills (F (1204.6, 1) = 1.055; p = 0.03) (Figure 15). This trend was not evident in the language cognitive composite (Figure 11).

Figure 11: Rates of cognitive change for the language composite factor. Error bars represent 95% confidence intervals.
As clearly shown in the following graphs, the performance of individuals with vascular risk factors was generally lower at all time-points compared to the no vascular risk factors group. More specifically, in the verbal memory composite factor (Figure 12), we found significant differences in the slope between individuals with and without vascular risk factors.

Figure 12: Rate of cognitive change for the verbal memory composite factor. Error bars represent 95% confidence intervals.
A different pattern was found when we studied the rate of cognitive change in the visual memory composite factor (Figure 13). The trend displayed by the group of participants without vascular risk factors suggested a constant improvement over time. This pattern was not evident in the vascular risk factors group.

Figure 13: Rate of cognitive change for the visual memory composite factor. Error bars represent 95% confidence intervals.
As illustrated in Figure 14, we found a significant difference in the cognitive trajectories between those participants with vascular risk factors and those without vascular risk factors on the executive function composite factor. Those without vascular risk factors demonstrated an improvement in executive function over time, and this apparent practice effect was not evident in the participants with vascular risk factors.

Figure 14: Rate of cognitive change for the executive function composite factor. Error bars represent 95% confidence intervals.
Figure 15 presents the rate of cognitive change for the visuospatial composite factor. The trajectory differed significantly between individuals with and without vascular risk factors, whereby individuals with vascular risk factors displayed more decline over time than the non-vascular risk factor group.

![Figure 15: Rate of cognitive change for the visuospatial skills composite factor. Error bars represent 95% confidence intervals.](image)

**Fifth Analysis – The Effect of Vascular Risk Factor Burden on Cognition**

This analysis focuses on the evaluation of the potential “dose effect” of vascular risk factors on cognitive function, whereby the higher the vascular risk factor burden the greater the cognitive decline. As mentioned previously, we divided the cohort into four groups: (1) those with no vascular risk factors, (2) those with one vascular risk factor, (3) those with two vascular risk factors and (4) those with three
or more vascular risk factors. With the purpose of investigating whether the number of vascular risk factors affects cognitive function, the Cohen's $d$ was calculated comparing each of the vascular risk factors groups with the no vascular risk factors group.

Figure 16 shows the magnitude of impairment represented by the Cohen's $d$ for the two factors that were obtained from the PCA in the second analysis (described above). The data showed that when individuals have three or more vascular risk factors, the Cohen's $d$ approaches the moderate range on the visuospatial skills and visual memory (Cohen's $d = 0.38$) and inhibition (Cohen's $d = 0.46$) factors. The Cohen's $d$ found for the group of participants with one or two vascular risk factors, on the other hand, was below 0.3 which is the threshold for a moderate range (Cohen, 1992). For the other two factors (verbal memory and language and Information processing factors), the Cohen's $d$ for all of the groups of participants with vascular risk factors was below 0.2.

![Figure 16: Magnitude of impairment at baseline assessment according to the number of vascular risk factors.](image-url)
We then calculated the magnitude of decline for the five cognitive tests used in the third analysis (described above), according to the vascular risk factor burden. The results (Figure 17) revealed that in the group of individuals with three or more vascular risk factors, the magnitudes of decline were highest for the Stroop Test (Cohen's $d = 0.53$), the COWAT (Cohen's $d = 0.38$) and the RCFT (Cohen's $d = 0.32$), with all three falling within the moderate range. The magnitude of decline found in the BNT was Cohen's $d = 0.29$, which is small to moderate in magnitude. In the CVLT II, there was no difference in magnitude of rate of decline, although individuals with vascular risk factors performed more poorly overall compared to those without vascular risk factors.

![Figure 17](image_url): Magnitude of decline over the 54-month follow-up period according to the number of vascular risk factors for the five neuropsychological tests.
We also calculated the magnitude of decline for the cognitive composite factors used in the fourth analysis (described above). In this case, we divided the participants into two groups: those with low vascular risk factor burden (one or two vascular risk factors) and those with high vascular risk factor burden (three or more vascular risk factors). As illustrated in Figure 18, individuals with higher vascular risk factor burden have a poorer performance across all cognitive composites factors. The magnitude of decline reaches the moderate range for individuals with three or more vascular risk factors on the visual memory (Cohen's $d = 0.47$), executive functions (Cohen's $d = 0.35$) and visuospatial skills (Cohen's $d = 0.35$) composite factors. Interestingly, this relationship was not evident in either of the language and verbal memory cognitive composite factors.

![Cognitive Composites](image)

**Figure 18:** Magnitude of decline over the 54-month follow-up period according to the number of vascular risk factors for the cognitive composite factors.
Sixth Analysis - Effect of Vascular Risk Factors on the Clinical Classification of the Participants

The last analysis focused on the group of participants who attracted a diagnoses of MCI. Demographic information for those who remain cognitively stable and those who progressed to MCI was compared (Table 20). The MCI group tended to be older ($F(1, 594) = 13.4, p < 0.000$), have a lower premorbid IQ ($F(1, 592) = 7.43, p = 0.007$), a lower MMSE score at baseline ($F(1, 592) = 6.66, p = 0.010$) and, as expected, have a higher percentage of $APOE \varepsilon 4$ carriers ($\chi^2(1, n = 579) = 5.15, p = 0.028$).

**Table 20: Demographic Characteristics of Stable and Transitioners Groups**

<table>
<thead>
<tr>
<th></th>
<th>Stable</th>
<th>Transitioners</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>553</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Mean Age at Baseline (SD)</td>
<td>68.8 (6.4)</td>
<td>72.5 (6.7)</td>
<td>$p &lt; 0.05$</td>
</tr>
<tr>
<td>Female %</td>
<td>58 %</td>
<td>44.2 %</td>
<td>$ns$</td>
</tr>
<tr>
<td>$APOE \varepsilon 4$ %</td>
<td>25.7 %</td>
<td>41.9 %</td>
<td>$p &lt; 0.05$</td>
</tr>
<tr>
<td>Education &lt; 12 years %</td>
<td>43.9 %</td>
<td>55.8 %</td>
<td>$ns$</td>
</tr>
<tr>
<td>Estimated IQ (WTAR)</td>
<td>108.5 (6.9)</td>
<td>105.4 (10.1)</td>
<td>$p &lt; 0.05$</td>
</tr>
<tr>
<td>MMSE (SD)</td>
<td>28.99 (1.1)</td>
<td>28.55 (1.0)</td>
<td>$P &lt; 0.05$</td>
</tr>
</tbody>
</table>

Notes: SD = Standard deviation. WTAR = Wechsler Test of Adult Reading. MMSE = Mini Mental State Examination.
Vascular Risk Factor Burden Distribution between Older Adults who Progress to MCI and those who remain Cognitively Stable

To determine potential differences in the vascular risk factor burden distribution between those participants who remained stable and those who transitioned to MCI, Chi-square tests for independence were performed. A significant difference in the cumulative vascular risk factor burden between both groups was identified \( (\chi^2 (2) = 44.88, p < 0.001) \) (Figure 19). It was found that there was a significantly greater proportion of individuals with vascular risk factors in the group of participants who progress to MCI compared to the stable healthy controls. We found that the proportion of stables with no vascular risk factors was over 40% higher than that for the transitioners. In both groups, the majority of participants belong to the “one vascular risk factor” group.

Figure 19: Vascular risk factors burden distribution between healthy older adults who progress to MCI and those who remain cognitively stable.
Interaction Effect between Presence/Absence of Vascular Risk Factors and Clinical Classification on the Visuospatial Skills Composite Factor

The composite factors were then subjected to a two-way ANOVA to explore whether there is an interaction effect between clinical classification and presence/absence of vascular risk factors on cognitive function. The cohort was divided into two groups according to their clinical classification (stable and transitioners). The five cognitive composite factors, which were described previously (in Table 10), were used as dependent variables in the statistical model. From the five cognitive composites, the statistically significant interaction between presence of vascular risk factors and the clinical classification of participants was for the visuospatial skills composite factor (Figure 20). Specifically, transitioners without vascular risk factors performed similarly to the stable participants, while transitioners with vascular risk factors exhibited a significantly poorer performance ($F(1, 513) = 5.52; p = 0.019; \text{partial eta square} = 0.011$).

Figure 20: Interaction effect between presence/absence of vascular risk factors and clinical classification on visuospatial composite
Risk of Developing MCI on Individuals with Vascular Risk Factors

We calculated the relative risk of developing MCI for the group of participants with vascular risk factors, compared to that for those without vascular risk factors. The following equation - \( \text{relative risk of developing MCI} = (1 - \text{relative risk}) \times 100\% \) - was used to calculate the likelihood of developing the disease, where a relative risk of more than 1.0 indicated an increased risk. The relative risk of developing MCI among participants with vascular risk factors was 1.39 (95% confidence intervals 0.6 – 3.4), indicating that individuals with vascular risk factors are 39% more likely to develop MCI than participants with no vascular risk factors (Table 21).

<table>
<thead>
<tr>
<th></th>
<th>Relative Risk</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence /Absence VRF</td>
<td>1.39</td>
<td>0.56</td>
<td>3.42</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.81</td>
<td>0.41</td>
<td>1.57</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>0.81</td>
<td>0.43</td>
<td>1.54</td>
</tr>
<tr>
<td>Obesity</td>
<td>1.51</td>
<td>0.69</td>
<td>3.31</td>
</tr>
<tr>
<td>Smoking history</td>
<td>1.18</td>
<td>0.48</td>
<td>2.90</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.05</td>
<td>0.36</td>
<td>3.07</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>0.93</td>
<td>0.12</td>
<td>7.27</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>0.99</td>
<td>0.98</td>
<td>1.0</td>
</tr>
</tbody>
</table>
We also calculated the relative risk for each vascular risk factor independently, with the objective of identifying if specific vascular risk factors increase the chances of developing MCI more than others. The results revealed that three vascular risk factors had a relative risk higher than 1. Participants who suffered from obesity (relative risk = 1.5 95% confidence intervals 0.7 – 3.3), smoking history (relative risk = 1.2 95% confidence intervals 0.5 – 3.0) and diabetes (relative risk = 1.05 95% confidence intervals 0.4 – 3.1) have 50%, 20%, and 5% more chances of developing MCI (compared to those without vascular risk factors), respectively. Even though the relative risk calculated for the remaining vascular risk factors was below 1, they were approaching this level, suggesting that suffering from any vascular risk factor is likely to increase the chances of developing MCI over time. It is important to interpret these results with caution given the small statistical power associated with the relatively small number of transitioners in our study.
“A scrutiny of the relationship between the extent of the neuropathologic changes and the degree of intellectual deterioration revealed numerous discrepancies; in many instances the psychosis could not be adequately explained by anatomic considerations alone. It is believed that the discrepancies are based on differences in the capacity of different persons to compensate for damage to the brain. Examples are given to illustrate that cerebral lesions do not inevitably produce psychotic disturbances. Attention is directed to qualities of the living patient as an important factor in the origin of the mental disorder. It is suggested that patients with an ill balanced mental makeup possess weaker compensatory powers and are thus more likely to acquire a psychosis than other persons with cerebral arteriosclerosis”.

Rothschild, 1942 pg 436

Prevalence of Vascular Risk Factors

Since the Industrial Revolution, changes in sleep patterns, physical activity and dietary habits have been associated with increased prevalence of inflammatory conditions and metabolic disorders (Carrera-Bastos, Fontes-Villalba, O’Keefe, Lindeberg, & Cordain, 2011; Thorburn, Macia, & Mackay, 2014). Adoption of this ‘modern’ lifestyle has been linked with a growing incidence of vascular risk factors
across all gender, geographic and socioeconomic groups (Deaton et al., 2011; Tunstall-Pedoe, 1988), making it a major public health problem, especially in developing nations (Cook & Strachan, 1997; D’Agostino et al., 2008; Howard et al., 2008; P. M. Kearney et al., 2005; World Health Organization, 2010, 2011).

The Australian population has one of the highest recorded rates of vascular risk factors among developed countries (Thorburn et al., 2014). Although the AIBL group is a convenience sample and not an epidemiological cohort, the results of our study are consistent with population-wide statistics; at baseline, 80% of participants had one or more vascular risk factors. However, even though diabetes (together with obesity) is one of the two most prevalent vascular risk factors in Australia (Cameron, 2003; Olds, Olds, Tomkinson, Ferrar, & Maher, 2010), only 6.2% of our participants were classified as having diabetes, in all likelihood attributable to the initial AIBL selection criteria.

Consistent with previous investigations (Daviglus et al., 2012), hypertension (45.1%) and dyslipidaemia (44.3%) were the two most prevalent vascular risk factors in our cohort of cognitively healthy older adults. Detectable variations among populations have been identified; in rural India, for example, rates of hypertension were lower (3.4% in men and 6.8% in women) than in countries like Poland (68.9% in men and 72.5% in women) (Kearney, Whelton, et al., 2005). In China, 32.8% of the adult population has dyslipidaemia (He et al., 2004), while 50% of Mexicans over the age of 50 suffered from this condition (Aguilar Salinas et al., 2001). Variations in diet, with increased consumption of animal-based fats and a decreased intake of plant-based fats (Farzadfar et al., 2011), may help explain these differences. A heightened
level of awareness, as well as enhanced treatment and control of vascular risk factors, could also explain differences among populations, particularly as these aspects have improved in developed countries over the past decade, but remain inadequate in developing nations (Kearney, Whelton, Reynolds, Whelton, & He, 2004).

Obesity was the third most prevalent vascular risk factor in our cohort after hypertension and dyslipidaemia, which is consistent with previous reports – half of adult Australians in 2003 were obese and the incidence keeps rising (Flegal, Carroll, Ogden, & Curtin, 2012; Kelly, Yang, Chen, Reynolds, & He, 2008; O’Brien, 2003; Tanner, Tanner, Brown, & Muntner, 2012). Globally, in 2000, for the first time in history, the number of obese individuals exceeded the number of those who were underweight (Caballero, 2007). Furthermore, the prevalence of obesity is rapidly increasing in both developed (35.2%) and developing (19.6%) countries (Catenacci, Catenacci, Hill, & Wyatt, 2009; Deitel, 2006; Kelly et al., 2008).

The majority of our cohort was of Caucasian background and no participants belonged to Australian Aboriginal groups. Nevertheless, studies have reported that in the Australian Aboriginal population the prevalence of vascular risk factors is also high. Data from the National Aboriginal and Torres Strait Islander Survey (NATSIS) conducted in 1994 (Altman & Taylor, 1996) revealed that 25% and 60% of all Indigenous Australian men and women, respectively, are obese and suffer from other vascular risk factors, such as hypertension and diabetes. It has also been reported that the prevalence of vascular risk factors is significantly higher among Aboriginal and Torres Strait Islanders than for the rest of the Australian population (Altman & Taylor, 1996).
For a developing community, Aboriginal Australians have experienced a rapid escalation in the prevalence of vascular risk factors. Changes in lifestyle and diet, from a traditional hunter-gatherer lifestyle to a settled western lifestyle (Altman & Taylor, 1996), are likely contributing factors, providing a clear example of how adoption of a ‘modern’ lifestyle can promote increases in the incidence of vascular risk factors in developing communities.

Taken together, these findings reflect the escalating rates of vascular risk factors worldwide, likely related to changes in human behaviour. Our findings showed that hypertension and dyslipidaemia, followed by obesity, were highly prevalent in our cohort of cognitively healthy older adults. This highlights the need for interventions that promote lifestyle and behaviour changes, including weight loss, variation in dietary habits and increased physical activity. Creating an environment that is supportive of healthy lifestyle habits is essential in order to control the rising prevalence of vascular risk factors and help address a growing global public health problem.

**Comorbidity in Vascular Risk Factors**

Increasing evidence indicates that vascular risk factors tend to coexist (Artaud et al., 2013; Poortinga & Poortinga, 2007; N. Pronk et al., 2004; Reaven, 1988). The synergistic health effect of vascular risk factors makes it critical to consider them in combination rather than in isolation (Poortinga & Poortinga, 2007). As discussed in Chapter 2, metabolic syndrome has been recognised as a clustering of three or more vascular risk factors (Grundy et al., 2005; Kalmijn et al., 2000) and is related to (1) abdominal obesity, (2) atherogenic dyslipidaemia, (3) raised blood pressure, (4)
insulin resistance and glucose intolerance, (5) pro-inflammatory state and (6) pro-thrombotic state (Antonopoulos, 2002).

An estimated 20-25% of adults worldwide suffer from metabolic syndrome (Tanner et al., 2012; Wille et al., 2011). This disorder is more common in developed nations than in developing countries (Ford, Ford, Giles, & Dietz, 2002; S. M. Grundy et al., 2005; Ninomiya et al., 2004) and its incidence has increased over the last 10 years. In the United States, for example, 34% of the adult population suffer from metabolic syndrome (American Heart Association, 2015), and 35% in Europe (Gu et al., 2005; Tanner et al., 2012). The pandemic of metabolic syndrome in Australia has also advanced during the last decade; it is estimated that around 37% of individuals aged 25 years and older suffer from this condition (Cameron et al., 2007).

Almost half (42%) of our cohort had more than one vascular risk factor, but only 14% of participants had three or more (the threshold for classification as suffering from metabolic syndrome) – considerably lower than the national prevalence figure (37%). The exclusion of individuals with a history of ischemic stroke and those with a history of alcohol dependence, together with a high proportion of participants undergoing treatment for vascular risk factors, may explain the lower proportion of individuals with a high vascular risk factor burden in our cohort.

In line with our results, dyslipidaemia has been reported in 50% to 80% of individuals who suffer from hypertension (O’Meara et al., 2004). In addition, studies have reported that obesity is the vascular risk factor most strongly associated with other vascular risk factors (Grundy, Brewer, Cleeman, Smith, & Lenfant, 2004).
Accordingly, metabolic syndrome has often been defined as a clustering of metabolic complications of obesity. Obesity was found to be in comorbidity with diabetes, hypertension and smoking in our study cohort. The combination of these vascular risk factors constitutes a serious health condition which can result in heart attack, stroke or peripheral vascular disease (Jokinen et al., 2009).

Importantly, some of these vascular risk factors are modifiable. Lifestyle changes involving particular dietary patterns, nutrient intake and different levels and types of physical activity can result in a reduction of vascular risk factors (Estruch et al., 2013). Limiting alcohol consumption and quitting smoking are also important (Artaud et al., 2013). Changes such as these can play a major role in the prevention of vascular risk factors (Eckel et al., 2014), while having a beneficial effect on general health. Even modest sustained lifestyle changes can substantially reduce the prevalence of vascular risk factors (Artinian et al., 2010). Evidence has shown that adherence to the Mediterranean diet, characterised by high intake of olive oil, fruit, nuts, vegetables and cereals, and low intake of dairy products, processed meats and sweets, can reduce the incidence of vascular risk factors by up to 30% (Estruch et al., 2013; Gardener et al., 2014; Gardener et al., 2012; Hooper et al., 1996).

**Age, Educational Level and Apolipoprotein E epsilon 4**

Our findings suggest differences in age, education and *APOE* ε4 carriage between vascular risk factors and non-vascular risk factors groups, which is consistent with the existing literature. Individuals with vascular risk factors tended to be older, less educated and more likely to carry an *APOE* ε4 allele. An association between vascular risk factors and age has been reported previously (Bangen et al.,
2009; De Leeuw et al., 2001; Di Carlo et al., 2000; Grolimund & Seiler, 1988; Muller et al., 2012; Yusuf et al., 2004; Yusuf, Reddy, Ounpuu, et al., 2001; Yusuf, Reddy, Œunpuu, et al., 2001), suggesting that age can be an important predictor of the presence of vascular risk factors (Johansson, 1997). Explanations regarding this association propose that increasing age results in alterations of the cerebrovascular system (Bangen et al., 2014). Even in healthy older adults, clinically asymptomatic vascular pathology is commonly found (DeCarli et al., 2005). It is also well established that age contributes to changes to specific pathophysiological mechanisms, such as increases in large vessel lumen, wall thickening, arterial stiffening and endothelial dysfunction (Celermajer et al., 1994; Lakatta, 1993; Virmani et al., 1991).

Nevertheless, there are important modifiable factors such as dietary changes and increased physical activity that may prevent or delay the vascular degenerative changes associated with ageing (DeCarli et al., 2005).

Existing literature has suggested a strong association between low education and a higher prevalence of vascular risk factors (Diez Roux, Nieto, Tyroler, Crum, & Szklo, 1995; Drewnowski & Specter, 2004; Kaplan & Keil, 1993; Pinsky, Pinsky, Leaverton, & Stokes, 1987; Reynes, Lasater, Feldman, Assaf, & Carleton, 1992; Sarlio-Lähteenkorva, Silventoinen, & Lahelma, 2004; Winkleby et al., 1992; Zhang & Wang, 2004); this finding was supported by our study. Higher levels of education tend to increase access to higher quality medical care, as well as the likelihood of living a healthier lifestyle in terms of diet and physical activity; together, these may be reasons for this relationship (Dennis et al., 1993). A number of studies have hypothesised the existence of an inverse relationship between education and the prevalence of vascular risk factors, whereby belonging to a lower socioeconomic
status (which is highly linked to low education level) can lead to: (1) poor nutrition, (2) lack of access to health care, (3) chronic diseases, (4) lack of social support and social networks, and (5) social stresses (Katzman, 1993; Kilander, Kilander, Nyman, Boberg, & Lithell, 1997; Kim & Johnston, 2011; Luepker et al., 1993; Winkleby et al., 1992). The AIBL cohort is highly educated relative to the general Australian population (Ellis et al., 2009; Ellis et al., 2010); however, the connection between relatively lower education levels and vascular risk factors was still apparent.

The relationship between vascular risk factors and education level has been identified predominantly in developed countries, where disadvantaged populations rely heavily on inexpensive and calorie-dense foods, while also having more limited opportunities for active travel and physical activity (Luepker et al., 1993; Luoto, Pekkanen, Uutela, & Tuomilehto, 1994; Pinsky et al., 1987; Reynes et al., 1992; Simon et al., 2006). Previous studies have suggested that in developing countries, in contrast with the situation described for developed countries, vascular risk factors tended to be more prevalent in higher socioeconomic classes (Brown 1991, Stunkard, Peña et al. 2000). This view has been disputed (World Health Organization 2000, Monteiro, Moura et al. 2004) and additional studies have found that the association between lower socioeconomic status and prevalence of vascular risk factors also exists in developing countries (Sobal, Sobal, & Stunkard, 1989; Yusuf, Reddy, Ôunpuu, et al., 2001). Studies in rural India, for instance, have shown that vascular risk factors are more prevalent in illiterate and low educated populations (Gupta, Gupta, & Ahluwalia, 1994). This is of special concern as it is estimated that there are approximately 774 million adults in the world who are unable to read and write. Approximately 17% of this global illiterate population is composed of people over the
age of 60 years (UNESCO, 2008). Not surprisingly, most of the illiterate older adults are residing in developing countries, where appropriate treatment for people with vascular risk factors might not be available.

*APOE* ε4 genetic allele carriage is thought to play a role in increasing an individual's susceptibility to cardiovascular disease (Davignon, Cohn, Mabile, & Bernier, 1999; Haan et al., 1999; Mahley, Huang, & Rall, 1999). Consistent with this relationship, the majority of individuals in our study cohort with at least one vascular risk factor were *APOE* ε4 carriers. When we divided the cohort according to the level of vascular risk factor burden, the group that had more than three vascular risk factors had a significantly higher proportion of *APOE* ε4 carriers compared to the no vascular risk factor group. Around 26% of the general Australian population can be classified as *APOE* ε4 carriers (Corbo & Scacchi, 1999); which is consistent with the rates of *APOE* ε4 carriage in our cohort. For those with no vascular risk factors, only around 18% were carriers, while 34% of those with three or more vascular risk factors carried the *APOE* ε4 allele.

In a meta-analysis that involved 15,492 individuals with cardiovascular disease and 32,965 healthy controls, *APOE* ε4 carriers were 42% more likely to develop cardiovascular disease than non-carriers (Song & Song, 2004). Animal models have shown similar results; 35% of mice carrying a mutant Apolipoprotein E ε4 gene died of cardiovascular disease over an 18-month period (Moghadasian et al., 2001). The genesis of this association is yet to be established; however, a number of potential mechanisms have been suggested, whereby the presence of the *APOE* ε4 genotype may be connected with the prevalence of cardiovascular disease.
Levels of Apolipoprotein E (ApoE, in contrast to genotype) have been shown to be an important modulator of the clearance of lipoproteins that are rich in triglyceride and cholesterol (Mahley, 1988; Schiele et al., 2000; Sing, Sing, & Moll, 1989; Stengård, Stengrd, Weiss, & Sing, 1998; Utermann & Utermann, 1987). Even though ApoE is primarily synthesised in the liver, synthesis also takes place in a number of other tissues in the body, including the spleen, kidney, adrenals, gonads, macrophages and brain, particularly astrocytic glia - (Davignon, Gregg, & Sing, 1988). As such, ApoE plays a key role in the lipoprotein metabolism and in the transport of dietary triglyceride and cholesterol from the liver to peripheral tissues (Mahley, Weisgraber, & Huang, 2009; Masliah et al., 1995; Tangirala et al., 2001).

In addition to its effects on cardiovascular disease and its role in lipoprotein metabolism, ApoE also contributes to the regulation of antioxidant systems (Miyata & Smith, 1996), inflammatory pathways and immunomodulatory properties (Zhou, Paulsson, Stemme, & Hansson, 1998), anti-platelet aggregation (Riddell, Graham, & Owen, 1997), anti-proliferative effects (Ishigami, Swertfeger, Granholm, & Hui, 1998), and regulations of other systems (Smith, 2000). In addition, the Insulin Degrading Enzyme has also been related with the presence of ApoE. Mice that carry the ApoE4 allele together with the Insulin Degrading Enzyme have shown an increase in insulin levels which has resulted in impairment of the glucose tolerance (Miyata & Smith, 1996). It has been shown that ApoE4 reduces the expression of the Insulin Degrading Enzyme in the brain but not in other tissues (Du, Chang, Guo, Zhang, & Wang, 2009). This association suggests that ApoE4 regulates the overall expression of the Insulin Degrading Enzyme and could impair the glucose metabolism, resulting in a higher risk of developing diabetes (Qiu & Folstein, 2006). Despite these promising findings,
the mechanisms underlying the relationship between the presence of \textit{APOE} polymorphism and of vascular risk factors are not completely understood and warrant further investigation.

\textbf{Cognitive Function and Vascular Risk Factors}

One of the strongest modifiers of cognition in healthy older adults is the presence of vascular risk factors. Our results are in line with prior studies (Anstey et al., 2007; Anstey, C. von Sanden, A. Salim, & R. O'Kearney, 2007; Bangen et al., 2013; Bangen et al., 2010; Chiang et al., 2007; Cukierman-Yaffe et al., 2009; Dregan et al., 2013; Gregg et al., 2000; McDowell, Guoliang, Lindsay, & Tuokko, 2004; O. C. Okonkwo et al., 2010; Oulhaj et al., 2010; Waldstein & Wendell) that showed a difference in cognitive performance between individuals with and without vascular risk factors.

The analyses in this thesis revealed that in healthy older adults, when cognition was considered at a single assessment, the presence of vascular risk factors manifested as impairment on specific cognitive tests, such as the RCFT and the Stroop test. Further, longitudinal data revealed that when compared to healthy older adults with no vascular risk factors, individuals with vascular risk factors also showed cognitive decline in the COWAT. No association was evident in the CVLT and the BNT. The former three neuropsychological instruments (RCFT, Stroop test and COWAT) have been recognised for having multidimensional underlying cognitive mechanisms and for measuring executive functions; as such, they may be particularly vulnerable to the effect of vascular risk factors when compared to other tests.
The Stroop Test examines cognitive inhibition, cognitive flexibility and speed of processing information (Djamshidian, Djamshidian, Osullivan, Lees, & Averbeck, 2011), all of which are classified as executive functions. The RCFT, on the other hand, was developed 70 years ago with the primary purpose of assessing cognitive capabilities in individuals with brain damage (Binder, 1982). It is generally used for the evaluation of visuospatial abilities in copy condition, as well as for assessing visual memory in recall condition (Meyers & Meyers, 1996). However, the cognitive mechanisms underlying the RCFT are sufficiently complex to provide a good indication of a series of cognitive tasks, including visuo-constructional skills, perceptual distortion and grapho-motor coordination, as well as executive functions, such as planning, organisational skills and problem-solving strategies (Jerskey & Meyers, 2011; Lezak, 2004; Waber, Waber, Bernstein, & Merola, 1989; Watanabe et al., 2005).

The COWAT assesses functions related to prefrontal regions (Welsh, Welsh, & Pennington, 1988) and has been commonly viewed as a test of executive function (Joanette, Joanette, & Goulet, 1986; Martin, Loring, Meador, & Lee, 1990; Miceli, Caltagirone, Gainotti, Masullo, & Silveri, 1981; Perret & Perret, 1974). The cognitive mechanisms underlying word generation are multidimensional and involve: (1) auditory attention, (2) short-term memory (in keeping track of words already said), (3) ability to initiate and maintain word production, (4) cognitive flexibility (in rapidly shifting from one word to the next, within a selected category), (5) response inhibition capacity and (6) long-term vocabulary storage (Delis et al., 2001).
We employed cognitive composites to enhance measurement precision and improve the detection of subtle differences in cognition (Gibbons et al., 2012; Harrington et al., 2013) at all time-points in the presence of vascular risk factor group. The cognitive composite measures were derived from multiple tests that shared the same neuropsychological architecture (Nuechterlein, Nuechterlein, et al., 2008; Silbert, Howieson, Dodge, & Kaye, 2009). When using cognitive composite measures, differences in the rate of cognitive change were no longer only found in tests that measure executive functions, but also across other cognitive domains, including memory. Even though we did not find an association between vascular risk factors and language, which has been previously reported (Breteler et al., 1994; Nation, 2010), the performance of individuals with vascular risk factors was generally lower in the language composite factor.

**Effect of Vascular Risk Factor Burden on Cognitive Function**

Seven vascular risk factors, which have been previously reported as potentially having an effect on cognition, were examined simultaneously in the present study. Using this approach enhanced the probability of detecting subtle additive effects and interactions. To our knowledge, this is the first study that has included this group of vascular risk factors in combination.

A dose-response relationship between the cognitive composite measures and vascular risk factors burden was identified. When we divided the cohort according to the number of vascular risk factors, we found that (compared to those with no vascular risk factors) the group with three or more vascular risk factors exhibited a significantly different rate of decline in the executive functions, visual memory and
visuospatial skills composite factors. No relationship was found in either the language or verbal memory factors.

Non-memory cognitive difficulties have been predominantly associated with the presence of vascular risk factors (Carmelli et al., 1998; A. Di Carlo et al., 2000; Jefferson et al., 2007; Pugh et al., 2003; Smith et al., 2011; Wiederkehr, Laurin, Simard, Verreault, & Lindsay, 2009). Memory impairment is usually observed as one of the earliest stages of AD (Albert et al., 2010; Petersen, 1999); however, difficulties in non-memory cognitive functions, such as executive functions and visuospatial skills, generally develop over time (Devanand, Folz, Gorlyn, Moeller, & Stern, 1997; Elias et al., 2003; Howieson et al., 1997; Luchsinger, Reitz, et al., 2005; Wolf et al., 2007). Hence, these findings raise the question of whether vascular risk factors act in a cumulative fashion, affecting cognitive mechanisms that are not typical of AD.

Executive functions, visuospatial skills and visual memory showed a particular vulnerability to the presence of vascular risk factors in our analyses. Even though previous studies have reported a link between vascular risk factors and memory (Kalmijn et al., 1995; Perlmutter et al., 1984; A. Solomon & M. Kivipelto, 2009; Strachan, Deary, Ewing, & Frier, 1997; Waldstein et al., 2005), there seems to be agreement that non-memory cognitive domains, such as visuospatial skills (Arvanitakis et al., 2004; Dahle et al., 2009) and executive function (Bangen et al., 2013; Debette et al., 2011; Dregan et al., 2012; Jefferson et al., 2007; McGuinness et al., 2009; Okonkwo et al., 2008; Smith, 2011) are the most commonly affected cognitive domains associated with the presence of vascular risk factors.
The analyses in this thesis showed that vascular risk factors predominantly affected executive functions and visuospatial cognition (including visuospatial skills and visual memory). Both cognitive domains are complex and are mediated by widely distributed cognitive networks (Burgess, Maguire, & O’Keefe, 2002; Ekstrom et al., 2003; Hartley, Maguire, Spiers, & Burgess, 2003; Sommer, Rose, Gläscher, Wolbers, & Büchel, 2005; Treyer, Buck, & Schnider, 2005). Brain-imaging and neurophysiological data have indicated that these widespread cognitive networks require the integrated action of many areas distributed throughout both cerebral hemispheres and involving cortical and subcortical areas (Alexander, Crutcher, & DeLong, 1989; Bressler & Bressler, 1995; de Oliveira Lanna et al., 2012; Hua et al., 2009; Johnson, Johnson, et al., 2012; Mishkin, 1982; Papez & Papez, 1937; Posner & Petersen, 1989; Posner & Snyder, 1980; Smith et al., 2011; Squire & Squire, 2004; Tekin & Cummings, 2002; Temel, Temel, Blokland, Steinbusch, & Visser, 2005; Walther, Walther, Birdsill, Glisky, & Ryan, 2010). This might influence cognitive susceptibility to vascular risk factors over time, suggesting that the effect of vascular risk factors on cognition might be more noticeable in complex and widespread cognitive systems.

**Risk of Developing Mild Cognitive Impairment in Individuals with Vascular Risk Factors**

In support of previous studies (Anstey et al., 2007; Ho et al., 2011; Lu, Lu, Lin, Kuo, & Zhang, 2009; Ott et al., 1999; Peila et al., 2002; Razay et al., 2006; Reitz, Tang, Luchsinger, & Mayeux, 2004; Solomon & Kivipelto, 2009), our findings showed that, relative to those with no vascular risk factors, the cohort with vascular risk factors had an increased risk (39%) of developing MCI. After 54 months, 5.6% of the vascular
risk factors group was classified as having MCI. Furthermore, the majority of individuals that attracted a classification of MCI had a higher vascular risk factor burden – 60% in the “transitioner” group had two or more vascular risk factors.

As discussed in Chapter 2, a number of studies have proposed that the presence of vascular risk factors, when occurring in the setting of incipient AD, might accelerate the transition to MCI (Albert et al., 1995; Riekse et al., 2004; Yoshitake et al., 1995). Even though memory impairment is one of the earliest areas of decline observed in individuals with MCI (Albert et al., 2010; Petersen, 1999), it is proposed that non-memory difficulties associated with the presence of vascular risk factors (such as visuospatial and executive dysfunction) (Devanand et al., 1997; A. Di Carlo et al., 2000; Jefferson et al., 2007; Johnson, Johnson, et al., 2012; Pugh et al., 2003; Smith et al., 2011) could be a secondary impairment process that makes the symptomatology more evident in individuals in which the underlying disease processes leading to AD are already underway. Previous studies have suggested that MCI has a preclinical stage characterised by subtle cognitive decline (Chen et al., 2001; Chen et al., 2000; Elias et al., 2000; Hall, Lipton, Sliwinski, & Stewart, 2000). When considering both aspects in combination, our findings suggest that individuals in the preclinical stage of MCI who also suffer from vascular risk factors, may have an even more accelerated transition to dementia characterised by an initial decline on executive functions and visuospatial cognition.

The underlying neuropathological mechanisms that precede MCI have shown a selective pattern of regional depositions. In the case of Aβ, depositions occur in a ‘top-down’ fashion, initiating in the neocortex area and spreading to subcortical
regions (Arnold, Hyman, Flory, Damasio, & Van Hoesen, 1991; Kemppainen et al., 2007; Klunk et al., 2004; Näslund et al., 2000; Tapp et al., 2004). Tau deposition, on the other hand, begins in the mesial-temporal regions and progresses to the neocortex area (Braak & Braak, 1991, 1997). The association between both pathological hallmarks and cognitive functions has been well established: Aβ depositions have shown a preferential correlation with non-memory cognitive domains (Hardy & Selkoe, 2002; Mawuenyega et al., 2010; Perl, 2010), while tau-related pathology has been associated with memory impairment (Braak & Braak, 1991; Giannakopoulos et al., 2003; Grober et al., 1999; Nagy et al., 1999; Nelson et al., 2012; Nelson, Braak, & Markesbery, 2009).

Using the BBB-permeability model as a framework, which argues that vascular risk factors increase the BBB permeability and thus enable Aβ to cross the barrier and accumulate in the brain (Kalaria, 1992, 1999; Wardlaw, 2010), it is postulated that the cognitive deficits associated with the presence of vascular risk factors is the result of amassing of Aβ in the anterior neocortex, manifested as non-memory impairment. Even though memory difficulties are the typical feature of AD, our findings suggest that vascular risk factors do not affect memory in a direct fashion; as an alternative, we argue that vascular risk factors initially affect widely distributed non-memory cognitive functions, such as executive functions and visuospatial cognition. The effect of vascular risk factors in non-memory cognitive functions is subtle but detectable, which raises the question of whether brain reserve is compromised in individuals with vascular risk factors, thereby resulting in the acceleration of the transition to MCI and, potentially, in the manifestation of the overt clinical symptoms of AD.
Vascular Risk Factors and the Brain Reserve Hypothesis

The influence of specific environmental exposures on the likelihood of progression to dementia remains unclear (Lee, 2007). Nevertheless, it has been postulated that neurodegenerative disorders, such as AD, are the result of several interrelated mechanisms, including the interaction of genetic, environmental and biological factors that diminish brain reserve (Fratiglioni, von Strauss, & Qiu, 2008; Reitz & Mayeux, 2009; Stern & Stern, 2003; Valenzuela, 2008). Within this context, we propose that the association between vascular risk factors and cognitive deterioration may be explained by the effect of vascular risk factors on widespread neurocognitive domains (such as executive functions and visuospatial cognition) that act as the cognitive matrix in which brain reserve relies. This implies that individuals who suffer from several risk factors may have less brain reserve and may therefore be more susceptible to developing dementia.

As was discussed in Chapter two, genetic predisposition, such as APOE ε4 carriage, has been previously associated with accelerated cognitive deterioration and with low levels of brain reserve, compared with non-carriers (Fennema-Notestine et al., 2011; Lind et al., 2006; Raz et al., 2009; Small et al., 2004; Ward et al., 2014; Wisdom et al., 2011). Environmental conditions in early life, such as education, mental activities, occupation and the use of leisure time, have also been recognised to have an effect on the formation of brain reserve and in the propensity to develop dementia later in life (Borenstein et al., 2005; Stern & Stern, 2003). Healthy older adults that engage in cognitive activities (such as reading books or newspapers, writing for pleasure, completing crossword puzzles, playing board games or cards, participating in group discussions or playing musical instruments) have been
estimated to have 63% less risk of developing dementia in the next 5 years, compared to those who are not cognitively active (Verghese et al., 2003). Similar results were found in a study that reported that a person who is frequently involved in cognitive activities was 47% less likely to develop DAT, compared to a mentally ‘inactive’ person (Wilson, Bennett, & Bienias, 2002).

The implementation of strategies, such as lifestyle changes that reduce vascular risk factors, have been suggested to be an alternate way of increasing brain reserve (La Rue & La, 2010; Nyberg, Lövdén, Riklund, Lindenberger, & Bäckman, 2012; Restrepo, Saling, & Ellis, 2010; Stern, 2012). Lifestyles that combine physical activities with cognitive and social activities, together with complex environments, have shown effective results in preventing cognitive decline and the onset of dementia (Brown, Peiffer, & Martins, 2013; Foster, Rosenblatt, & Kuljiš, 2011; Gates, Singh, Sachdev, & Valenzuela, 2013; Gates & Valenzuela, 2010; Karp et al., 2006; Kempermann G.; Gast, 2002; Lautenschlager, Cox, & Cyarto, 2012; Lautenschlager, Cox, & Kurz, 2010). Even though there is no specific treatment for those individuals who are at risk of developing AD, it may be possible to delay or prevent the appearance of the disease symptoms through the reduction of vascular risk factors and the implementation of healthy lifestyle changes.

Physical activity has been associated with decreased risk of many chronic diseases (Bailey & Arco, 2010; Bijnen et al., 1998), including cardiovascular disease (Luepker et al., 1996) and colon (Thune & Furberg, 2001) and breast (Brody et al., 2007) cancer. Maintaining a good level of physical health may also preserve cognitive function and slow dementia progression (Barber et al., 2012; Lautenschlager et al.,
It has thus been suggested that individuals at risk of developing dementia, or who exhibit cognitive difficulties, may benefit from some type of physical exercise, such as walking on a daily basis (Barella, Etnier, & Chang, 2010; Middleton & Yaffe, 2009; Podewils et al., 2005; Ruthirakuhan et al., 2012; Scarmeas et al., 2009). Aside from helping to maintain their functional independence (Artaud et al., 2013), exercise can augment brain reserve by preserving neuronal plasticity and increasing synapses and dendritic receptors (Stern & Stern, 2003). Studies in animal models have shown that physical activity promotes neurogenesis in the dentate gyrus (Van Praag, Shubert, Zhao, & Gage, 2005) and resistance to cell death (Jessberger, Jessberger, & Gage, 2008).

Unhealthy behaviours such as physical inactivity, poor diet, smoking and high alcohol consumption have been associated with an increased risk of cognitive decline in elderly populations (Artaud et al., 2013; Harrington et al., 2009; Nepal, Brown, & Ranmuthugala, 2010; Organization, 2010). Unfortunately, these lifestyle behaviours tend to coexist in the same individual (Poortinga, 2007; Pronk et al., 2004). Lifestyle modifications (such as having a BMI of less than 25 kg/m², adopting a diet high in cereal fibre and polyunsaturated fat and low in trans-fat and glycaemic load, and not smoking and lowering alcohol consumption to an average of half a drink per day) have resulted in decreased vascular risk factors (Cornelissen, Buys, & Smart, 2013; Villegas, Creagh, Hinchion, O’Halloran, & Perry, 2004; Villegas, Kearney, & Perry, 2008; Villegas, Salim, Flynn, & Perry, 2004) and reduced cognitive decline (Brown et al., 2012; Cassilhas et al., 2007; Gorelick et al., 2011; Karp et al., 2006; La Rue & La, 2010; van Uffelen, Paw, Hopman-Rock, & van Mechelen, 2008; Williamson et al., 2012; Leone, 2008; Lindsay et al., 2002; Rolland, Rolland, Abellan van Kan, & Vellas, 2010; Vance, Fazeli, Grant, Slater, & Raper, 2013).
Furthermore, the American Heart Association recommends engaging in moderate to vigorous physical activity for at least half an hour per day in order to prevent the onset of dementia (Rolland et al., 2010). Similarly, The National Physical Activity Guidelines for Australians, recommend for people aged 65 years and older a minimum of half an hour of daily moderate intensity physical activity for lowering dementia risk, as well as for improving cognitive function (Australian Government Department of Health and Ageing, 2013). The adoption of a healthy lifestyle is therefore recognised as potentially likely to be beneficial in reducing the prevalence of vascular risk factors, and thereby increasing brain reserve and lowering the risk of developing MCI and dementia (Brown, Peiffer, Taddei, et al., 2013; Crawford, 1996, 1998; Hamer & Chida, 2009; Heyn, Abreu, & Ottenbacher, 2004; Pate et al., 1995; Sofi et al., 2011).

**Proposed Model**

This thesis sought to examine the relationship between vascular risk factors and cognition in healthy older adults, as well as the influence of vascular risk factors on the transition from normal ageing to MCI. Our findings revealed an association between the presence of vascular risk factors and deleterious impacts on widespread cognitive networks, including executive function and visuospatial cognition. Such a link suggests that vascular risk factors may affect the broader cognitive framework within which memory function occurs, rather than memory itself directly, raising the notion of the existence of a negative effect of vascular risk factors on brain reserve. This, in turn, increases the likelihood of memory difficulties being manifested early in the cognitive deterioration process, thereby promoting the transition to MCI.
Taking into consideration the overall findings of this study, we propose that a higher vascular risk factor burden, together with genetic (APOE ε4 carriage) and demographic factors (advanced age and lower educational level), reduces brain reserve and in so doing contributes to the acceleration of the transition to MCI and might influence the manifestation of the clinical symptomatology of AD. The implication may be that individuals who suffer from several risk factors might have less brain reserve and might therefore be more susceptible to developing dementia.
CHAPTER SIX – FUTURE DIRECTIONS & LIMITATIONS

Future Directions

The results of this study open the possibility for several new lines of research. Vascular risk factors have recently received more attention in the field of AD (Arvanitakis et al., 2004; Gorelick, 2004; Gustafson et al., 2003; Lautenschlager et al., 2010; Luchsinger & Mayeux, 2004; Luchsinger, Reitz, et al., 2005; Rusanen et al., 2011). Even though their role on the pathogenesis of AD is still unclear, individuals with vascular risk factors, particularly those with a high vascular risk factor burden, might represent a critical target for the implementation of early prevention strategies and for conducting lifestyle modification studies. An expanded longitudinal investigation of the effect of cumulative vascular risk factor burden, particularly from earlier life stages, may better inform on the purported relationship between vascular risk factors and cognitive function over time. Coupled with biomarker and neuroimaging analyses, such studies may enhance understanding the role of vascular risk factors in the transition to MCI and in the preclinical stage of AD. Similarly, further elucidation of interactions among vascular risk factors could identify particular problematic comorbidity, and assist with identification of the underlying pathological mechanisms that may inform prevention strategies.

The principal purpose of this thesis was to define the neurocognitive impact of an increasing burden of vascular risk factors. While the impact of APOE genotype is more established, there is also emerging evidence that other genetic risk factors such as the BDNF Val66Met polymorphism may also play a role in increasing cognitive vulnerability in healthy older adults (Bueller et al., 2006; Lim et al., 2014; Lim et al.,
2014; Raz et al., 2009; Ward et al., 2014). Future research might aim to identify the interaction between lifestyle induced vascular risk factors, genetic risk factors and neurocognitive networks.

During the past decades, previous studies have markedly enhanced the understanding regarding the pre-symptomatic phase of neurodegenerative disorders, such as AD. Nevertheless, an important challenge yet to be resolved is how to recognise individuals most at risk of developing AD, as well as those who are already in the pre-clinical stage of the disease. Evidence has suggested that the interactions between genetic, early life and current environments are potentially crucial in determining the likelihood of developing dementia. As such, a principal focus of this research project was to promote the identification of cognitive markers in those individuals who have no overt manifestation of the clinical symptomatology of AD, across individuals with varying risk factor profiles. The findings of this thesis offer an advance in understanding of the potential role of vascular risk factors on impairment and decline of specific cognitive domains in healthy older adults.

Our findings strongly suggest that vascular risk factors have a detectable effect on cognitive function in healthy older adults, and this may be due to potentially accelerating the emergence of the clinical symptomatology of AD in some individuals. We observed that vascular risk factors affect cognitive functions, such as executive functions and visuospatial cognition, which are subserved by distributed cortical networks. Further, both of these cognitive domains assist in the formation of other cognitive functions, such as memory. Individuals with vascular risk factors might
therefore be more susceptible to cognitive difficulties as a consequence of information overload, which is commonly interpreted as forgetfulness.

The trend of selectivity of vascular risk factor on cognition raises the question of whether there may be a more specific neurocognitive pathway for the action of vascular risk factors. We propose that in individuals who are at the pre-clinical stage of AD, the effect of vascular risk factors could be a secondary impairment process, following the AD-pathology process. When considering both aspects in combination, our findings suggest that individuals in the preclinical stage of AD who also suffer from vascular risk factors may exhibit an initial decline on executive functions and visuospatial cognition, which potentially may be interpreted as memory impairment, and that could result in a faster transition to MCI.

Brain reserve may play an important role in the association between vascular risk factors and cognition, which is mediated in part by the effect of vascular risk factors in non-memory cognitive functions that constitute the cognitive matrix in which brain reserve occurs (Stern, 2012). An association between vascular risk factors, cognition and brain reserve would indicate that lifestyle decisions may play a crucial role in an individual’s risk of developing dementia. Taken together with existing literature, the outcomes of this study suggest that relatively simple changes in lifestyle may have dramatic benefits by delaying the onset of neurodegenerative dementia.
Limitations

Limitations of each analysis conducted as part of this thesis have been described in detail in each respective section. Nevertheless, the main limitations of this study are as follows: (1) the study cohort composition; this is one of the most frequently cited threats to external validity. The AIBL study is not an epidemiological study and implemented strict inclusion and exclusion criteria. As such, the majority of participants were highly educated and lead a healthy lifestyle. In addition, the majority of participants were of Caucasian descent, and as was previously described, the prevalence of vascular risk factors differs among various populations; (2) the adequacy of vascular risk factor measurements; different ways of measuring vascular risk factors have been reported. In the current study, self-report was one of the criteria used to identify individuals with vascular risk factors. Studies have suggested that self-report may not be a highly reliable measure of risk factors or disorders (O’donnell, Araujo et al. 2005, Jürges 2007). In addition, BMI was used as a measure of obesity and some studies have shown that abdominal circumference (Pouliot, Després et al. 1994, Jürges 2007) may be a more reliable measure; (3) the relative small sample size for some aspects of the study, such as the analysis that focused on the number of participants who transition to MCI during the 54-month follow-up period. However, the AIBL study is ongoing and therefore it will be of interest to determine if the observed associations between the presence of vascular risk factors and the conversion to MCI are maintained over time; and (4) the presence of additional cofounder factors, such as genetic variations, might have to be considered for future studies. Although the presence of APOE ε4 was included in the statistical models as a covariate, other genetic factors such as the brain derived neurotrophic
factor (BDNF) gene Val66Met polymorphism may also need to be included. A separate study that contained a large portion of the sample used in this thesis reported that healthy adults with high Aβ, Met carriers, showed significant declines in episodic memory, executive function and language, and greater hippocampal atrophy over 36 months, compared with those with Val/Val homozygotes (Lim, Villemagne et al. 2013).

**Reflection**

Our modern lifestyle is characterised by a detachment from the land that provides our sustenance, as well as by living environments where access to opportunities for physical activity is increasingly more limited. From an evolutionary perspective, humans have remained primarily unchanged since the agricultural revolution 10,000 years ago; however, our diet and lifestyle have become progressively more divergent from those of our ancestors. The human hunter-gatherers consumed only wild and unprocessed food foraged and hunted from their environment. In contrast, modern diets are characterised by being rich in saturated fats and sugars, and by the extensive use of preservatives. The ability to identify healthy food has relied heavily on the information available to people about simple things such as the true ‘origin’ of foods and their composition. Also, the use of vitamins and other supplements has become widespread as an alternative to complement or supplant our food intake.

The separation of land uses, whereby the distances to basic goods and services are too onerous for even the young and fit, result in people using non-active modes of travel – such as private vehicles and public transport – to reach most destinations,
leading to a generalised lack of adequate levels of physical activity in our modern society. Accumulating evidence suggests that the divergence between our modern diet (rich in saturated fats, sugar and highly processed foods) and sedentary lifestyle, and our genetic characteristics is playing a substantial role in the ongoing epidemics of vascular risk factors, such as obesity, hypertension and diabetes. Together, dietary and physical activity aspects of our modern lifestyle are having profound effects in our society, with significant health and economic consequences. As such, there is a critical need to change our lifestyle; achieving this will, however, require a true ‘paradigm shift’ at both the individual and societal levels.
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Friday, 7 July 2006

Prof D Aman

Ninewells House

SCH

Attention: N K Hills

Dear Prof James

Protocol No: HERCA  02/806

"The Australian Emerging Biomarkers and Lifestyle (ABEL) Flagship Study of Ageing"

Prof D Aman
Dr K Hills

Prof C Masters

Prof H Marian

Dr T Lackett

Prof E Chis

Dr O Vanstekerken

Mr K Draper

The President/Secretary of Human Research Ethics Committee A (HERCA) has agreed that your latest correspondence dated Friday, 30 June 2006, has satisfied the conditions imposed and granted approval for this project to be undertaken at St. Vincent’s Health.

HERCA is consistent with the NHMRC National Statement on Ethical Conduct in Research Involving Humans 1999 (including supplementary note 7 issued November 1999).

HERCA has a policy of granting approval for five years. Ethical approval is valid for five years from the date of this letter. Approval may be renewed at the end of this period by submission to HERCA.

Approval is subject to:
1. Immediate notification to HERCA and sponsor of any serious adverse effects on participants;
2. Immediate notification of any adverse events that may affect the continuing ethical acceptability of the project;
3. notification and reasons for causing the project to be suspended or delayed; and
4. the submission of an annual report on progress of the project;
5. HERCA approval of any proposed modification to the project; and
6. the submission of a final report and papers published on completion.

St Vincent’s Hospital Melbourne  •  P.O. Box 2000  •  Flemington 3010  Australia  •  Telephone (+61) 3 2093 2511

ACN 002 337 957

Continuing the Mission of the Sisters of Charity  •  Companions: Justice  •  Human Dignity  •  Goodness  •  Unity
Tuesday, 13 April 2010

Prof D Ames
Normanby House
SGH

Dear Prof Ames

Protocol No: HREC-A 028/06
'The Australian Imaging Biomarkers and Lifestyle (AIBL) Flagship Study of Ageing'

Prof D Ames        Dr K Ellis        Prof C Masters        Prof R Martins
Prof E Chiu         A/Prof O       Ms K Pike             Mr C O'Halloran
Yastrubetskaya

Ms D DeFazio      Ms E Koziopoulo    Ms S Walker         Ms A Rooney
Ms A Kaldi         Mrs J Ellis       Miss C Copolov      Mr A Kamer
Ms C Restrepo      Ms F Lamb        Ms J Robertson      Miss B Dridan
Miss R Buckley     Mrs R McVeigh     Miss K Harrington

The Human Research Ethics Committee-A (HREC-A) has granted final approval to the following amendment:

Request to amend the protocol incl: repeating the AIBL x2 additional times, addition of procedure to collect buccal cells, addition of 4 tasks to collect data and interview to gather more information. PICF is now version 11 dated 3 March 2010

This approval will be noted by the full Human Research Ethics Committee - A at its next meeting on Wednesday 05 May 2010.

There will be no further correspondence regarding this amendment unless a member of the HREC-A raises a concern at the next HREC-A meeting.

The conditions of approval of this amendment are the same as those governing approval of the original protocol.

Yours sincerely,

Ms Anita Arndt
Senior Administrative Officer and HREC-A Secretary
Direct Tel: 9288 3924
Author/s:
Restrepo, Carolina

Title:
The effect of vascular risk factors in dementia of the Alzheimer's type

Date:
2016

Persistent Link:
http://hdl.handle.net/11343/91456

File Description:
The Effect of Vascular Risk Factors in Dementia of the Alzheimer's Type